Army Medicine Peer-Reviewed Publications

September 2012

Index

Executive Summary

September 2012-- Journal coverage for September focused primarily on post-traumatic stress disorder, traumatic brain injury and surgery with journals also discussing substance abuse and medical technology. Journal articles on PTSD showcased research that delves into the complicated and often misunderstood disorder. Most notable was a journal article revealing preliminary research on a combination treatment of healing touch and guided imagery that yields successful results. This treatment was featured prominently in the media throughout the last two weeks of the month. Journal articles on TBI focused on treatment methods and noted several adjustments that could be made to enhance recovery and full rehabilitation. Also of note was coverage of surgery that focused on adjustments in protocol that may expedite surgery and make it more efficient. Coverage of medical issues related to the military was spread across medical journals with The Lancet, The New England Journal of Medicine and MedScape printing multiple articles relevant to military medicine.

Upcoming journal coverage will likely continue to discuss PTSD and TBI as the Departments of Defense and Veterans Affairs announced a $100 million grant to study both medical issues. At the end of the Army's Suicide Prevention Month, traditional media may turn its attention to some of the studies on underlying issues causing suicide in the military including substance abuse, PTSD and TBI. Expect enhanced coverage from traditional media on journal research and findings.

Medical journal coverage

PTSD

Forbes: Military PTSD - All-Star Scientists Start Mental Health Mega-Project

Because PTSD is typically a self reported issue, clinicians often have difficulty treating and diagnosing the disorder. Military practitioners face additional obstacles because Soldiers can go undiagnosed if they do not come forward for assistance, and military physicians face considerable scrutiny as to whether their diagnosis process is in fact accurate and effective. Secretary of the Army John McHugh has called for research into more effective PTSD diagnosis, and Draper Industries, an MIT non-profit, has taken the lead. The research team plans to follow 2,000 people, including non-military, who have endured traumatic events.

The Lancet: Three promising ideas in psychiatric drug development

As part of his interview on psychiatric drug development, Dr. Thomas Insel briefly spoke about PTSD. He highlighted PTSD as the largest single project the National Institute of Mental Health is undertaking and the organization's collaboration with the Army. The NIMH and the Army are working together to enroll 100,000 Soldiers in a comprehensive study to understand the causes of PTSD. The study will address TBI as a potential cause of depression and suicide and will attempt to determine factors that might indicate which service members are at risk of PTSD, depression and suicide.

MedScape Today: Memory training can alleviate depression

This memory-training program improved memory specificity and reduced depression symptoms. Preliminary research indicates that memory training may be a viable option for treating depression, anxiety and PTSD. This research seeks to treat depression by enhancing memory, which can be compared to previous research on removing memories to treat PTSD and depression.

Military Medicine: Healing Touch With Guided Imagery for PTSD in Returning Active Duty Military - A Randomized Controlled Trial

The research, led by Scripps Center for Integrative Medicine, involved active-duty Marines at Camp Pendleton. Findings indicate that combining healing touch with guided imagery substantially alleviates PTSD symptoms and depression, and improved outlook and quality of life. Healing touch is a form of aligning massage, and guided imagery utilizes the imagination to reduce stress and decrease pain through visualization. Guided imagery was administered through the use of a CD during healing touch treatment. Subjects were instructed to continue the guided imagery treatment at home, once per day. The treatment was so successful that it lowered PTSD symptoms beyond the threshold for diagnosis. The treatment does not utilize opiates or any other drugs and can be replicated at home. This treatment may be especially desirable as suicide and opiate abuse rates increase. Coverage of this research was included in national and local print, broadcast and trade publications.

Traumatic Brain Injury

The Lancet: Early management of severe traumatic brain injury

Though advances have been made in understanding severe TBI, a better understanding of the injury has not as of yet led to improvements in treatment outcome. Participants of a workshop discussed the necessity of reclassifying TBI, as the current classification into categories of mild, moderate and severe fails to identify the complexity of the injury and minimizes the severity of mild TBI. Paramedic, pre-hospital treatment continues to reveal mixed results, but researchers should continue to look for an effective pre-hospital

treatment procedure. Randomized trials revealed that decompressive craniectomies, surgeries that remove a portion of the skull to allow the brain to swell without compression, have worse outcomes than medicinal treatment. Potentially effective drugs include erythropoietin, statins, ciclosporin-A, tranexamic acid and progesterone. Additionally, the International Initiative for Traumatic Brain Injury Research is developing the first comprehensive dataset to form a solid base for research.

Neurology: Neurodegenerative causes of death among retired National Football League Players

Professional football players are three times more likely to die from neurodegenerative diseases than their peers. Football players are four times more likely to die from Alzheimer disease and amyotrophic lateral sclerosis than their peers. Research indicates that speed players, who work up momentum before impact, are at particular risk. Though the study does not conclusively determine the cause of increased risk it does suggest that multiple concussions is the likely cause. This research is particularly applicable to service members who encounter blasts from IEDs and face the potential for multiple concussions.

MedScape: Emergency Department Visits for Traumatic Brain Injury in Older Adults in the United States: 2006–08

Research indicated that the rate of emergency services for TBI is increased in people over the age of 65. Though data from this age set is not immediately pertinent to the military, it indicates that TBI may become a more important public health issue as the population ages. This information could encourage the medical community to focus future research on TBI.

Medical Science Sports Exercise: Identifying Impairments After Concussion: Normative Data versus Individualized Baselines

Research indicates that comparing a post-concussion evaluation with a normative mean is more effective in assessing impairments than using individualized baseline data. This finding is useful for military applications, as medical personnel may not always have access to baseline data and medics in the field do not have access to individualized baseline date. This research indicates that medical care in the military does not suffer from an inability to access individualized baseline data.

Surgery

The Lancet: Haemorrhage control in severely injured patients

Exsanguinating hemorrhage, or bleeding out, is the leading preventable cause of post-trauma death. Because surgery to stop blood loss is often abbreviated to allow resuscitation, better pre-hospital blood loss protocol will allow more effective and definitive surgery. Recent research indicates that a move away from fluid resuscitation as the only treatment for hemorrhagic shock will lead to better outcomes. Additionally, treatments for

coagulopathy and drugs that affect inflammation, coagulation and fibrinolysis could reduce the need for surgery to stop hemorrhages, enhancing a surgeon's ability to immediately treat the injury.

The Lancet: Advances and future directions for management of trauma patients with musculoskeletal injuries

For Soldiers, musculoskeletal injuries and subsequent treatment are major determinates of the level of outcome and recovery. Research indicates that tissue injury influences inflammatory response and that individually timing the bone setting process will enhance musculoskeletal recovery. New research on tissue engineering is emerging with studies that focus on using stem cells to form scaffolds that aid in bone regeneration. Other research notes that rigid bone setting is preferable to early motion in large bone injuries.

BMC Medicine: Transforming growth factor beta1 inhibits bone morphogenic protein (BMP)-2 and BMP-7 signaling via upregulation of Ski-related novel protein N (SnoN): possible mechanism for the failure of BMP therapy?

Preliminary research notes that 36 percent of patients studied did not respond to protein treatments intended to promote bone growth. The study shows that the protein is blocked by a transforming growth factor. Research on this topic will accelerate bone healing, which will aid in rehabilitation and has the potential to decrease to rate of Soldiers handicapped by severely broken bones and traumatized musculoskeletal systems.

Technology

Reuters: UK Paraplegic Woman First to Take Robotic Suit Home

The robotic exoskeleton allows the wearer to walk up and down stairs as well as stand up and sit down independently. The suit costs $71,000, but medical costs to treat bone density issues, atrophy and other difficulties common in a paralyzed person could reach up to $3 million over a patient's life. This technology could not only enhance a paralyzed Soldier's quality of life, but it may reduce the financial burden to TRICARE. Coverage notes that the Military has expressed interest in the technology.

Substance Abuse

American Journal of Psychiatry: Cognitive Dysfunction and Anxious-Impulsive Personality Traits Are Endophenotypes for Drug Dependence

Although not everyone who takes drugs becomes addicted, those with family members who are addicted to drugs are predisposed to becoming addicted themselves. The researchers in this study sought to clarify the extent of cognitive dysfunction and personality traits that are shared by family members. This could mean that some of these traits are present in predated drug dependence, and some are specific to drug-dependent individuals. This research compared the characteristic phenotypes of drug-dependent individuals with those of their unaffected siblings and unrelated healthy volunteers to determine endophenotypes for drug dependence. Better understanding of drug addiction could lead to a screening process that would prevent susceptible Soldiers from being prescribed certain drugs.

Other

The American Journal of Gastroenterology: The Incidence and Risk of Celiac Disease in a Healthy US Adult Population

The study utilizes U.S. Military records to assess celiac disease, a gluten intolerance, noting that incidents of celiac disease increased five times from 1999 to 2008. Research notes that celiac disease is increasing in the military. This could affect nutrition requirement and present medical personnel with more instances of fatigue, weight loss, anemia, lymphoma or other symptoms associated with this autoimmune disorder

The New England Journal of Medicine: From Sick Care to Health Care- Reengineering Prevention into the U.S. System

Despite the amount of money the United States pays for health care, many problems are still frequent in the system. Chronic disease accounts for a majority of deaths in the country, and a proactive prevention model that addresses issues before they become life threatening could be the best solution. The prevention model does not eliminate disease entirely, but seeks to compact the effects from a life threatening disease into a shorter span at the end of someone's life. This is based off of Fries model of "morbidity compression." In the beginning of the 20th century, acute care and marginalized prevention and treatment were prevalent given the shorter lifespans and prominence of acute infectious diseases in a young population. This is not the case in today's society, and research seeks to change this in current medical practice.

Journal of American Medical Association: Engaging Physicians and Leveraging Professionalism: A Key to Success for Quality Measurement and Improvement

Physicians and medical professionals are expected to demonstrate the value of the service they provide by measure of care, reporting to patients and increasing public transparency. The medical community is learning from other industries how to eliminate defects in the system, increase reliability and reduce waste. The public has begun to pay for quality and expect more professionalism from physicians. The Centers for Medicare & Medicaid Services have begun to develop an idea called value-based purchasing, outlining the need to move from fee-for-service payment to purchasing based on value.

The New England Journal of Medicine: Tattoo Ink–Related Infections — Awareness, Diagnosis, Reporting, and Prevention

As tattoos have become increasingly popular, the rate of patients contracting nontuberculous mycobacterial infections associated with contaminated tattoo ink has also risen. After a cluster of patients in New York contracted nontuberculous mycobacterial infections following recently acquired tattoos, the Food and Drug Administration collaborated with the Center for Disease Control and Prevention and state and local health departments to investigate the outbreak. Findings from this investigations revealed that the problem was nationwide, involved multiple species of mycobacteria, and spread through contaminated ink. Nontuberculous mycobacterial infections are difficult to diagnose and treat, although most patients had a favorable response to macrolide therapy. The FDA is developing strategic messaging and outreach to raise awareness of this issue, which may impact military populations.

Medical journal clips

PTSD

Military PTSD: All-Star Scientists Start Mental Health Mega-Project

Forbes
Katie Drummond
4 Sep 2012

There's no question that plenty of soldiers from the wars in Iraq and Afghanistan are afflicted with post-traumatic stress disorder (PTSD). But exactly how many soldiers? That's a question that even top medical experts, not to mention military officials, still can't quite answer.

Now a new consortium, manned by some of the nation's top scientists where PTSD is concerned, is hoping to develop an objective means of diagnosing the condition. In other words, the group hopes that the illness can — one day soon — be diagnosed using medical techniques like blood tests or brain scans, rather than self-reported symptoms.

"If you think about it, most PTSD assessment is done by self-reporting," Dr. Roger Pitman, one of the consortium leaders and himself the director of the PTSD Research Lab at the Massachusetts General Hospital, tells me. "But we've found that patients can, of course, be imperfect reporters of their own states."

Relying on self-reported symptoms to make a diagnosis is, even for the best clinicians, difficult enough. Among military populations, the diagnosis of PTSD has been hampered, quite publicly, by additional challenges. Soldiers who avoid seeking help and therefore go undiagnosed, as well as concerns over just how accurate the military's diagnosis process actually is, are but two examples.

"Just as our behavioral health professionals are committed to providing the best care, we, too, must ensure that our processes and procedures are thorough, fair and conducted in accordance with appropriate, consistent medical standards," Army Secretary John McHugh said in a recent statement that announced plans for a widespread review of Army policies on PTSD diagnoses.

This new consortium, which was spearheaded by Draper Laboratories (a non-profit spin-off of MIT), could make those medical standards much more consistent. Researchers, including top-notch experts at Harvard, Boston University, Mount Sinai Hospital and several VA Medical Centers,

plan to track more than 2,000 people (military and civilian) who are exposed to traumatic events — most likely car accidents — from across the country.

The intent is to measure, both shortly after the experience and in later years, several different biomarkers — including hormones, genetic data and neurological factors — to parse out a select group of "markers" that can accurately diagnose PTSD. From there, the group hopes to come up with a systematic diagnostic plan, say a combination of blood test and fMRI scan, that can replace (or at least markedly enhance) self-reporting.

"Nobody has embarked on a study of this scope, to turn subjective strategies of diagnosis into objective ones," Dr. Pitman says. Indeed, although researchers at several institutions have found biomarkers that suggest either vulnerability to PTSD or an outright diagnosis, there's yet to be a widespread collaboration that looks at a host biomarkers in a single study population.

The study, which will cost an estimated $50 million, according to Dr. Len Polizzotto, Draper Lab's vice-president, is in the final planning stages. That said, the consortium still needs to secure funding — which they hope to do, in part, with military research dollars. And while the Pentagon is already funding plenty of research into PTSD, including pharmaceuticals that target fear response and tests to pin down PTSD biomarkers, they've yet to embark on a project of this scope.

"To have an impact on such an important issue, you need to expand the efforts," Dr. Polizzotto says. "We have the best of the best in the country, and they're ready to do this."

BACK TO TOP

Three Promising Ideas in Psychiatric Drug Development

Medscape
John C. Reed, MD
Sep 2012

Dr. Reed: This conference is all about the importance of medical research. In the case of mental health disorders, I don't think any of us would argue that we wouldn't benefit from more medical research, given the huge toll that mental health disorders exact on society. Depression, for example, is a leading cause of disability. And neuropsychiatric disorders are a leading cause of homelessness, along with alcohol and drug addiction.

These mental health challenges are so prevalent. About 1 in every 4 of us at some point will seek medical attention for a neuropsychiatric disorder. Tell us about what you're working on at the NIMH. What are you excited about in terms that activities that are going on there?

Dr. Insel: Just to emphasize your point about the unmet medical need, it is extraordinary. People tend not to recognize the huge public health burden and the huge costs for several reasons, one of which is that mental disorders are chronic and they begin in childhood. In fact, we often say these are the chronic disorders of children. We don't think about it that way often, but almost all of the disorders we're concerned with start in childhood. Schizophrenia; depression; most of the anxiety disorders, post-traumatic stress disorder (PTSD), for instance; and such disorders as autism all begin in childhood. And then they often take someone out of the productive parts of their life thereafter.

At the NIMH, we're very concerned about how to better understand these conditions and finding ways to better intervene. What we're most excited about is a complete rethinking of what these disorders are about. For the past many, many decades, we thought about these diseases as behavioral problems. We even call them mental disorders. These are problems of the mind.

But today we have a new biological understanding that lets us be able to study the mind through understanding the brain. That has brought about a revolution in the way to think about these diseases. We're able now to see that these are not just behavioral problems, but they are problems of brain function, problems of brain circuits. Sometimes that leads us to rethinking the way we diagnose and, hopefully, the way we treat them.

Developing Research Domain Criteria

Dr. Reed: Any of us who personally battle with mental illness or care for a family member with mental illness knows just how challenging it is to get the right diagnosis. And, of course, that's the starting point for figuring out what the therapy is.

I understand that NIMH is trying to develop a new classification system and new ways to really think about how these diseases work. There's a concept around a Research Domain Criteria (RDoC) that could replace the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) for the diagnosis of psychiatric disorders. Can you tell us more about that?

Dr. Insel: RDoC is this very interesting new effort. I don't think it's going to replace the DSM in the short term, because we still need a clinically useful diagnostic system. RDoC is really meant for research purposes. It is a way of saying, just as we've done in the rest of medicine, that it's important to look at subjective complaints and to understand the symptoms and to use physical diagnosis to get an objective image and picture of what the patient is experiencing.

But let's add to that the use of biomarkers. Let's look at family history. Let's look at genetics. Let's bring a whole series of different kinds of information to the table to say, is autism one disease? Does everybody who has a label of depression by their symptom cluster have the same disorder? Or is it going to turn out to be more along the lines of the way we think about fever today? Sure, everybody may have a temperature of 103°F, but that could be from many different causes. And, of course, those would be treated with very different interventions.

That's probably the way we want to think about depression, autism, schizophrenia -- all of these terms, these labels, that we have presumed somehow match with the biology of these disorders. We're finding out that they don't match. In fact, depression is probably many different disorders requiring many different kinds of treatment.

What we're looking for is a kind of precision medicine where we can do, for instance, what's happening today in cancer, where we think beyond just the presenting symptom. Instead, we begin to bring many levels of information to the table to give the most precise diagnosis.

Genomic Medicine for Psychiatry: Ready for Prime Time?

Dr. Reed: The challenge of disease heterogeneity is always a real struggle for trying to understand how to treat the patient. You mentioned the research context, using genomics and biomarkers. How soon do you think it will be before those sorts of approaches will be ready for prime time? Before a psychiatrist in practice will be using genomics and biomarkers to help decide how to best approach the management of patients?

Dr. Insel: I'm absolutely confident that will happen, but I'm not confident about when. I think we are at the point where we can bring neuroimaging in a research framework to say that these different patterns are associated with this different form of thinking or emotion regulation. That's actually part of what RDoC is trying to do. It's to get away from the kinds of labels we have today and to begin to understand abnormal behavior and abnormal thinking in terms of abnormal circuitry of normal brain function.

And we're getting there. We actually are getting there much more quickly than I might have thought 5 years ago, because we have much better tools to do this than we had in the past. But whether it's going to be 2 years or 10 years, I think will depend on a lot of the specific problems that we're wrestling with.

The key part now is to reframe the conversation and to help people to understand that this is where we need to go. We don't need to try to fit all of the data into the DSM. We need to fit what we're seeing in the clinic into what we understand about brain function and brain circuitry.

A Better Understanding of PTSD

Dr. Reed: We also heard at the Celebration of Science conference some of the poignant stories of some of our wounded warriors who are coming back from the wars of the Middle East. These challenges have left our nation with a huge mental health burden in the form of military personnel who are returning with neuropsychiatric disorders, particularly PTSD. What's your personal opinion about the severity of this problem? And what should we be doing about it as a nation?

Dr. Insel: This is probably the largest single project that we have going on today at NIMH. It's a large collaboration with the Department of Defense and specifically with the Army. And we are enrolling 100,000 soldiers into a massive study called the Army Study to Access Risk and Resilience in Servicemembers. This is with the army. And it's very much modeled on the Framingham Heart Study.

The argument is that we just don't understand enough about the problem of what it is that causes some people to be susceptible to neuropsychiatric disorders, whether it's traumatic brain injury (TBI) or PTSD or depression, and ultimately suicide. The Army came to us asking for help because they were so concerned about the increase in suicides. As you probably know, since 2009 the Army has lost more soldiers to suicide than to combat.

So, this is a major issue for them. The suicide rate has more than doubled, and it continues to be high. When we first got into this and started looking at what might be the drivers for this increasing rate, everybody had an idea. And everybody was partially right and partially wrong. It turns out to be far more complex.

We actually do need a Framingham-like study that helps us to understand over time what the drivers are and where we can best intervene. The key for this now is to identify what we call concentration risk -- to understand whom, out of the 500,000 soldiers that we're looking at in total, are the 1% or 2% that we need to be most concerned about. We're getting a pretty good handle on that. We're not quite where we want to be. But we've been able to concentrate risk already to a large degree.

I think the next stage is to get a little bit better; hand this off to the Army; and work with them to be able to intervene to make sure that we can bring down the rate of PTSD, depression, and suicide in a group that is at very high risk.

Research vs Public Service

Dr. Reed: I want to change gears a little bit. In addition to your leadership role at NIMH, you're also a very active researcher. You've been doing work in a variety of areas of neurobehavior and neurodevelopmental disorders. Tell us a little bit about what's happening in your shop.

Dr. Insel: I wish I had a shop. When I came to NIMH, I had been a very active scientist. I had for 20 years been at the bench doing experiments every day, and it was a huge part of my life. When I came to NIMH, I decided that I was going to do strictly public service, and that this was a job that required 120% of my time and 120% of my energy.

So I handed off the laboratory to people who really could give it 100%. And they're doing great stuff. That laboratory worked on the neurobiology of social behavior, which we did in a whole range of different interesting organisms and had a huge amount of fun with it. One thing that it did give me was an appreciation for the power of being able to go from good ideas, from fundamental neuroscience, to thinking about how to translate that into what it is we need to do in the clinic.

Where that became most important was in the study of autism, where a deficit in social attachment and social behavior is a core problem. I'm delighted to see that some of the work that we did 10 years ago or more that had to do with how to increase social interaction and social engagement is now actually finding its way into the clinic. People are testing out whether some of the compounds and some of the ideas we had then might actually be the first effective treatment for the core symptoms of autism.

Dr. Reed: That's exciting. I know you must be personally gratified to see some of that foundation work you've done is now finding clinical application.

Dr. Insel: What's great about it is it reminds us all that a lot of the basic science that we do has got to continue because we just don't understand enough. But what's really curious is that often we are working on a problem on a very basic level that has an application we could never have dreamt of. And that some of the most exciting applications are the ones we're not smart enough to think about. It's all the more important that we continue to support and we continue to build this base or foundation of outstanding basic biomedical and biobehavioral science, so that we have some kind of a pool to be able to select from when we need to do the applications.

Using Stem Cell Technologies in Mental Health Research

Dr. Reed: The next thing I want to talk to you about is a good example then: stem cell technologies and their role in neuropsychiatric disease research. Stem cell technologies now make it routine to capture cells from patients with neuropsychiatric diseases, synthetically convert those cells into embryonic stem cells in the laboratory, and then program those stem cells to become neurons so scientists can study the patient's brain cells.

How is this type of technology changing the course of mental health research?

Dr. Insel: It's going to be huge. I mean obviously, we're talking about disorders that start in childhood. They're fundamentally neurodevelopmental. But we can't see that. And the sense that we have as we think about these illnesses is that behavioral symptoms are a late phase. There's a lot going on in the brain before the behavioral manifestations of schizophrenia or depression, or perhaps even autism, begin to manifest.

But how do you get to that, because you don't know where to look and you don't know when to look? This spectacular new technology allows us to take cells from a person with a disorder and rerun the tape; grow them up in a dish and to the extent possible create what we call a "disease in a dish"; actually look at the cell of interest and perhaps eventually the circuit of interest; and see how that plays out over time with a particular genetic mutation or without, or be able to compare that to people who don't have that disorder, or maybe people who have the same mutation and don't develop the disorder; and get a feeling for what the mechanisms might be. When does development go off the track?

That's going to be the fundamental biology. I think this is going to be a revolution in the way we think about and the way we can ultimately potentially diagnose and treat any of these neurodevelopmental disorders.

Treating Psychiatric Illness Before It Manifests

Dr. Reed: It sounds a little reminiscent of what we heard today at the Celebration of Science conference about the stories around Alzheimer disease, for example, where we don't see symptoms until the brain is quite diseased and quite damaged. And yet we know that very early, there are telltale symptoms and changes in the brain that we can detect with advanced MRI and other technologies.

Dr. Insel: This is really a key issue, John, and I guess in this conversation is one of the most important messages to send. We talk about these as behavioral or mental problems. I think we need to think about them as brain disorders. Why is that so important? It's important because if behavior is a late manifestation, and if that's how we make a diagnosis, it's like saying we're only going to diagnose heart disease after the heart attack. We wouldn't do very well. We wouldn't have gotten the 67% reduction in cardiac death if we waited until everybody had their heart attack to intervene.

But that's exactly what we do in schizophrenia. We wait for the psychosis. We wait for the late stage of behavioral manifestation. Why do I care so much about calling these brain disorders? Because if we can start to talk about them and start to detect the brain changes years before the behavior starts, then there's the opportunity to intervene early. And that's where we do best in medicine. Early intervention, preempting the later stages, is where we've had our greatest successes.

We haven't been able to do that in psychiatry because we've locked ourselves in to saying that these are mental behavioral problems. We have to change our language. We have to change our concepts. We have to change our expectations. And at that point, we'll start to see, I think, the really big public health impact.

Matching the Right Patient to the Right Drug

Dr. Reed: Speaking of interventions -- at least with respect to medical interventions, one of the current frustrations with treatment of many psychiatric illnesses is the trial and error process that many patients endure with respect to medications. By some estimates, the average patient will try 5 different medications before finding one that works for them.

How do you see the field of neuropsychiatry improving our ability to match the right patient to the right drug?

Dr. Insel: That is in some ways the Holy Grail. We certainly want to get to the point where we have precision medicine, meaning precise diagnosis and then targeted therapies for the individual in need. Some of that could come from pharmacogenomics. Some of it could come from cognitive testing that allows us to define what different kinds of disorders somebody has.

But I would push you a little bit on this issue, because I think the idea that there will be a single treatment is probably not the way to go. These are complex disorders, and we understand in many areas of medicine that it takes a combination of treatments. In the case of brain disorders, it's likely that there will be medications, devices, some great new cognitive interventions that we can do with video games, and other kinds of rehabilitative services. I don't think we're ever going to get to the point where there will be a single pill for autism or a single pill for schizophrenia.

In fact, I think what we'll find is that part of the problem that we've had with the lack of public health impact in the treatments that have been prescribed over the past 3 or 4 decades is that we have too often expected that there will simply be a pill to fix what is a very complex and difficult biomedical and behavioral problem. It's going to require many different kinds of interventions to get to where we want to go.

Dr. Reed: That's to be expected. Certainly, the brain is the most complex organ we have. And if we think about the way we treat other diseases, such as cancer and heart disease, we rarely rely on a single magic bullet to get the job done. With HIV and other diseases, it's always a combination of therapies used to attack the problem multiple ways. So I think we can relate to what you're saying there. We'll be excited to see how your research and the research sponsored by NIMH are going to help us come up with those right combinations.

Dr. Insel: Doctors know this, because in practice almost all patients with serious mental illness are on multiple drugs. The problem is that we haven't provided the evidence base or the best guidance on how to do this. It goes back to your question of figuring out what is the specific need of each individual and providing a road map for how to match those needs to the various treatments that we now have, and ultimately developing much better ones.

Promising Ideas in Psychiatric Drug Development

Dr. Reed: One of the other great needs is that although we have a number of medicines we can use to try to approach neuropsychiatric disorders, we need far more with new mechanisms of action. The alarming thing is that neuropsychiatric drug development has virtually dried up, with several large pharmaceutical companies exiting the field.

To quote a recent *Schizophrenia Bulletin* editorial, "not a single mechanistically novel drug has reached the psychiatric market in more than 30 years." What are the current challenges and the opportunities with discovery and development of innovative therapeutics for neuropsychiatric disorders? Do you see any improvements coming around the corner in the near term?

Dr. Insel: I think there are some opportunities, and I would agree that there has been a real desert of innovation here. In some ways, we're victims of our own success. We had compounds discovered by serendipity that were pretty good. They're not good enough, but good enough for the marketing process. And so we've seen a lot of marketing of compounds that help some people to get better, but help very few people to get well.

The next generation of medications and the next generation of treatments are badly needed. The reality is that we don't know enough about how to do that, partly because so much of what we've done has been to study the current medicines rather than to study the disorders themselves. It's as if schizophrenia was caused by lack of Thorazine or depression was a matter of being a quart low in serotonin. We now know that we can study these disorders in a far more sophisticated way. And there will be that kind of science, that kind of new biology -- biology that has to do with synaptic efficacy and synaptic plasticity, with neurodevelopment, and with a whole series of complex aspects of neuroscience that will guide us in the future.

But that is very much a future project. In terms of the here and now, what are we going to be able to do in the next 2 years? Let me give you 3 ideas that I think are promising.

One is the idea that as a proof of concept, we now know that for people with severe depression -- often treatment-resistant depression -- a single injection of ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, can resolve this depression within 3 hours. Now, the effect doesn't last; symptoms come back in 3-5 days. But the concept of not waiting 6-8 weeks for an antidepressant to work, and realizing that there could be antidepressant compounds that would work in 3 hours, is a game-changer. And it's one that says to us that we need to rethink the expectations and the kinds of interventions that we've been developing, to get to something that is far more effective much earlier. So the first promising idea is rapidly acting antidepressants.

The second is that we have had a very robust market for antipsychotic compounds. There is something like 20 on the market now. It's about a $14 billion industry. But you know they don't help people recover in the sense of getting people back to work, getting them through school, and helping them be able to relate to their families. We still are left with people who may not have delusions and hallucinations, but they have a whole range of cognitive problems that keep them from being successful. That's unacceptable.

What we need now is the generation of compounds that affect that particular target, the cognitive deficits. We've got some ideas about how to do that. And there's a whole series of compounds now being developed with just that kind of a target. That's a game-changer as well and could really alter the public health prospects for people with this chronic illness.

Third, we look at autism and the social deficits that you see in that whole range of disorders that we now call the autisms, along with schizophrenia, where social deficits are huge. The possibility that there could be a family of compounds that are prosocial and would actually increase social behavior is just emerging. We're seeing this with some of the neuropeptides, with metabotropic glutamate receptor 5 (mGluR5) antagonists, and with the first studies that are being done with fragile X syndrome, and we're finding that some of the compounds that are being given to persons with fragile X syndrome seem to be most helpful for the social deficits in that disorder.

This is a kind of new era to think about a whole new category of compounds. These 3 ideas -- the idea of rapidly acting antidepressants, therapies for cognitive deficits in schizophrenia, and the possibility of a prosocial group of compounds -- I think could really be exciting areas for research and development in the near term, with the idea that in the longer term, we're really going to be able to tap into the new biology, which in some cases may be much more transformative to tell us where the actual cures might come from in the future.

The National Center for Advancing Translational Sciences

Dr. Reed: The concept of new biology to be discovered certainly emphasizes the importance of public investment in medical research, and that's what the Celebration of Science conference has been all about.

I want to close by asking you one other question about your role at the NIH, because you wear a second hat as the director of the exciting new center, the National Center for Advancing Translational Sciences. Tell us a little bit about what you're doing there, and about what some of your vision is. How does your work there relate back to some of your goals and what you're doing as the director of the NIMH?

Dr. Insel: Well, I had enough to do with NIMH without taking on a second full-time job. But it's been a fun ride. At the end of December, NIH launched this new center, called the National Center for Advancing Translational Sciences (NCATS). NCATS has as its mission to essentially catalyze innovation in the space between basic discovery and its translation into clinical practice.

How do we figure out the ways to get around all of the barriers to translation? There are many. What we've been doing at NCATS is making a small investment -- only about 2% of the NIH budget. But it is a catalyst. It is an opportunity to create some of the tools the community needs, as well as the resources, databases, and places that people can go to learn about where we can use the fundamentals and make them move more quickly into new diagnostics and new therapeutics.

Two examples of this are projects that we've launched in the past few months, which have been our first few months with NCATS. The first was to put together a sort of medicine chest that could be crowd-sourced to the academic community. We have lots of compounds, including some in the central nervous system space that pharmaceutical companies have decided not to pursue. They may have invested $10 million, $20 million, or $30 million into getting these compounds into a phase 2 trial space. And then for lots of reasons, sometimes business reasons, they've decided to go elsewhere. That has happened a lot in neuropsychiatry.

If they're not going to develop those compounds, we might have an interest, either for the same indication or perhaps for a novel one. We put these into this medicine chest that academics could use. We've done that with 8 companies -- 58 compounds initially, along with the data that went with them -- and we're inviting the academic community to come play with us, to try to help with many of these compounds to use them for some new indication that hadn't been thought about before.

The second project, which is something we heard a lot about when we were developing NCATS, is that we went to a lot of industry and to various stakeholders and lots of different patient communities and said, what do you need? Where's the problem? Why aren't we able to do better? Why is it that with 4500 diseases for which we understand the molecular basis, we're only able to actually provide therapies for a small fraction, maybe 100 or 150? And we're only getting 35 or 37 new compounds a year through the US Food and Drug Administration (FDA). Where's the problem? Where are the roadblocks?

One of the things we heard a lot about was the problem of toxicity: that we don't have good predictive toxicity, and that the studies that have been done in mice and rats don't translate well. So we're looking at toxicity and we've launched DARPA (Defense Advanced Research Projects Agency) as our second project. This is an opportunity to create human tissues on chips for high-throughput screening. We just put this project out there with the first set of awards, which will be about $140 million between DARPA and the NIH. NCATS is directing this project.

The hope here is for lung; for kidney; and for a whole range of tissues, especially liver, that we'll be able to predict much better than we have been with mouse and rodent studies because we'll be using human cells in a human context. And we'll be able to do this in a high-throughput way so that we'll have a sense of what we do need to worry about before we move into a phase 1 trial.

Those are a taste of the kinds of things NCATS hopes to do going forward to make the process of translation a little faster, and hopefully a little more efficient, so it's a little more productive. I think you'll see us crowd-sourcing a lot more, using a lot more kind of innovative approaches to catalyze this entire process to deliver better -- which is very much what people are looking for when they look to biomedical science, as you heard today in all the conversations.

Dr. Reed: It's certainly been an area that has been exciting to hear about in some of these advancements in so-called regulatory sciences. And the idea that if we can identify where these bottlenecks are, where the attrition occurs in drug discovery and drug development, and come up with scientific tools that allow us to figure out those problems early on and make sure we get the right compound in the clinic, it's really going to help hopefully drive down the cost and increase the efficiency.

I think we've all heard the terrible statistics where it takes an average of 13 years and about $1.3 billion to develop a new medicine. We really applaud you for taking on this area and trying to develop some of these tools that are so much needed.

Dr. Insel: We're excited about it. But I need to put in a note of caution here. This is hard. If it were easy, it would have been done before. And lots of people have tried, often with a lot more investment than what we're able to put into this through NCATS.

We're going to bite off little pieces and work on those. And we're probably going to do them in partnership, just like this idea of working with industry for the compounds that they're not going to pursue. I think what you'll see through NCATS are new ways for NIH to begin to partner with a range of stakeholders to provide more value.

BACK TO TOP

Memory Training Can Alleviate Depression

Medscape Today
Fran Lowry
25 Sep 2012

Memory training can alleviate depressive symptoms, new research suggests.

In a small study, investigators at the Cognition and Brain Sciences Unit, Medical Research Council, Cambridge, United Kingdom, found that a stand-alone memory training program significantly improved memory and reduced symptoms of depression.

"This suggests there is value in incorporating this training program into standard psychological therapies, either as an adjunct or a precursor to therapy, as a novel way in which to improve memory recall and mood," study author Tim Dallies, MD, told *Medscape Medical News*.

The findings were published online September 7 in *Clinical Psychological Science*.

Particularly Beneficial for Teens?

Preliminary research suggested that the program, known as Memory Specificity Training, improves memory specificity and mood in adults with depressive symptoms.

However, it had not been tested using a controlled design, and several important questions remained unanswered.

"Specifically, it was unknown whether improvements were maintained over time and would generalize to an adolescent sample in a non-Western culture. Therefore, we decided to conduct this study to address these important questions and to begin to examine the parameters under which Memory Specificity Training would be effective," said Dr. Dalgleish.

In addition, he said, Memory Specificity Training may be particularly beneficial for adolescents with depression because adolescence represents a critical developmental period, key to the onset and course of depressive illness.

Memory Specificity Training improves the recall of specific memories through repeated practice. In 5 sessions, participants are required to practice recalling specific memories in response to a range of positive, negative, and neutral cue words.

In addition, weekly homework involving similar practice exercises is given as a way to consolidate what has been learned during the session.

"By engaging in repeated practice, participants learn how to distinguish between different kinds of memories and have the opportunity to practice recalling specific memories both in a structured context, where immediate feedback is available, such as during the session, but also in their everyday life, for example, through homework," said Dr. Dalgleish.

Afghan War

Together with psychological scientist and study author Hamid Neshat-Doost, PhD, of the University of Isfahan, Iran, the researchers invited adolescent Afghani refugees attending a charity school in Iran to participate in the trial.

They assessed potential participants on a range of psychological measures and selected individuals who were experiencing significant depressive symptoms. All of the adolescents had lost their fathers in the war in Afghanistan.

Of 23 eligible participants, 12 were randomly assigned to receive the Memory Specificity Training, and the remaining 11 were allocated to the control condition.

The groups were matched according to age, education, and baseline depression symptoms.

All of the adolescents completed a memory test in which they saw 18 positive, neutral, and negative words and were asked to recall a specific memory related to each word. They also completed questionnaires designed to measure symptoms of both depression and anxiety.

The treatment group then received 5 80-minute, weekly sessions of Memory Control Training, in which they learned about different types of memory and memory recall and also practiced recalling specific memories after being given positive, neutral, and negative key words.

The control group did not receive any treatment.

Novel Treatment Target

At the end of the 5 weeks, the baseline memory test was administered again to the training and control groups. The same memory test was also administered at 2-month follow-up.

The researchers found that memory training was associated with improved memory specificity and reduce depressive symptoms in the teen Afghani refugees, compared with their counterparts in the control group.

After the training, the group who had received the Memory Specificity Training retrieved a significantly greater proportion of specific memories than the control group and also provided a significantly greater proportion of specific memories (*P* =.0001).

Depression symptoms were also improved among the teens who received the Memory Specificity Training. They were significantly less depressed than the control group at follow-up (*P* = .03)

"Notably, these improvements were maintained over the 2-month follow-up period," Dr. Dalgleish said.

However, he added, Memory Specificity Training is still in its infancy, and the technique is not yet readily available.

"I would like our study to prompt researchers to conduct large-scale, well-controlled clinical trials so that the efficacy of the treatment can be established, as well as the limits and parameters under which this training is likely to be most valuable to be identified," he said.

"It would also be beneficial to draw attention to the role of memory and disturbances to memory in emotional disorders. Difficulty in recalling specific memories is not only important in depression but has implications transdiagnostically," Dr. Dalgleish added.

"For example, poor memory specificity is linked to problem solving difficulties, poor executive control, and cognitive avoidance. The promising results of this and other memory specificity studies emphasizes the importance of considering autobiographical memory as a novel treatment target as a way to improve existing treatments for individuals who experience emotional disorders."

Provocative Questions

Commenting on the study for *Medscape Medical News*, Eric M. Plakun, MD, from the Austen Riggs Center, Stockbridge, Massachusetts, and past chair of the American Psychiatric Association's Committee on Psychotherapy by Psychiatrists, said that despite limitations, the study raises some "provocative questions."

"In Afghanistan and in other areas, even more than here, there are no doubt many, many traumatized teens facing losses who also have depressive symptoms."

However, he noted, the study sample size is small and "there is no real diagnostic assessment of the students, just a depressive symptoms questionnaire."

"This is a limitation, but was also intentional since they are trying to think beyond diagnosis. But how many had major depression versus PTSD [posttraumatic stress disorder] or both or uncomplicated grief? These categories tell us something, and their absence limits our ability to think about this from a diagnostic standpoint."

The biggest problem with the study in Dr. Plakun's view is that the control group not only did not get the treatment but also received nothing comparable to the 80-minute sessions, which were given under the guidance of a senior clinical psychologist.

"Despite the finding that improved recovery of autobiographical memory seemed to mediate improvement in depression at 2 months, I wonder how much improvement had to do with the degree of their engagement in a group process that linked them together in a shared effort to gain mastery over their losses and associated depression," said Dr. Plakun.

Being part of a special group run by a senior psychologist is a big deal — apart from the power of the memory training itself. And they were being taught something intended to improve their sense of mastery over their feelings and painful memories. "The control group didn't get anything like the memory training or the group experience or the focus on mastery," he added.

This study was funded by the Children and War Foundation. The study authors and Dr. Plakun have disclosed no relevant financial relationships.

BACK TO TOP

Military Medicine: Healing Touch With Guided Imagery for PTSD in Returning Active Duty Military: A Randomized Controlled Trial

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ABSTRACT Post-traumatic stress disorder (PTSD) remains a significant problem in returning military and warrants swift and effective treatment. We conducted a randomized controlled trial to determine whether a complementary medicine intervention (Healing Touch with Guided Imagery [HT+GI]) reduced PTSD symptoms as compared to treatment as usual (TAU) returning combat-exposed active duty military with significant PTSD symptoms. Active duty military (n = 123) were randomized to 6 sessions (within 3 weeks) of HT+GI vs. TAU. The primary outcome was PTSD symptoms; secondary outcomes were depression, quality of life, and hostility. Repeated measures analysis of covariance with intent-to-treat analyses revealed statistically and clinically significant reduction in PTSD symptoms ($p < 0.0005$,Cohen's $d = 0.85$) as well as depression ($p < 0.0005$, Cohen's $d = 0.70$) for HT+GI vs. TAU. HT+GI also showed significant improvements in mental quality of life ($p = 0.002$, Cohen's $d = 0.58$) and cynicism ($p = 0.001$, Cohen's $d = 0.49$) vs. TAU. Participation in a complementary medicine intervention resulted in a clinically significant reduction in PTSD and related symptoms in a returning, combat-exposed active duty military population. Further investigation of GT and biofield therapy approaches for mitigating PTSD in military populations is warranted.

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a common and persistent problem in military populations that warrants swift and effective treatment. Recent estimates suggest that among recent Iraq and Afghanistan veterans, 21.8% are diagnosed with PTSD, with prevalence rates increasing 4 to 7 times after the invasion of Iraq.1 Substance use disorders, depression, and interpersonal conflicts also substantially increase in these soldiers,1,2 and physical health-related consequences such as increased risk for hypertension and diabetes have also been noted.3,4 Not surprisingly, the incidence of PTSD appears to increase with combat exposure. Despite all best efforts to treat PTSD in our military, it remains untreated in a substantial number of those on active duty and/or recently deployed. These soldiers are more likely to report mental health issues compared to their reserve comrades,8 and yet are significantly less likely to engage in mental health services.8,9 In general, the younger cohort of Operations Enduring Freedom/Iraqi Freedom veterans are notably loathe to seek conventional PTSD treatment, in part, because of perceived stigmatization and negative beliefs about conventional mental health care (i.e., psychotherapy and medications9–12). Even for those who may be open to seeking treatment, data suggests there are large numbers of military personnel who may not meet clinical cutoffs for PTSD immediately upon return from deployment, but whose symptoms escalate to clinical levels even up to 12 months postdeployment.2,13 These findings suggest a need for swift, effective, and nonstigmatizing treatment of PTSD symptoms in postdeployment active duty personnel, as well as speak to the need to address PTSD symptoms for active duty military in general health care settings as opposed to providing PTSD treatment solely in mental health care settings.

Complementary Medicine: Approaches and Use in the Military

Similar to civilian populations, complementary and alternative medicine (CAM) approaches are often sought out by military personnel, for a variety of health conditions. Recent studies estimate CAM use in U.S. Military populations to range between 39.3 and 50.7%.14–16 The largest epidemiological study reported that 41% of military personnel had reported CAM use in the past year, with 27% reporting use of practitioner-assisted CAM therapies (such as acupuncture, biofeedback, and biofield/energy healing14). Interestingly, the study reported that use of CAM was nearly doubled compared to no CAM use for those with a PTSD diagnosis, suggesting that military personnel with PTSD are relatively high users of CAM.

Study Purpose and Hypotheses

Given the high prevalence of PTSD symptoms in active duty personnel, a noted lack of initiation and/or adherence to mental health treatments for PTSD in this population, and supporting literature suggesting a potential openness to

CAM approaches in those with PTSD symptoms, we conducted a pilot, two-armed randomized controlled trial (RCT) of a CAM intervention (Healing Touch with Guided Imagery [HT**+** GI]), compared to treatment as usual (TAU), in 123 active duty military personnel at Camp Pendleton, California. We hypothesized that this intervention would be effective in reducing PTSD symptoms (primary outcome) as well as depression, health-related quality of life, and hostility (secondary outcomes).

METHOD

Recruitment, Eligibility, Screening, and Enrollment

The study took place at the Marine Corps Base Camp in Camp Pendleton, California and was approved by the Clinical Investigation Department, Naval Medical Center San Diego and Scripps Office for the Protection of Research Subjects. Recruitment and enrollment took place from July 2008 to July 2010. Flyers announcing the study were posted at the Deployment Health Clinics (DHC) and the hospital mental health department on Camp Pendleton. Health care providers at these locations were introduced to the study by research staff members. During the postdeployment health reassessment for military personnel returning from a combat zone, the Base DHC providers identified potential candidates for the study via screening of PTSD symptoms. To be potentially eligible for the study, participants were identified by DHC providers to be currently experiencing at least one or more of the following hallmark PTSD symptoms: re-experiencing of trauma (via, e.g., flashbacks, nightmares, intrusive thoughts/images, exaggerated physical and/or emotional responses to triggers of trauma), exaggerated arousal (including insomnia and/or sleep disturbance, irritability, exaggerated startle response), emotional numbing, and/or avoidance (i.e., of people, places, or situations that might remind them of the trauma). Potentially eligible participants were then referred to the research staff for further screening via telephone. If the person was eligible, appointments were made to sign consent, complete pretest questionnaires and after completion, obtain randomized group status.

Inclusion criteria were as follows: (1) female or male subjects 18 years or older, (2) postdeployment from a combat zone, (3) referred by Camp Pendleton clinician, and (4) identified by postdeployment health reassessment to have PTSD symptoms (as described above). Exclusion criteria were as follows: (1) Currently pregnant or nursing, (2) currently using HT or GI from other sources, and (3) inability to sign informed consent. The study screened 205 potential participants; of these, 123 were eligible and enrolled in the study.

Overview of Research Design

This was a Phase 2, two-armed, RCT with one arm randomized to receive HT**+** GI and one arm randomized to a TAU control group. Each participant was studied over a 1-month period. Although follow-up assessment was originally planned for this study, it was not possible as the active duty study participants were awaiting further deployment and would not be available for follow-up assessment. Participants were randomized using a computer-generated randomization table by a statistician not affiliated with the study. This table was provided to two study co-ordinators who, each assigned patients to their respective groups upon entry. Both the principal investigator and data analyst were blind to group assignment (group status was coded with study numbers until data analyses were completed, at which point the group assignment was revealed). Those randomized to the HT**+** GI group received 6 treatments over a 3-week period in addition to any other standard care, and those in TAU continued to receive their standard care for PTSD, which included various forms of psychotherapy (including cognitive behavioral therapy, biofeedback, and relaxation training), as well as in many cases, medications.

Intervention

Participants randomized to the intervention group received a combined intervention of HT**+** GI. The purpose of combining these interventions was to provide the participant both with practitioner-based treatment (HT) to establish a "safe space" using a nonstigmatizing touch-based therapy aimed at eliciting the participant's own healing response, whereas also engaging in a self-care therapy (listening to GI CD) that helped the patient to work with trauma-related issues including trust and self-esteem. HT is a type of biofield therapy that involves gentle, noninvasive touch by trained practitioners, who utilize specific techniques with the intention of working with the body's vital energy system to stimulate a healing response. Two nurses certified in HT, with several years of experience in using HT with patients, provided the HT intervention. Practitioners met on a regular basis to discuss use of specific techniques and ensure intervention delivery consistency. Practitioners utilized three specific HT techniques: Chakra Connection (involving techniques used along the body, intended to stimulate movement of vital energy through the body), Mind Clearing (techniques performed on the head, intended to stimulate mental relaxation), and Chakra Spread (an advanced technique utilized by HT practitioners and generally reserved for patients with more severe symptoms, intended to promote deep healing for emotional and/or physical pain). GI is a complementary therapy that utilizes visualization to induce a state of deep relaxation. The GI recording (CD) used in this study was specifically for use in PTSD (Healing Trauma (PTSD)—Healthy Journeys by Belleruth Naparstek). This recording does not utilize imagined exposure but uses imagery and affirmations to enhance relaxation, reduce negative emotions associated with PTSD (such as terror and shame), and promote healthy self-esteem and sense of protection. Participants randomized to the HT**+** GI group received 6 sessions of HT over a 3-week period (two sessions per week). Each session was of 1 hour's duration and consisted of the participant lying fully clothed on a massage table, listening to the GI CD, whereas the practitioner provided HT. After the first HT**+** GI session, participants were given the GI recording on CD and encouraged to listen to the GI recording at least once daily or more often if desired. Participant's adherence to listening to the GI CD was not assessed.

Outcome Measures

Primary Outcome Measure—PTSD Symptoms (PCL-Military)

The primary outcome examined was PTSD symptoms as indexed by the gold-standard PTSD Checklist (PCL)-Military. This reliable and valid17 17-item self-report measure was developed by the National Center for PTSD and measures PTSD symptom severity in reference to stressful military experiences. Scores range from 17 to 85. A clinical cutoff score of 50 has been established as an optimal cut point for PTSD diagnosis using this measure.18 Secondary Outcome Measures—Depression (BDI), Quality of Life (SF-36), and Hostility (Cook–Medley Hostility Inventory)

Given recent data indicating the clustering of depression and poorer quality of life as well as higher hostility with higher PTSD in military populations,19,20 we examined potential changes in depression, quality of life, and hostility as secondary outcomes. Depression was measured via the Beck Depression Inventory (BDI-II), a highly reliable and valid 21-item self-report scale that measures depressive symptomatology

including sadness, feelings of guilt, perceptions of self-worth, suicidal ideation, and changes in appetite and body weight, among other characteristics.21 Scores range from 0 to 63; scores above 18 indicate likelihood of major depressive disorder (MDD).22 Quality of life was measured using the goldstandard SF-36 measure, which has been found to have high reliability and validity23 and is widely used to examine both mental quality of life (summated via the mental component score [MCS]) as well as physical quality of life (summated via the physical component score [PCS]). Scores range from 0 to 100 with higher scores representing higher quality of life. Norms for the general U.S. population for the PCS and MCS are 50.24 Finally, we utilized the reliable and valid Cook– Medley Hostility Inventory, to measure the derived scales of hostile affect, cynicism, and aggressive responding.25

Statistical Analysis Strategy

To determine sample size, a power analysis using the program G-Power was performed for the primary variable of interest (PCL-Military), using means and SDs derived from the instrument's standardization report, a = 0.05, and a power of 0.90. A mean initial PCL score of 64 was hypothesized based on previous norms. For a hypothesized reduction of _ 10% in the mean PCL score from 64 to 58, a total of 126 (63 subjects per group) were needed. Data were analyzed via repeated measures analysis of covariance (RMANCOVA), using SPSS 17.0. Outcome data were examined for potential outliers and verification of normal distribution. Demographic and behavioral characteristics (age, gender, ethnicity, marital status, number of children, years of service, number of times deployed in a combat zone, alcohol use, and PTSD medication use) were examined for potential correlations with outcome variables and entered as covariates in the analysis if associated with the dependent variable at $p < 0.05$. Intent-to-treat analyses were performed using the last-score carried forward approach; this approach was compared to per-protocol analyses (using casewise deletion) to confirm agreement in results. Alpha was set to 0.05; to avoid Type 1 error with multiple comparisons, alphas for secondary outcome measures comprised of separate subscales (i.e., SF-36 and Cook–Medley Hostility Inventory) were Bonferroni corrected (0.05/2 or 0.025 for SF-36 MCS and PCS scales, and 0.05/3 or 0.016 for Cook–Medley Cynicism, Hostile Affect, and Aggressiveness scales). Effect sizes were calculated using absolute values of Cohen's d, using the standard formula: dIGPP = (Mpost , E − Mpre , E)/SD pre, E − (Mpost , E −Mpre , C)/SDpre , C.

(CONSORT) flow diagram for participants through the study. Of the 123 participants, there were 21 dropouts for a total attrition rate of 17%. Of these dropouts, 15 were in the control group (28.3% attrition rate) and 6 were in the treatment group (12.2% attrition rate). No adverse effects were reported.

Demographic/behavioral characteristics of participants are found in Table I. All data were normally distributed with no outliers. Intent to treat analyses based on RMANCOVA were conducted using relevant covariates in each analysis. Means and SDs for primary and secondary outcome measures are depicted in Table II.

Primary Outcome—PTSD Symptoms

PTSDmedication use was significantly positively correlatedwith increased PCL scores and entered as a covariate in analysis. RMANCOVA analysis for PCL scores controlling for medication use indicated a significant group **+** time interaction (**F**1, 113 = 23.0, **p <** 0.0005), with PTSD symptoms markedly declining for the HT+ GI group (Cohen's **d** = 0.85). This group by time interaction is depicted in Figure 2. Secondary Outcomes**—**Depression, Quality of Life, and Hostility Alcohol use was significantly positively correlated with BDI depression scores and was entered as a covariate in RMANCOVA analyses. Results indicated a significant group **+** time interaction (**F**1, 117 = 15.3, **p <** 0.0005), with the HT+ GI group showing notable decreases in depression over time (Cohen's **d** = 0.70).

For quality of life, PTSD medication use was significantly associated with poorer SF-36 mental health as indexed by MCS scores, and alcohol use was significantly positively correlated with poorer physical health as indexed by PCS scores. These were entered as covariates in subsequent analyses. RMANCOVA for MCS scores indicated a significant group **+** time interaction (**F**1, 114 = 10.0, **p** = 0.002), with those in the HT+ GI group showing increases in mental health quality of life over time (Cohen's **d** = 0.58). Results for the PCS scores when controlling for alcohol use were not significant when Bonferroni corrected (**p =** 0.04, Cohen's **d** = 0.2).

For Cook–Medley Hostility scales, increasing age, years of military service, and number of children were negatively associated with Cynicism; ethnicity was significantly associated with Hostile Affect, and increasing age and number of children were negatively associated with Aggressive Responding. These were entered as covariates in respective analyses. Results indicated a significant group by time interaction for cynicism (**F**1, 114 = 11.2, **p =** 0.001, Cohen's **d** = 0.49), a trend for hostile affect (**F**1, 105 **=** 5.3, p **=** 0.02, Cohen's **d** = 0.58), and no effect for aggressive responding (**p =** 0.67, Cohen's **d** = 0.03).

To verify that our use of the last-score carried forward approach for intention-to-treat analyses was appropriate, we conducted per-protocol analyses (RMANCOVA without substitution of missing values using casewise deletion). Results were identical in terms of significance/nonsignificance of outcomes with comparable effect sizes, suggesting that the intention-to-treat analyses in this study were appropriate.

DISCUSSION

This phase 2 RCT examined the effectiveness of a combined complementary medicine intervention (HT**+** GI) compared to TAU on PTSD and related symptoms in active duty military. Results indicate significant and substantial reductions in PTSD symptoms, depression, and cynicism as well as improved mental quality of life for those receiving the intervention.

Clinical cutoffs for PTSD diagnosis using the PCL are 50,18 and changes of 10 to 20 points are considered to be clinically significant.26 The drop in PTSD symptoms for the intervention group by 14 points (from 54.7 to 40.7) thus has clinical as well as statistical significance. A score of 18 on the BDI has been found to be optimal in predicting major depressive disorder22 ; thus, the pre–post drop from 26.1 to 16.4 for the intervention group also suggests a clinically meaningful reduction in depression. Although these results may generalize to other active duty military with

combat-related PTSD symptoms, it is unclear how these results may generalize to other military populations (e.g., veterans with continued PTSD). The decrease in cynicism (with a medium effect size), for participants receiving the intervention, is particularly noteworthy.

Reports of higher cynicism are common among active duty combat soldiers and likely relate to issues of perceived stigma and negative beliefs about traditional mental health care (i.e., clinical psychology and psychiatry) that appear to hinder these soldiers from seeking help from mental health sources for PTSD. Our data support the notion that engagement in a complementary medicine approach that is less explicitly focused on "mental disorder" may serve to reduce soldiers' potential stigmatizing beliefs about mental health care (ostensibly through the positive perception and development of a patient–practitioner relationship) and possibly provide them with tools to better cope with PTSD symptoms as they emerge (potentially through enhancement of the relaxation response and increased sense of safety).

However, specific dose-response effects and the potential longterm effectiveness of this intervention on maintaining reductions in PTSD symptoms are unclear. In contrast, the short- and long-term efficacy of gold-standard approaches (such as exposure, cognitive behavioral therapy, and eye movement desensitization and reprocessing) to reducing and preventing relapse of PTSD has been demonstrated.27,28 However, initiation of treatment and adherence to these therapies is noted to be problematic in this population.29 A future direction for studies in this area may be to directly examine the effectiveness of complementary medicine interventions on increasing adherence and positive clinical outcomes in response to other gold-standard treatments for PTSD and/or depression. One might examine the potential mediating roles of decreased stigmatizing beliefs and enhanced sense of safety, on complementary medicine interventions' effects on adherence and outcomes to gold-standard approaches for eliminating PTSD.

There are notable limitations to this study, including lack of follow-up (which was not feasible for this studied population), lack of adherence monitoring (for listening to the GI recordings outside of sessions), and lack of an active comparison group. The study also had notably low representation among certain ethnic minority groups; although, this may be partly because of the lack of representation of these groups in the geographical area, it may also be due to selection bias. Some may point to the combining of the interventions of HT and GI as a limitation. However, this study was aimed at determining feasibility and effectiveness of the combined intervention, not mechanisms of action for each component.

The decision to combine the two complementary medicine interventions was based on consultations with expert practitioners who, based on prior experience with similar populations, suggested that the combination of both biofield healing and GI would synergize to provide maximum effectiveness in reducing PTSD symptoms in the following manner: the GI, which focuses on creating a sense of spiritual safety and deep relaxation, provides an atmosphere where the participant could allow him or herself to safely and deeply engage into a relaxation response and therefore also gain maximum benefit from the interaction with the HT practitioner. The continued pairing of this relaxation response with the positive and trusting interaction with a health care professional and invitation for spiritual grounding and selfconnection would further the possibility of the mind–body to "let go" of the residual conditioning of previous trauma, and thus reduce PTSD symptoms. The underlying rationale for combining the two techniques is not unlike the underlying rationale for many psychotherapeutic approaches, where it is

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BACK TO TOP

Traumatic Brain Injury

Early management of severe traumatic brain injury

The Lancet
Jeffrey V Rosenfield, MD; Andrew I Maas, MD; Peter Bragge, PhD; M. Christina Morganti-Kossman, PhD; Geoffrey T. Manley, MD; Russell L. Gruen, MD
22 Sep 2012

Summary

Severe traumatic brain injury remains a major health-care problem worldwide. Although major progress has been made in understanding of the pathophysiology of this injury, this has not yet led to substantial improvements in outcome. In this report, we address present knowledge and its limitations, research innovations, and clinical implications. Improved outcomes for patients with severe traumatic brain injury could result from progress in pharmacological and other treatments, neural repair and regeneration, optimisation of surgical indications and techniques, and combination and individually targeted treatments. Expanded classification of traumatic brain injury and innovations in research design will underpin these advances. We are optimistic that further gains in outcome for patients with severe traumatic brain injury will be achieved in the next decade.

Introduction

Traumatic brain injury is a major global health problem. Country-based estimates of incidence range from 108 to 332 new cases admitted to hospital per 100 000 population per year. On average, 39% of patients with severe traumatic brain injury die from their injury, and 60% have an unfavourable outcome on the Glasgow Outcome Scale. The incidence of traumatic brain injury is rising in low-income and middle-income countries because of increased transport-related injuries and young men (who are over-represented in transport, work, and recreational injuries) are particularly affected. In most countries, ageing populations have given rise to a new cohort—elderly people—who sustain substantial traumatic

brain injuries from fairly low-impact falls. Furthermore, blast injury to the brain, which has distinctive pathological changes, treatment, and prognosis, is common in civilians and military personnel who are exposed to improvised explosive devices and suicide terrorist attacks.

Key messages

- Incidence of traumatic brain injury is increasing worldwide and overall mortality rates have only slightly improved since 1990. The weighted average mortality for severe traumatic brain injury is 39%, and for unfavourable outcome on the Glasgow Outcome Scale is 60%.
- The randomised trial of early decompressive craniectomy for diffuse brain injury noted worse outcomes after surgery than with medical treatment. Further trials are needed. Steroids are not indicated after traumatic brain injury, except in cases of anterior pituitary insufficiency. Induced hypothermia and hyperoxia need further assessment in clinical trials.
- Promising drug candidates are erythropoietin, statins, ciclosporin-A, tranexamic acid, and progesterone.
- Multimodal monitoring, including cerebral oximetry and microdialysis, needs further assessment to determine if it leads to improved outcomes.
- The IMPACT and MRC-CRASH online prediction models are valuable for clinical practice and research. Promising new biomarkers are glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1.

Survivors of severe traumatic brain injury have a low life expectancy, dying 3·2 times faster than the general population. Furthermore, survivors face prolonged care and rehabilitation, and have consequent long-term physical, cognitive, and psychological disorders that affect their independence, relationships, and employment. In 2007, a conservative estimate of lifetime costs per case of severe traumatic brain injury was US$396 331, with costs for disability and lost productivity ($330 827) outweighing those for medical care and rehabilitation ($65 504).

Mortality and functional outcomes, and resulting long-term dependence and disability, are determined by the initial injury and subsequent treatment. However, an audit[6] of 774 patients treated at an urban, level 1 trauma centre between 2006 and 2008 showed only 17% compliance with Brain Trauma Foundation guidelines for craniotomy, intracranial pressure monitoring, and reversal of coagulopathy. Adherence to clinical practice guidelines for traumatic brain injury, such as those of the Brain Trauma Foundation, are likely to reduce mortality, optimise clinical outcomes, and create substantial economic savings by reducing costs of medical care, rehabilitation, and lost productivity. Survival after severe traumatic brain injury was three times higher in a regionalised trauma system in which patients with serious head injury were transferred to neurosurgical centres, than in a less organised system in which fewer patients were treated in specialist centres.

In this report, which is aimed especially at surgeons and other clinicians who care for patients with acute traumatic brain injury, we summarise advances in the understanding of severe traumatic brain injury and recovery, and give an update of clinical interventions in the crucial early stages of care.

Classification

Although modern approaches to disease classification use anatomical, physiological, metabolic, immunological, and genetic attributes, traumatic brain injury remains largely classified on the basis of clinical signs. With the Glasgow Coma Scale, patients are divided into crude categories of mild, moderate, and severe injury. These categories not only fail to identify the heterogeneity and complexity of severe injuries, but also minimise the real burden of mild traumatic brain injury. This issue was addressed in 2007, at a consensus workshop on classification of traumatic brain injury for targeted treatments, in which participants concluded that a new classification system was needed. This effort would be facilitated by a prospective, multicentre database with uniform collection criteria based on common data elements for traumatic brain injury. With the support of 49 institutes and agencies and global participation, the first generation of these data elements was developed, with their feasibility and use being validated in the multicentre prospective Transforming Research And Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study. This high-quality, standardised dataset is a store of modern knowledge that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers of traumatic brain injury to drive the development of a new classification system. As shown in other diseases, precise classification of traumatic brain injury could revolutionise diagnosis, guide patient-specific treatment, and improve outcome.

Pathophysiology

Traumatic brain injury has a dynamic pathophysiology that evolves in time. The mechanism consists of the primary injury, followed by a combination of systemic derangements (hypoxia, hypotension, hypercarbia) and local events, which together cause secondary brain injury. Changes to the cerebral environment involve a complex interplay between cellular and molecular processes, in which glutamate-driven excitotoxic effects, oxidative stress, inflammation, ion imbalance, and metabolic disarray are major components. These pathways induce progressive neuronal loss through necrosis and apoptosis. Also important are the intracellular changes that are determined by the excessive influx of calcium, which affects mitochondrial integrity, depleting cells of an essential source of energy. The metabolic disarray caused by accumulation of lactate results in cytotoxic swelling of cells, which, together with the increased permeability of the cerebral vasculature, leads to brain oedema, elevated intracranial pressure, and reduced cerebral perfusion. Elucidation of these cascades has paved the way for targeted preclinical studies.

The figure simplifies the most characterised pathophysiological molecular pathways. Excitotoxic effects are mediated by an increased concentration of extracellular glutamate resulting from neuronal death and overproduction. Normally glutamate is taken up by astrocytes, which convert it into glutamine and deliver it back to neurons as an alternative energy source. However when excessively produced, astrocytes cannot remove glutamate from the extracellular space. Glutamate binding to neuronal receptors, such as NMDA, induces the influx of Ca^{2+} and Na^{+} and the efflux of K^{+}. This ion imbalance causes depolarisation of the cell membrane and overload of intracellular Ca^{2+}, which leads to mitochondrial dysfunction, decreased ATP formation, energy failure, and cell death. Alteration of mitochondrial integrity is followed by release of reactive oxygen species and nitric oxide species, which together cause the oxidative stress that damages membrane lipids, proteins, and DNA. Furthermore, free Ca^{2+} activates several enzymes, such as caspases, which contribute to DNA fragmentation and cell apoptosis. Other calcium-activated enzymes (eg, calpains) disrupt the axon's cytoskeletal filaments, thus impairing axonal transport and function. Hypoxia or ischaemia lead to a shift to anaerobic metabolism by astrocytes, producing lactate, which provides an alternative energy source to neurons in a process called coupled lactate metabolism. Neuroinflammation consists of activation of glial cells, the astrocytes, and microglia, which undergo several morphological and molecular changes. Together with fibroblasts, these cells form the glial scar, which impairs axonal regrowth. Microglia accumulate in the injured

brain region and phagocytose the debris that originate from dying cells. Glial cells secrete inflammatory cytokines, chemokines (which stimulate the transmigration of activated blood leucocytes into the brain), and reparative factors such as neurotrophins. Infiltrated neutrophils and monocytes sustain the immune response to injury, thus impairing the integrity of the blood—brain barrier, which leads to increased extracellular fluid that, combined with cell swelling, leads to brain oedema and increased ICP. ICP=intracranial pressure.

Interventions

Pre-hospital

Despite the potential benefits of early intervention, few pre-hospital treatment options have proved effective. In nine randomised controlled trials and one cohort study of pre-hospital fluid treatment in patients with traumatic brain injury, hypertonic crystalloids and colloid solutions were not more effective than was isotonic saline. Results from observational studies of pre-hospital endotracheal intubation have been conflicting. Poor outcomes in intubated patients were probably due to misplaced tubes or excessive hyperventilation once intubated. In the only randomised trial of intubation versus non-invasive ventilation, paramedics received intensive training in airway management and monitored end-tidal carbon dioxide after intubation. In this trial, 51% of patients in the pre-hospital paramedic rapid sequence intubation group had good neurological outcomes (extended Glasgow Outcome Scale score 5—8) at 6 months compared with 39% of those in the hospital intubation group (p=0·046). Whether paramedic advanced life support is beneficial overall for severe traumatic brain injury remains uncertain;18 however, many possibilities exist for expansion of pre-hospital research in traumatic brain injury.

Non-surgical

Normobaric and hyperbaric hyperoxia in severe traumatic brain injury aims to improve mitochondrial function in the brain, which increases formation of adenosine triphosphate and the cerebral metabolic rate of oxygen. However, PET scans have not shown clinically significant improvement in brain oxygen metabolism caused by normobaric hyperoxia. This finding might be because once the haemoglobin is fully saturated, the dissolved plasma oxygen is less than 1% of that transported. Therefore, oxygen delivery is affected much more by correction of anaemia than it is by hyperoxia treatment. Additionally, although the partial pressure of brain oxygen is dependent on cerebral blood flow and the magnitude, timing, and duration of hyperoxia, it might not improve in areas of low cerebral blood flow, which is where the therapeutic effect should be evident.

Hyperoxia has potential toxic effects, including formation of free radicals and pulmonary injury. Furthermore, hyperbaric hyperoxia is difficult to deliver and is not available in most centres. Although normobaric hyperoxia is simple, cheap, and widely available, evidence is insufficient to recommend it for routine clinical use. Bullock has proposed a large phase 3 multicentre randomised trial with 60% FIO2 normobaric hyperoxia for 48 h; a regimen that seems to be safe for the lungs. A trial comparing 40% normobaric hyperoxia to 70% normobaric hyperoxia is underway.

Therapeutic hypothermia resulted in many beneficial effects in animal models of traumatic brain injury, including: reductions in cerebral metabolic disarray, cerebral oedema, apoptosis, formation of free radicals, and concentrations of excitatory neurotransmitters; amelioration of dysfunction at

the blood—brain barrier; and improvement in neurobehavioural outcomes. Although therapeutic hypothermia can successfully treat refractory intracranial hypertension, results from trials are conflicting, and whether this treatment is effective remains uncertain.

The success of therapeutic hypothermia is probably dependent on the timing of hypothermia onset and duration, temperature targets, rate of rewarming, and avoidance of rebound rises in intracranial pressure. Hypothermia has many possible unwanted effects, including perturbations of clotting, increased infection, cardiac dysrhythmias, and insulin resistance. New technologies, such as automated cooling blankets, provide rapid, accurate, and controlled cooling. Several techniques for selective cooling of the brain have been developed, but await robust assessment.

Clifton and colleagues' hypothermia trial was stopped early for futility; two other hypothermia trials are in progress: the Eurotherm hypothermia trial, which started in January, 2009, with an initial target of 1800 patients; and the POLAR trial in which pre-hospital cooling is achieved by infusion by trained paramedics of intravenous saline at 4°C to patients with isolated severe traumatic brain injury, and controlled rewarming is done in the intensive-care unit after 48 h.

Questions remain as to whether maintainence of normal body temperature (therapeutic normothermia) by prevention of hyperthermia is beneficial.

Pharmacological

The appendix summarises randomised controlled trials of pharmacological interventions for early management of traumatic brain injury. In the CRASH trial of intravenous corticosteroid in adults with severe traumatic brain injury, risk of death was higher in the treatment group than in the control group (26% *vs* 22%; p=0·0001). Thus, high-dose steroids are not indicated for use in severe traumatic brain injury. However, anterior pituitary insufficiency is an under-recognised problem in patients with severe traumatic brain injury, particularly in elderly people or those who have diffuse axonal injury and skull base fracture. Guidelines have been produced for screening of patients for pituitary insufficiency. Administration of hydrocortisone in physiological doses and endocrine follow-up are indicated.

Although treatment with magnesium has been fairly effective in animal models of traumatic brain injury; it had worse outcomes and increased mortality in human beings in Temkin and colleagues' randomised trial.

Statins are inhibitors of cholesterol biosynthesis, suppressing inflammation, rescuing neurons from excito-toxic effects, and reducing apoptosis. Atorvastatin and simvastatin improved spatial learning, reduced neuronal loss, and enhanced neurogenesis in the dentate gyrus in rats, with simvastatin being more therapeutically effective than atorvastatin. Another animal study found that simvastatin inhibits interleukin-1 production and reduces microglia activation and astrogliosis. In a small clinical trial, rosuvastatin reduced amnesia time in moderate traumatic brain injury. Premorbid statin use improves survival and functional outcomes in patients aged 65 years and older with traumatic brain injury.

Different gender responses to traumatic brain injury have stimulated interest in hormone treatments. Progesterone is synthesised by oligodendrocytes and its receptors are expressed on neural cells. The neuroprotective effects of progesterone or its metabolites have been shown in animal studies. Mechanisms include inhibition of glutamate toxic effects, cell death, and inflammation. Additionally, progesterone regulates

expression of aquaporin, which might have a role in development of brain oedema. Progesterone has shown some benefits in three randomised trials, with a further two large phase 3 trials (SyNAPSe and ProTECT III) underway.

Ciclosporin-A is an immunosuppressive drug, which, by stabilising the mitochondrial transition pores, attenuates mitochondrial failure after traumatic brain injury.This drug diminished oxidative stress and lipid peroxidation in mice.A further animal study showed that ciclosporin-A attenuates axonal failure and disconnection after traumatic brain injury. Two trials have shown clinical safety of ciclosporin, with no difference in mortality or clinical outcome.

Erythropoietin is an endogenous hormone that stimulates haemopoiesis and has neuroprotective and neuroregenerative effects through reduction of apoptosis, inflammation, oxidative stress, and excitotoxic effects. This hormone decreases lesion volume and brain accumulation of leucocytes while promoting angiogenesis and neurogenesis and improving motor and cognitive function. Erythropoietin crosses the blood—brain barrier and binds to receptors on most brain cells. The brain is susceptible to erythropoietin treatment because its receptor is upregulated after injury or hypoxia. Erythropoietin has a long half-life and maintains its effectiveness with delayed administration; however, risk of thrombotic events is increased with this drug. Clinical trials are underway in the USA and Australia.

Tranexamic acid is an inexpensive antifibrinolytic drug that could reduce mortality and disability from traumatic brain injury. In the CRASH-2 trial, tranexamic acid reduced mortality in trauma patients. Inconclusive findings from a small substudy of CRASH-2 of intracranial haemorrhage in trauma patients with traumatic brain injury spawned the CRASH-3 study of tranexamic acid versus placebo in patients with moderate to severe traumatic brain injury.

Surgical

Surgery, especially prompt evacuation of intracranial haematomas, has a vital role in improving outcomes in many patients with severe traumatic injury. The Surgical Trial in Traumatic Intracerebral Haemorrhage (STITCH Trauma Trial) is assessing whether surgery makes a difference for patients with traumatic intracerebral haemorrhage and contusion.

Decompressive craniectomy is the removal of skull segments to reduce intracranial pressure. Prophylactic unilateral decompressive craniectomy is frequently undertaken for acute subdural haematoma and for severe contusions and unihemispheric swelling. Decompressive craniectomy has been recommended as a second-tier treatment for intracranial hypertension in severe traumatic brain injury.This technique is standard practice for military blast injury to the brain. Delayed decompressive craniectomy is increasingly used as a salvage procedure for intractable intracranial hypertension in patients with diffuse bilateral swelling. Complications, such as haematoma, subdural hygroma, and hydrocephalus are frequent after decompressive craniectomy.

The decompressive craniectomy (DECRA) trial—a randomised trial of early bifrontotemporoparietal decompressive craniectomy for patients with severe traumatic brain injury with diffuse brain swelling—unexpectedly showed a significantly worse outcome at 6 months in patients in the craniectomy group than in those in the standard-care group (p=0·03). This finding has resulted in controversy about the technique, timing, and

selection of patients for decompressive craniectomy. The randomised evaluation of surgery with craniectomy for uncontrollable elevation of intracranial pressure (RESCUEicp) trial is a continuing randomised trial of decompressive craniectomy. The trial has a higher intracranial pressure threshold for decompressive craniectomy than did the DECRA trial, and includes patients with mass lesions and unilateral or bilateral decompressive craniectomy.

Transplantation of stem cells and neural precursor cells to repair the injured brain shows potential as a regenerative treatment. The ideal timing for such treatment is unknown. Cells transplanted into the injured brain variably replace lost neurons, reduce inflammation, and produce local trophic effects. The few studies in human beings of this therapeutic approach indicate its complexity. Although intravenous infusion of autologous bone marrow-derived cells has been safely done in children nd adults after traumatic brain injury, 96% of the cells are sequestered in the lungs and only 0·001% are engrafted in the brain. The targeted delivery of cells to the brain by direct transplantation is technically very challenging.

Monitoring of the injured brain

Continuous intensive-care monitoring of patients with severe traumatic brain injury provides information to help prevent and treat secondary cerebral ischaemia. Monitoring of intracranial pressure is standard practice for severe traumatic brain injury in most neurosurgical centres. Guidelines from the Brain Trauma Foundation detail indications for such monitoring alongside supporting evidence. However, the first randomised trial to test the effectiveness of treatment based on intracranial pressure monitoring is being done in six Latin American centres that do not presently monitor intracranial pressure.

Multimodal monitoring of cerebral function is increasingly being used in advanced intensive-care units. Brain tissue oximetry, monitoring of cerebral blood flow, microdialysis, brain temperature monitoring, and continuous electroencephalography allow for early detection of potentially correctable physiological derangements, by providing more information than is possible with intracranial pressure monitoring.

Brain tissue oxygen tension independently correlates with outcome, but is poorly predicted by standard monitoring, and intracranial pressure and cerebral perfusion pressure often remain normal after cerebral hypoxia. With brain tissue oximetry, episodes of cerebral hypoxia can be identified and subsequently corrected, but whether clinical outcomes consequently improve is uncertain. Two studies showed benefit and one study showed harm from management guided by brain tissue oxygen monitoring. The phase 2 BOOST trial of management based on brain oxygen monitoring is underway. The Brain Trauma Foundation recommends 15 mm Hg brain tissue oxygen tension as a threshold for intervention, on the basis of weak evidence.

Cerebral microdialysis—use of a semipermeable membrane microcatheter to sample metabolites and other small molecules—provides unique insights into neurochemical mechanisms after severe traumatic brain injury. Although microdialysis might become widely available in advanced intensive-care units after technological improvements, this technique is invasive and its use remains experimental.

The cerebral pressure reactivity index is a marker of cerebral autoregulation, which is derived at the bedside and enables identification of the optimum pressure for cerebral perfusion in the individual patient. Targeting of an optimum pressure might prevent episodes of cerebral ischaemia,

but no evidence is available to confirm that this technique improves outcomes. Detection of seizures with continuous electroencephalography is commonly done, but the electroencephalographic signal degrades with sedation. Continuous electrocorticography, which is started at the time of craniotomy, provides high-fidelity recordings, thus enabling detection of secondary brain insults and ictal discharges that are not readily apparent on electroen-cephalography. Cortical spreading depressions, which are slow waves of depolarisation, have been noted in half of patients with severe traumatic brain injury at up to 1 week after injury, and are a source of secondary damage. These depressions are predictive of poor outcome, and can be stopped by N-methyl-D-aspartate receptor antagonists, such as ketamine, and by cooling of the brain. Although monitoring of depressions might have a role in future critical-care management, this technique is invasive because it requires craniotomy.

Multimodal monitoring has several limitations: these modalities are mostly focal measures; invasive monitoring can cause morbidity; highly trained staff are needed to manage the equipment and data so that artifacts are not generated and results misinterpreted; so far, little trial-based evidence exists to show that correction of these derangements improves outcome; and the optimum combination of monitoring is not yet identified. The European Society of Intensive Care Medicine has developed recommendations for multimodal monitoring.

Advanced MRI technologies, including volumetric analysis, diffusion tensor imaging, and high-definition fibre tracking, are increasingly being used to define the extent of brain injury and correlate this extent to neurological deficits. These technologies can identify the precise pattern and degree of axonal fibre damage and this information will probably help to track disease process and aid prognostication. However, such imaging is not available until the patient can be safely transported to the imaging facility.

Outcomes and their prediction

Comparison and prediction of outcomes in traumatic brain injury is challenging because of heterogeneity within the patient population, substantial differences in baseline prognostic risk, and the complexity of outcomes. Seemingly, mortality after traumatic brain injury has decreased and outcome has improved. Mortality rates of 10—15% noted in selected trials are compared with historial cohorts, such as the US Traumatic Coma Databank, which reported a mortality rate of 39% in 1984—87. Such conclusions, which are based on data combined from randomised trials and observational studies with no access to individual patient data to adjust for case mix, are flawed. Stein and colleagues' random-effects meta-analysis, which accounted for inter- and intrastudy heterogeneity, showed a steady decline in mortality of about 9% per year in 1970—90, but the rates changed only slightly between 1990 and 2005. Therefore, these findings do not support the perceived continued decline in mortality, and contrast those from previous reports. Furthermore, despite being a so-called hard endpoint, mortality might not be the most appropriate index to assess outcome in traumatic brain injury. Lifelong disability is common and often serious because of cognitive, physical, behavioural, and subjective sequelae. In traumatic brain injury, investigators commonly use the Glasgow Outcome Scale or its extended version to assess functional outcome. In 2006—11, seven studies, each enrolling more than 300 patients with severe traumatic brain injury, reported outcome results according to the Glasgow Outcome Scale. We noted no clear improvement in outcome in time; however, this finding should be interpreted

with caution because comparisons of outcome over time are confounded by changes in epidemiology, such as increased injuries in elderly patients.

Such complexities emphasise the need for high-quality prognostic research in traumatic brain injury. For a long time, predictions were little more than prophecies. The science of clinical decision making, advances in statistical modelling, and availability of large datasets have facilitated evidence-based approaches that regard prognosis in terms of probabilities. Prognostic research has evolved from descriptions of univariate and multivariable associations, to quantifications of added predictive value and development of prognostic models. Most prognostic information is contained in a restricted number of predictors that are available on admission: age, clinical severity, pupillary reactivity, second insults (eg, hypotension, hypoxaemia), computed tomography abnormalities, and laboratory variables (glucose, haemoglobin). However, when combined, these variables explain only about 35% of the variability in outcome.

In the past few years, much interest has focused on biomarkers. Despite initial enthusiasm for the biomarkers S100B and neuron-specific enolase, these biomarkers are not specific to brain injury and, despite some promising results, their value beyond that of traditional predictors is still unclear. Novel biomarkers purported to have increased specificity to neuronal-cell or glial-cell damage are being assessed, with encouraging results reported for glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1. However, the numbers of patients studied is fairly low, and identification of their specificity and added value compared with other predictors needs further investigation. Results from a moderately small study suggest a possible added predictive value of these biomarkers compared with a model of clinical predictors. Serum ubiquitin carboxy-terminal hydrolase L1 and α II-spectrin breakdown product 145 kDa have correlated with outcome after severe traumatic brain injury.

Although various predictive models have been developed for use in traumatic brain injury, substantial limitations have been identified in the development of many of these models. Specific issues relate to overfitting and scarcity of external validation. To be of clinical use, a prognostic model should be robust and widely applicable with large generalisability. The prediction models of the International Mission for Prognosis and Analysis of Clinical Trials in traumatic brain injury (IMPACT) study group, and the Medical Research Council Corticosteroid Randomisation After Significant Head injury (CRASH) trial collaborators, which were developed on large numbers, meet these criteria. These models are similar and show that the greatest prognostic information is contained in a core set of three predictors: age, Glasgow Coma Scale (particularly Glasgow Coma Scale motor score), and pupillary reactivity. Various studies show high generalisability of the IMPACT model in other settings and populations. Furthermore, these models create new opportunities in clinical decision making and research. These models have great potential in assessing the quality of health-care delivery and comparing predictive and actual outcomes.

Implications for research

Disappointingly, discoveries in the laboratory have translated into few new treatments for traumatic brain injury in human beings. Strategies for addressing this failure have been identified, including more research in larger animals, such as pigs and sheep with gyriform brains, rather than in rodents, whose brains are small and lissencephalic. CNS drugs take about 18 years to go from the laboratory bench to the patient, and spend on average 8·1 years in human testing. The cost of development of new CNS drugs is one of the highest in any therapeutic area, and many drug

companies are eschewing such investment.A recently formed consortium of research groups will hopefully accelerate the process of finding new therapeutic drugs and biomarkers for brain injury.

Clinical trials of traumatic brain injury are challenging to design and undertake because of patient heterogeneity, the absence of early mechanistic endpoints, and the moderate insensitivity of outcome measures. The IMPACT study group provided three recommendations to overcome patient heterogeneity, which could increase statistical power by up to 50%: enrolment criteria should be as broad as is compatible with understanding of the mechanism of action; covariate adjustment should be used in the analysis phase to mitigate effects of heterogeneity; and an ordinal approach to the analysis of treatment effects should be used, on the basis of either sliding dichotomy or proportional odds methodology.

Diffusion tensor imaging, proteomic biomarkers, and multimodal monitoring might offer new methods for tracking of disease processes and enable more mechanistic assessments than are presently possible. Previous trials have unsuccessfully targeted discrete disease mechanisms in the hope of finding a magic bullet; investigators might therefore do better to think in terms of therapeutic strategies or combination treatments.

Outcome in traumatic brain injury is complex and a multidimensional approach to outcome assessment and classification is needed. Although randomised trials are the gold standard for proving effectiveness of new treatments, they are costly, may have restricted generalisability, and importantly, are unlikely to ever be sufficiently powered to address all the existing uncertainties in clinical management of traumatic brain injury. In a workshop jointly organised by the European Commission and the US National Institute of Neurological Disorders and Stroke, a strong plea was made for comparative effectiveness research in traumatic brain injury. Heterogeneity in the traumatic brain injury population, and the variability in treatment, makes this injury particularly suitable for comparative effectiveness research, whereby differences in processes and patients can be related to outcome.

This research goes beyond the aim of classic randomised trials, which aim to establish effectiveness in carefully controlled settings, to provide real-world answers to questions about clinical management by measurement of benefits and risks of systems of care and interventions in ordinary settings and broad populations. Comparative effectiveness research in traumatic brain injury would necessitate a large-scale contemporary prospective dataset of high quality. As such, the International Initiative for Traumatic Brain Injury Research has been developed for collaboration between international funding agencies. This initiative signals the strong desire of researchers, clinicians, and funding agencies to work together within international collaborations to improve care for patients with traumatic brain injury.

Conclusion

The outcome of severe traumatic brain injury is dependent on delivery of high-quality care by a well-integrated multidisciplinary team of health professionals. Further improvements will probably result from precise classification, innovations in trial design, implementation of comparative effectiveness research, selection of patients who are likely to benefit from particular interventions, and individualised treatment in intensive-care units based on multimodal monitoring. Preclinical laboratory research in traumatic brain injury will remain a fundamental means for generation of new treatments and biomarkers, and for elucidation of pathophysiology. The findings from RESCUEicp will further define the indications for

decompressive craniectomy, which are presently controversial for diffuse brain swelling with intractable intracranial hypertension. Therapeutic hypothermia and hyperoxia are experimental treatments being investigated in large multicentre trials. Strategies to enhance neural plasticity and brain repair with stem-cell and precursor-cell implants will continue to evolve. We are optimistic that further gains in outcome for patients with severe traumatic brain injury will be achieved in the next decade.

Search strategy and selection criteria

We searched Medline, evidence-based medicine reviews, Cochrane Central Register of Controlled Trials, CENTRAL, and Embase from Jan 1, 2006, to Nov 28, 2011, using the core terms “brain injuries”, “craniocerebral trauma” and “traumatic brain injury” and keywords for the following topics: monitoring, decompressive craniectomy, haematoma evacuation, steroids, antifibrinolytics, therapeutic hypothermia, hyperoxia, stem cells, outcomes, predictors of outcome, and novel predictors of outcome. All searches were limited to English language studies in human beings. The appendix (pp 8—12) shows the full search strategies used in Medline. Reference lists of relevant publications and reviews were scanned to identify further relevant citations. 7293 citations were screened, 462 reviewed in full text, and 273 were relevant. We further identified trials with two neurotrauma evidence databases: The Global Evidence Mapping Initiative and Evidence-Based Review of Acquired Brain Injury (ERABI). To identify continuing trials, we did a separate search of the International Clinical Trials Registry Platform on Jan 31, 2012, for decompressive craniectomy, haematoma evacuation, aminosteroids, tranexamic acid, therapeutic hypothermia, hyperoxia, and stem cells.

Contributors

JVR planned the report and drafted the abstract, interventions, pharmacological, monitoring, implications for research, and conclusion sections, and appendix pp 3—7. AIM drafted the outcomes and implications for research sections, and appendix p 2. PB drafted the abstract, introduction and table, appendix pp 3—12, searched for and selected citations, and coordinated referencing and formatting of the manuscript. MCM-K drafted the pathophysiology and pharmacological sections and the figure. GTM drafted the classification section. RLG planned the report, drafted the abstract, introduction, and appendix pp 3—7, and coordinated the report and the evidence searches. All authors revised and edited the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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BACK TO TOP

Neurodegenerative causes of death among retired National Football League players

Neurology

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ABSTRACT

Objective: To analyze neurodegenerative causes of death, specifically Alzheimer disease (AD), Parkinson disease, and amyotrophic lateral sclerosis (ALS), among a cohort of professional football players. Methods: This was a cohort mortality study of 3,439 National Football League players with at least 5 pension-credited playing seasons from 1959 to 1988. Vital status was ascertained through 2007. For analysis purposes, players were placed into 2 strata based on characteristics of position played: nonspeed players (linemen) and speed players (all other positions except punter/kicker). External comparisons with the US population used standardized mortality ratios (SMRs); internal comparisons between speed and nonspeed player positions used standardized rate ratios (SRRs).

Results: Overall player mortality compared with that of the US population was reduced (SMR 0.53, 95% confidence interval [CI] 0.48_0.59). Neurodegenerative mortality was increased using both underlying cause of death rate files (SMR 2.83, 95% CI 1.36_5.21) and multiple cause of death (MCOD) rate files (SMR 3.26, 95% CI 1.90_5.22). Of the neurodegenerative causes, results were elevated (using MCOD rates) for both ALS (SMR 4.31, 95% CI 1.73_8.87) and AD (SMR 3.86, 95% CI 1.55_7.95). In internal analysis (using MCOD rates), higher neurodegenerative mortality was observed among players in speed positions compared with players in nonspeed positions (SRR 3.29, 95% CI 0.92_11.7).

Conclusions: The neurodegenerative mortality of this cohort is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher. These results are consistent with recent studies that suggest an increased risk of neurodegenerative disease among football players. Neurology® 2012;79:1–1

GLOSSARY

AD_Alzheimer disease; ALS_amyotrophic lateral sclerosis; CI_confidence interval; CTE_chronic traumatic encephalopathy; ICD _ International Classification of Diseases; MCOD _ multiple cause of death; NDI _ National Death Index; NFL _National Football League; NIOSH _ National Institute for Occupational Safety and Health; PD _ Parkinson disease; SMR _standardized mortality ratio; SSR _ standardized rate ratio.

In 1994, the National Institute for Occupational Safety and Health (NIOSH) conducted a mortality study of National Football League (NFL) players.1 One notable result was an increase in “nervous system” deaths due to 4 cases of amyotrophic lateral sclerosis (ALS). Little additional study on neurologic disorders in football players was conducted until several prominent NFL players retired from the game with lingering and

unresolved neurologic sequelae from recurrent mild traumatic brain injuries (concussions).2 Since then multiple studies have raised concerns about the longer-term health effects of recurrent concussions.3,4 Research based on autopsy data has identified chronic traumatic encephalopathy (CTE) as a pathologically distinct neurodegenerative condition affecting a wide range of individuals, including football players, who have experienced multiple concussions.5–7 CTE results from the progressive decline in neuron functioning occurring years or From the Centers for Disease Control and Prevention, The National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies, Cincinnati, OH.

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The purpose of this article is to report the results of an analysis of NFL player mortality from neurodegenerative disorders including Alzheimer disease (AD), Parkinson disease (PD), and ALS. It is not possible to directly examine mortality from CTE because the pathologic refinement of the CTE diagnosis has only occurred within the last few years, and CTE is not listed as a cause of death in any revision of the International Classification of Diseases (ICD). As an alternative, because it is now known that neurologic conditions previously attributed to AD, PD, and ALS may actually have been related to CTE,4,9 an analysis that combined all neurodegenerative causes of death was conducted; this analysis included deaths that may be related to CTE even if not reported as such on death certificates.

METHODS

Full details of the cohort have been described previously.1,10 In brief, the cohort includes 3,439 NFL players identified by a pension fund database of vested players with at least 5 credited playing seasons between 1959 and 1988. Vital status was ascertained from pension fund records, the Social Security Administration, and the Internal Revenue Service. Players were matched to the National Death Index (NDI) beginning in 1979 (when the NDI began) with follow-up through 2007. The NDI provided underlying and contributing causes of death, coded to the ICD revision in effect at the time of death. Death certificates were obtained from state vital statistics offices and were coded by a certified nosologist when death information was not provided by the NDI.

Mortality was analyzed using the NIOSH life table analysis system (LTAS.NET).11 Analyses used US male mortality rates (1960_2007) for 119 cause of death categories.12 Mortality for 3 neurodegenerative causes of death was evaluated using updated custom rate files.13 Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) were adjusted for race, age (in 5-year categories), and calendar year (in 5-year categories). Because AD and PD are more likely to be listed as a contributing cause than as the underlying cause, additional analyses used multiple cause of death (MCOD) rate files to examine all causes listed on the death certificates. Good candidates for MCOD analyses are diseases of long duration, not necessarily fatal, that are serious enough to be noted on the death certificate.

Recent studies suggested that football players who play certain positions are at higher risk of concussion because of the high acceleration, rotational acceleration, and multiple impacts they experience during games.15,16 Data collected using exposure assessment methods including video analysis, simulation and reconstruction techniques, and helmet-mounted accelerometers suggest that although linemen experience the highest number of head impacts, other positions experience higher acceleration impacts that result in concussions.16–18 To examine possible neurologic mortality differences from the high acceleration head impacts, we stratified the players into 2 categories based on positionplayed10 (identified using annual data compiled in commercial publications): speed (quarterback, running back, halfback, fullback, wide receiver, tight end, defensive back, safety, and linebacker) and nonspeed (all defensive and offensive linemen); punters and kickers were excluded from the stratified analysis.

LTAS.NET was used to calculate directly standardized rate ratios (SRRs) and 95% CIs for the neurodegenerative causes using the nonspeed players as an internal referent; 95% CIs that excluded unity were considered to be statistically significant. Standard protocol approvals, registrations, and patient consents. The protocol for this study was approved by the NIOSH Institutional Review Board and has been assigned approval number HSRB 06-DSHEFS-04XP.

RESULTS

Approximately 39% of the cohort is African American, and 62% played speed positions (table1). African American players comprise almost half (48%) of the speed stratum but only 28% of the nonspeed stratum. There were minimal differences between the strata for all other cohort characteristics. The cohort is relatively young (median age of 57 at date last observed), and only 10% are deceased.

Compared with that of US men, the overall mortality in the cohort was significantly reduced (table 2); however, mortality was significantly elevated for all neurodegenerative causes combined and for the subclassifications of AD (when all causes on death certificates were considered) and ALS. Mortality from PD was elevated but did not reach statistical significance. Overall, results based on all contributing causes were similar to results based on underlying causes with the exception of AD, which was more likely to be listed as a contributing cause rather than the underlying cause on death certificates. Neurodegenerative mortality stratified by speed position considered all death certificate causes (table 3).

Compared with those for US men, SMRs for the speed positions were significantly elevated for all neurodegenerative causes combined, AD, and ALS, but not for PD. Neurodegenerative mortality was not elevated for the nonspeed positions. Compared with the nonspeed positions, mortality was nonsignificantly elevated for the speed positions for all neurodegenerative causes combined, AD, and ALS, but not for PD. These results were highly imprecise because of the small numbers.

DISCUSSION

Although the overall mortality of this cohort is significantly lower than expected (SMR 0.53), the neurodegenerative mortality is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher. These results are

consistent with recent studies that suggest an in-2 Neurology 79 November 6, 2012 creased risk of neurodegenerative disease among football players.

It is not possible to determine from our study what has caused this increased risk. Research suggests that football players who have experienced one or more concussive blows to the head are at increased risk of neurologic disorders. In retired professional players, one study observed a 5-fold prevalence of mild cognitive disorders and a 3-fold prevalence of significant memory problems for players who experienced 3 or more concussions compared with players with fewer than 3 concussions. Excess neurologic mortality and morbidity has also been reported in players of other sports for which head impacts and concussion are common: soccer, boxing, horse racing, and hockey. Studies that examined the incidence of concussion in football players found that players in speed positions experienced concussions more commonly than players in nonspeed positions. Speed players are those who are able to build up considerable momentum before the point of being tackled or tackling another player. Offensive and defensive linemen (nonspeed players) usually engage other players soon after the football is snapped, thus mitigating the potential to build up momentum before a tackle or a block. Although our study used causes of death from AD, PD, and ALS as reported on death certificates, recent research now suggests that CTE may have been the true primary or secondary factor in some of these deaths.

Whereas CTE is a clinically distinct neurologic diagnosis, CTE symptoms are often similar to those found in patients with AD, PD, and ALS.6,21 In addition, CTE is not listed as a distinct cause of death recognized in current or previous ICD revisions, precluding the calculation of CTE-specific results. To account for possible misclassification, we reported combined results for all neurodegenerative causes.

Our study had several limitations. Our analysis is based on a few neurodegenerative deaths; therefore, the confidence intervals surrounding our SMR and SRR values are relatively broad. The few deaths also limited our ability to stratify players into more than 2 broad position categories; therefore, we were not able to identify potentially important differences.

AUTHOR CONTRIBUTIONS

Study concept and design: E.J. Lehman, M.J. Hein. Acquisition of data: S.L. Baron, C.M. Gersic. Study coordination: C.M. Gersic. Analysis and interpretation of data: E.J. Lehman, M.J. Hein, S.L. Baron. Drafting/revising manuscript: E.J. Lehman, M.J. Hein, S.L. Baron, C.M. Gersic.Critical revision of the manuscript for important intellectual content: E.J. Lehman, M.J. Hein, S.L. Baron. Statistical analysis: E.J. Lehman, M.J. Hein. Obtain funding: E.J. Lehman. Administrative, technical, or material support: E.J. Lehman, C.M. Gersic. Study supervision: E.J. Lehman, S.L. Baron.

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Disclosure

The authors report no disclosures relevant

BACK TO TOP

Emergency Department Visits for Traumatic Brain Injury in Older Adults in the United States: 2006–08

MedScape
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24 Sep 2012

Abstract

Introduction: Traumatic brain injury (TBI) can be complicated among older adults due to age-related frailty, a greater prevalence of chronic conditions and the use of anticoagulants. We conducted this study using the latest available, nationally-representative emergency department (ED) data to characterize visits for TBI among older adults.

Methods: We used the 2006–2008 National Hospital Ambulatory Medical Care – Emergency Department (NHAMCS-ED) data to examine ED visits for TBI among older adults. Population-level estimates of triage immediacy, receipt of a head computed tomography (CT) and/or head magnetic resonance imaging (MRI), and hospital admission by type were used to characterize 1,561 sample visits, stratified by age <65 and ≥65 years of age.

Results: Of ED visits made by persons ≥65 years of age, 29.1% required attention from a physician within 15 minutes of arrival; 82.1% required a head CT, and 20.9% required hospitalization. Persons ≥65 years of age were 3 times more likely to receive a head CT or MRI compared to younger patients presenting with TBI (adjusted odds ratio [aOR] 3.2; 95% confidence interval [CI], 1.8–5.8), and were 4 times more likely to be admitted to an intensive care unit, step-down unit, or surgery (aOR 4.1; 95% CI 2.1–8.0) compared to younger patients presenting with TBI, while controlling for sex and race.

Conclusion: Results demonstrate increased emergent service delivery for older persons presenting with TBI. As the United States population ages and continues to grow, TBI will become an even more important public health issue that will place a greater demand on the healthcare system.

Introduction

Injury among older persons can be complicated by frailty and an increased number of chronic conditions which results in poorer outcomes compared to younger adults.[1] Use of emergency department (ED) services and the resulting use of rehabilitation services for injury-related morbidity are greater among older persons compared to younger persons.[2] Additionally, falls resulting in head trauma have been implicated as a more common cause of injury-related morbidity among older persons compared to younger persons.[3]

Traumatic brain injury (TBI) has been identified as a leading cause of injury-related morbidity and mortality among older adults (≥ 65 years of age) in the United States (U.S.).[4] Earlier work suggests that differences in both the treatment and outcomes of TBI for older persons compared to younger persons. Older age has been suggested as an independent predictor of receiving increased numbers of procedures and medications for treatment of TBI in the ED, as well as poorer outcomes after treatment in the ED.[5–8] Another risk factor among older patients for poor outcomes is the higher prevalence of cardiovascular conditions (e.g. atrial fibrillation and heart valve replacements) that require anticoagulant medications such as warfarin (Coumadin), low-molecular weight heparin (Lovenox), Clopidogrel (Plavix), and aspirin. Among older patients, use of these medications is a risk factor for intracranial hemorrhage and hematoma.[9] It has also been demonstrated that as age increases, hospitalization rates for TBI increase, possibly due to the increased medical complexity of the patients presenting for treatment.[10–11]

As the U.S. population ages and continues to grow, it is likely that there will be an increased demand for emergency services to treat TBI among older Americans, who will present with more complicated treatment requirements. To better understand the use of emergency services for TBI among older persons, we conducted this study to use the latest available nationally representative ED data to characterize the visits for TBI among persons 65 years of age and older and to compare these visits to those made by persons less than 65 years of age.

Methods

We combined data from the 2006, 2007 and 2008 National Hospital Ambulatory Medical Care Survey– Emergency Department (NHAMCS-ED) data to examine ED visits for TBI by patients 65 years of age and older. The NHAMCS-ED is conducted annually as a stratified, national probability sample of ED visits in all 50 U.S. states and the District of Columbia. Information on visits is collected over a 4-week period, for each year of the survey, in each selected ED. Further information on the design and conduct of the survey can be found elsewhere.[12]

TBI was identified using International Classification of Diseases, 9th Revision Clinical Modification (ICD-9-CM) codes collected in the ED. We used the Centers for Disease Control and Prevention (CDC) definition of TBI and included the codes: (800.0–801.9) fracture of the vault or base of skull; (803.0–804.9) other and unqualified multiple fractures of the skull; (850.0–854.1) intracranial injury, including concussion, contusion, laceration, and hemorrhage; (950.1–950.3) injury to optic nerve and pathways, and (959.01) head injury, unspecified. We collected three admission diagnoses for each patient presenting to the ED and used identification of any of the previously described codes in any of the three admitting diagnoses for inclusion of the patient visit in the analyses. Using this definition of TBI produced a sample size of 1,561 visits.

Using data from these visits, triage immediacy, receipt of a head computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and admission to specialty care within the hospital were used to characterize the severity of the injury. We chose these variables based on availability of data within the dataset. Other indicators of severity, such as Glasgow Coma Scale (GCS), intubation of the patient and other indicators, were not available due to insufficient sample size or lack of inclusion in the dataset.

We categorized triage immediacy as being either "emergent" or "non-emergent." Emergent visits were defined as visits requiring immediate physician attention or visits requiring physician attention within 14 minutes or less and those triaged as being urgent (attention required in 15–60 minutes). We defined non-emergent visits as those triaged as being semi-urgent (attention required in > 1 hour – 2 hours), and non-urgent (attention required in > 2 hours – 24 hours). We excluded visits requiring no triage from analyses as these visits represent patients who died during transport to the ED. Receipt of head imaging was defined as receiving either a head CT or MRI of the head and dichotomized into receiving imaging or not. Admission to specialty care included admission to an intensive care unit (ICU), step-down unit, or to surgery and was dichotomized into being admitted or not.

We estimated the total number of visits for TBI and stratified them by age, sex, and race. Percentage estimates of triage immediacy, receipt of head CT and/or head MRI, and admission to specialty care were made for all visits and compared among three age groups including visits where patients were 0–34 years of age, 35–64 years of age and 65 years of age and older. We tested differences in receipt of services among these age groups using Pearson's Chi-square analyses. These differences were further tested using multivariate logistic regression models controlling for sex and race. We conducted all analyses in SUDAAN to take into account the complex sampling design of the survey.[13] These secondary analyses were considered to be exempt under institutional review board guidelines.

Results

Estimates of the number of visits to EDs for TBI increased each year beginning with nearly 1.6 million in 2006, 1.7 million in 2007 and 2.1 million in 2008. During the 3-year study period (2006–2008) there were an estimated 5.4 million total visits to U.S. EDs for TBI. Approximately 15% of these visits were made by persons greater than 65 years of age, among these the average age of the patient was 80 years. Just over 60% of the visits were made by females and just over half were whites. Among those between 35 and 64 years of age, the average age was 48.6 years. Approximately 47% were female and less than half of the visits were made by whites. Finally, among visits made by person 0–34 years of age, the average age was 14.5 years. Almost 38% of the visits were made by females and just over 40% were made by whites (Table 1).

Table 1. Demographic characteristics of visits to United States emergency departments for traumatic brain injury by age group, 2006–2008.*

N=1,561	0–34 years	35–64 years	65+ years

Total visits (n)	954	370	237
Population estimate of visits	3,325,491	1,317,480	799,879
Average age in years	14.5, (13.5–15.4)	48.6, (47.5–49.7)	80.0, (78.7–81.4)
% Female	37.5%, (33.1% – 42.2%)	46.8%, (40.9% – 52.8%)	61.1%, (54.2% – 67.5%)
% White	44.4%, (39.4% – 49.5%)	45.9%, (38.7% – 53.3%)	55.9%, (47.9% – 63.6%)

Source: 2006–2008 National Hospital Ambulatory Care Survey – Emergency Department Visits
*Weighted estimates and (95% confidence intervals)

We noted differences in the triage severity of the visits by age group. Just over two-thirds (66.9%) of visits made by persons 0–34 years of age were triaged as being immediate or urgent, compared to nearly three-quarters (74.8%) of visits made by persons 35–64 years of age, and over three-quarters (84.0%) of visits made by persons greater than 65 years of age. However, the difference in the percentage of visits triaged as being immediate or urgent made for persons 65 years of age and older and visits for persons 35 to 64 years of age was not statistically significant. However, the percentage of visits made by persons 65 years of age and older and triaged as being immediate or urgent was significantly greater than the percentage of visits made by those 0 to 34 years of age and triaged as being immediate or urgent ($p<0.01$). Significant differences were found for receipt of a head scan and being admitted for advanced care (ICU or step-down) or surgery. Over three-quarters (83.5%) of all visits made by persons 65 years of age and older received a head CT and/or MRI, compared to 72.2% of visits made by persons 35 to 64 years of age and 55.9% of persons 0 to 34 years of age ($p<.01$). Just over 2 percent (2.1%) of visits made by persons 0 to 34 years of age were admitted to the ICU, step-down unit, or to surgery compared to 10% of visits made by persons 35 to 64 years of age and 14.1% of visits made by persons 65 years of age and older. Differences in receipt of advanced care between visits made by persons 65 years of age and older were significantly greater compared to visits made by persons 0 to 34 years of age ($p<.01$) (Table 2).

Table 2. Characterization of services for traumatic brain injury visits by age group.*

N=1,561	0–34 years	35–64 years	65+ years	P**
Triaged as immediate/urgent***	66.9%, (61.1% – 72.2%)	74.8%, (66.6% – 81.5%)	84.0%, (74.2% – 90.5%)	<0.01

Receipt of head CT and/or MRI	55.9%, (50.8% – 60.8%)	72.2%, (64.6% – 78.7%)	83.5%, (74.4% – 89.7%)	<0.01
Admission to ICU, step-down, or surgery	2.10%, (1.3% – 3.4%)	10.0%, (6.2% – 15.8%)	14.1%, (9.1% – 21.1%)	<0.01

Source: 2006–2008 National Hospital Ambulatory Care Survey – Emergency Department Visits
*Weighted estimates and (95% confidence intervals)
**Chi-square test
***includes patients needing physician attention < 60 minutes of arrival
CT, computed tomography; *MRI*, magnetic resonance imaging, *ICU*, intensive care unit

Adjusted logistic regression models controlling for patient sex and race demonstrated similar differences found in the bivariate analyses. No significant differences were found among the three age groups for triage immediacy; however, older age groups tended to demonstrate increased odds of being triaged at a higher acuity. This was not statistically significant. Visits made by persons 65 years of age and older were nearly 4 times more likely to have received a head CT or MRI compared to visits made by persons 0 to 34 years of age (3.93 O.R.; 2.20–7.02 95% C.I.) and were nine times more likely to be admitted to the specialty care, such as ICU, a step-down unit, or to surgery, compared to visits made by persons 0 to 34 years of age (9.12 O.R.; 4.47–18.62 95% C.I.). Admission to specialty care was also significantly higher for persons 65 years of age and older compared to visits made by persons 35 to 64 years of age (Table 3).

Table 3. Multiple logistic regressions for receipt of services for traumatic brain injury by age group.*

N = 1,561	Odds Ratio	95% Confidence Interval
Triaged as immediate/urgent**		
65 + years	1.27	0.71–2.25
35–64 years	1.29	0.81–2.04
0–34 years	1.00	1.00–1.00

Receipt of head CT and/or MRI		
65 + years	3.93	2.20–7.02
35–64 years	2.05	1.36–3.09
0–34 years	1.00	1.00–1.00
Admission to ICU, step-down, or surgery		
65 + years	9.12	4.47–18.62
35–64 years	5.53	2.95–10.37
0–34 years	1.00	1.00–1.00

Source: 2006–2008 National Hospital Ambulatory Care Survey – Emergency Department Visits
*controlling for sex and race
**includes patients needing physician attention < 60 minutes of arrival
CT, computed tomography; *MRI*, magnetic resonance imaging, *ICU*, intensive care unit

Discussion

The results of this study demonstrate an increased level of advanced care for older persons presenting to an ED with TBI. Persons 65 years of age and older were more likely to receive a head CT and/or MRI in the ED and to be admitted to either the ICU, step-down unit, or have surgery after presenting to the ED with TBI compared to younger persons. It is important to note that age was not a statistically significant predictive factor in determining the triage immediacy for visits, but still was an indicator for increased services. This could point to a possible opportunity to use age as a triage consideration in patients with head trauma presenting to an ED. Visits for head trauma were triaged as requiring immediate or urgent

attention regardless of age. However, age could be a surrogate for anticoagulant use and should be further studied. In addition to these findings, our results also suggest that the numbers of ED visits for TBI are increasing.

Among older adults, falls are the leading cause of head injuries resulting in TBI. As the U.S. population continues to age and rapidly grow, falls resulting in injury will become an even more important public health issue.[14] Falls from ground level are common in older populations, resulting in significant morbidity and mortality.[15] Furthermore, due to the increased use of anticoagulants in this population, complications from falls can have deleterious outcomes such as subdural hematomas resulting in death.[9–16] Even minor head injuries in older patients result in a higher incidence of intracranial hemorrhage due to the use of antiplatelet and anticoagulant medications and could be a plausible explanation for the increased ICU, step-down unit, or emergent surgery rates found in this study.[17] Therefore, quick identification of this type of injury is important in older populations.

Age can also be related to the trajectory of recovery for those suffering from TBI, and can result in higher costs for care. Patients 65 years of age and older require greater levels of inpatient rehabilitation and do not progress as quickly with rehabilitation as do younger patients.[18] Rehabilitation charges for older patients were significantly higher compared to younger patients, as was total length of stay for inpatient rehabilitation services after TBI, due to more severe injuries.[19–20] To better understand the relationship of age on use of services, we examined age as a continuous variable and found that each year of age contributed to increased use of services ($p<.01$).

Costs from TBI can be considerable. Finkelstein et al[21] have suggested that the lifetime costs for TBI in the U.S. in 2000 dollars was $60.4 billion. Data from the CDC Web-based Injury Statistics Query and Reporting System (WISQARS) estimates that total 2005 costs from TBI among persons 65 years of age and older were over $5 billion.[22] Older patients suffering from TBI have also been found to become physically and financially dependent on others after injury and suffer significant decreases in independence.[23] This suggests that there an increase in medical costs for TBI in the inpatient and outpatient setting, but in costs at a societal and personal level due to a loss of both physical and mental functionality. It has been proposed that a reduction in societal costs, which appear to be the most significant contributor of cost, could be achieved through widespread adoption of the Brain Trauma Foundation (BTF) treatment guidelines that address treatment of patients with severe TBI who account for approximately 10% of all TBIs.[24]

The main limitation of this study was the small sample size. We took the data used for these analyses from the NHAMCSED sample, which collects data from the ED during a four-week period in selected hospitals with just three admission diagnoses. The total sample size for each collected year of data was no greater than 35,000 records. With the overall incidence of TBI for each year, this limited the likelihood of collecting information on TBIs within the four-week sampling period of the survey. Therefore, a complete characterization of each ED visit for TBI that described all procedures was not possible. However, by combining three years of data, robust estimates of overall visits by age, sex and race were possible, as well as several descriptors of the visit, including triage immediacy, receipt of a head CT and/or MRI and admission to the hospital. Furthermore, by using this dataset, national estimates were possible. To the authors' knowledge, this is the first presentation of this level of data for older persons presenting with TBI to an ED.

A second limitation of this study was that there was no measurement of GCS collected in the dataset. Use of this scale is a commonly used measure of severity for head injury. Even so, this study demonstrates that older persons presenting to an ED with diagnosed TBI potentially require higher acuity treatment compared to younger persons, which could be indicative of a more deleterious GCS measure. Furthermore, antiplatelet and anticoagulant use was not collected in this database, preventing comparisons with prior studies on these medications.

A final limitation was our inability to determine the specific reason for increased triage immediacy, receipt of head CT and/or MRI or admission to the hospital for each of these cases from this data. Both age and comorbidities could be the driving factors that would require additional service provision. This study only searched for a diagnosis of TBI among the three listed diagnoses on admission to the ED. However, it is reasonable to believe that complications, such as increased risk of subdural hematomas and the increased frailty of older persons, are most likely the driving forces behind the outcomes examined in this study.

Conclusion

As the population ages, there will be increasing numbers of older Americans on antiplatelet and anticoagulant medications, who are prone to falling, and therefore at substantial risk of sustaining life-threatening traumatic brain injuries requiring the use of significant health services for treatment. Increasing dissemination of fall prevention programs could reduce this public health threat. Furthermore, understanding the scope of these healthcare needs and the impact of this phenomenon on EDs will help decision makers allocate resources for optimal treatment of injury.

BACK TO TOP

Identifying Impairments after Concussion: Normative Data versus Individualized Baselines

Medical Science Sports Exercise
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Sep 2012

Abstract

Purpose : This study aimed to determine whether agreement exists between baseline comparison (comparison of postconcussion scores to individualized baseline scores) and normative comparison (comparison of postconcussion scores to a normative mean) in identifying impairments after concussion.

Methods : A total of 1060 collegiate student-athletes completed baseline testing as part of an ongoing clinical program. Gender-specific normative means were obtained from a subset of 673 athletes with no history of self-reported concussion, learning disabilities, or attention-deficit disorders. Concussions were later diagnosed in 258 athletes who had completed baseline testing.

The athletes completed their first assessment within 10 d after injury. Athletes completed a computerized neurocognitive test (Automated Neuropsychological Assessment Metrics), postural control assessment (Sensory Organization Test), and a 15-item graded symptom checklist at baseline and again after injury. We computed two postconcussion difference scores for each outcome measure: 1) baseline difference = postconcussion score − individualized baseline score and 2) normative difference = postconcussion score − normative mean. Athletes were considered impaired if postconcussion difference exceeded the reliable change parameters. McNemar tests were used to assess agreement on impairment status (impaired and unimpaired) between comparison methods for each outcome measure.

Results : The baseline comparison method identified 2.6 times more impairments than the normative comparison method for the Simple Reaction Time Test 1 ($P = 0.043$). The normative comparison method identified 7.6 times more impairments than the baseline comparison method for Mathematical Processing ($P < 0.001$). No other disagreements were observed for postural control or symptom severity.

Conclusions : Our findings suggest that, when using these concussion assessment tools, clinicians may consider using normative data in lieu of individualized baseline measures. This may be especially useful to clinicians with limited resources and an inability to capture valid baselines on all athletes.

Introduction

As many as 3.8 million sport-related traumatic brain injuries occur annually in the United States, with evidence that many go unrecognized, unreported, and untreated.[20,36] Sports medicine professionals are faced with the challenging task of evaluating and managing sport-related concussion. Evaluation of concussion should involve a multifaceted approach including a thorough clinical evaluation, a self-reported symptom checklist, postural control assessment, and computerized neurocognitive testing.[13,25] Recent concussion consensus statements urge clinicians to establish preinjury baseline scores for each athlete.[25] Baseline scores are thought to account for individual preinjury differences in neurocognition, symptoms, and postural control abilities, thereby providing a valid comparison for postconcussion outcomes. Despite a strong theoretical rationale for using baseline measures, there are several concerns regarding the application of baseline testing.

Completing a comprehensive baseline testing battery on every athlete can be very time-intensive and cost-prohibitive. Sports medicine professionals who have limited time to complete baseline testing may be forced to test multiple athletes at once. Environmental distractions such as talking, loud typing, or movement could negatively affect test performance, resulting in invalid representations of the athletes' true capabilities.[27,33] Baseline testing provides a single cross-sectional representation of an individual athlete's state at the time of testing, which can easily be influenced by external factors such as the previous night's sleep,[8] temporary states of psychological distress,[1] and effort put forth during testing.[16] Athletes aware that their baseline scores will be used for postconcussion comparisons may intentionally choose to "throw" their baseline by extending less-than-maximal effort.[16] Invalid baselines are a concern, as a recent study suggests that only 52% of athletic trainers verify that baseline neurocognitive scores are a valid representation of each athlete's individualized performance.[10] These results hold a significant clinical implication because comparing postconcussion scores to invalid baseline scores could cause a clinician to make a premature

decision to return an athlete to play. Although the risks of premature return to play are not fully understood,[26,29] recent guidelines suggest that athletes refrain from physical and cognitive activity until they have fully recovered.[25]

Recent reports suggest that many concussion assessment tools do not meet the diagnostic criteria needed to properly track an athlete's recovery after concussion.[29,30] The most widely used neurocognitive,[30] postural control,[12] and symptom assessment tools[21] have limited research regarding sensitivity, reliability, validity, and reliable change algorithms for identifying clinical impairment. Some studies suggest that these tools may have poor reliability, thereby limiting their clinical applicability.[5–7,35,37] The combined use of symptom scores and neurocognitive values increases the sensitivity of concussion diagnoses but may simultaneously increase the rate of false-positive diagnoses in athletes without concussion.[39] Using assessment tools with poor sensitivity and low reliability may yield unreliable and potentially invalid data for making return-to-play decisions.

The psychometric properties of neurocognitive scores, and the cognitive domains that they represent, can be difficult to understand and interpret without proper training. Most athletic trainers and team physicians do not receive formal training in neurocognitive score interpretation as part of their educational or medical training. There are no standard qualifications that clinicians must maintain to assess an athlete with concussion. Although educational workshops are offered for most neurocognitive test platforms, most clinicians who use the test batteries choose not to attend.[10] Clinicians who have never received formal education regarding score interpretation should not be in charge of determining whether declines or improvements in postconcussion scores represent a true clinical change. Uncertainty and misunderstanding of postconcussion scores could cause a sports medicine professional to either act conservatively and unnecessarily hold a recovered athlete from returning to play or, worse yet, act hastily and prematurely return an athlete to play.

Many medical professionals rely on normative values to diagnose a wide variety of pathological conditions because individualized baseline values are not available for their patient populations. Normative values are available for most commonly used concussion assessment tools and are derived by administering the test to a specific group (or groups) of individuals. A normative sample provides a standard against which an individual's performance can be compared. In the absence of an individualized baseline, normative data are available for the most commonly used concussion assessment tools and may be useful in clinical scenarios where baseline testing is not feasible.[8,21,31,34] Using normative neurocognitive, postural control, and symptom severity scores would allow clinicians to bypass the lengthy process of baseline testing while ensuring that valid scores were used for postconcussion comparison. If the two comparison methods, baseline comparison and normative comparison, identify the same postconcussion impairments, clinicians would be better served to use normative values.

We aimed to determine whether agreement existed in identifying immediate impairments after concussion using two comparison methods: 1) comparing postconcussion scores to *individualized baseline scores* and 2) comparing postconcussion scores to gender-specific *normative means*. We hypothesized that there would be strong agreement between the two comparison methods in identifying impairment.

Methods

Subjects

Between 2001 and 2010, 1060 Division I male and female collegiate student-athletes completed preseason baseline testing at the University of North Carolina at Chapel Hill as part of an ongoing clinical program. We computed gender-specific normative means from preseason baseline measures collected in a subsample of 673 athletes with no history of self-reported concussions, learning disabilities, or attention-deficit disorders. The normative sample consisted of incoming freshmen and transferees, approximately the same age, completing baseline testing for the first time at our institution (Table 1). Two hundred fifty-eight student-athletes (males = 182, females = 76) were later diagnosed with concussion. Concussion was defined as an injury resulting from a direct or an indirect (i.e., impulsive) blow to the head that resulted in an alteration of mental status and any of the following symptoms: headache, nausea, vomiting, poor balance, sensitivity to noise, sensitivity to light, blurred vision, difficulty concentrating, difficulty remembering, trouble falling asleep, drowsiness, fatigue, sadness, and/or irritability, difficulty remembering, and/or difficulty concentrating.[14] Athletes were evaluated for possible concussion if our medical staff observed demonstrable signs of concussion or if an athlete reported symptoms consistent with concussion to our medical staff. Data from athletes with concussion were obtained from two separate concussion assessment programs. Of the 258 athletes with concussion, 175 were baseline tested and later evaluated at the University of North Carolina at Chapel Hill. An additional 83 athletes were evaluated as part of a separate multisite assessment program. All athletes completed their first postconcussion assessment within 10 d after injury (2.66 ± 2.35 d after injury). We chose to exclude athletes with concussion who were not evaluated during the acute stages, within 10 d, of their recovery.[15,23,24] All athletes read and signed an informed consent form approved by the university's institutional review board. Demographic data for our normative and concussed sample are presented in Table 1.

Table 1. Demographics by gender for the normative and concussed samples at baseline

	Normative Sample (*n* = 673)				**Concussed Sample (*n* = 258)**			
	Males (*n* = 446)		**Females (*n* = 227)**		**Males (*n* = 182)**		**Females (*n* = 76)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Height (inch)	72.32	3.45	66.10	3.48	72.24	3.12	66.87	3.76
Weight (kg)	89.69	19.93	62.03	9.16	91.69	18.39	64.63	11.12

Age (yr)	18.50	1.10	18.29	0.82	18.80	1.61	18.51	1.14

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	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Height (inch)	72.32	3.45	66.10	3.48	72.24	3.12	66.87	3.76
Weight (kg)	89.69	19.93	62.03	9.16	91.69	18.39	64.63	11.12
Age (yr)	18.50	1.10	18.29	0.82	18.80	1.61	18.51	1.14

Multifaceted Baseline and Postconcussion Test Battery

The multifaceted concussion baseline test battery consisted of a computerized neurocognitive test (Automated Neuropsychological Assessment Metrics (ANAM)), postural control assessment (Sensory Organization Test (SOT)), and a 15-item graded symptom checklist. Athletes completed baseline testing in groups no larger than four people. This same test battery was repeated for all athletes diagnosed with a concussion as part of an ongoing clinical program. Although most participants had complete neurocognitive, postural control, and symptom severity data, the clinical nature of this study resulted in a small number of missing outcome measures for individual athletes. Unequal sample sizes across analyses resulted from physician-driven clinical decisions to only use some portions of the battery, participant error, and minor research-driven changes in testing procedures as more literature became available over the 10 yr of data collection. Because of the slight differences in the evaluation tools between sites, athletes who were not evaluated at the University of North Carolina at Chapel Hill did not complete the Procedural Reaction Time and Code Substitution subtests of ANAM and the SOT.

Computerized Neurocognitive Assessment

The ANAM test battery consists of a series of subtests designed to examine several neurocognitive domains. The ANAM test battery has been observed to be both reliable and valid.[4,11] The following subtests (and their cognitive domains) were included in our ANAM test battery: Simple Reaction Time Test 1 (reaction time), Simple Reaction Time Test 2 (reaction time), Mathematical Processing (concentration and working memory), Sternberg Memory Search (working memory), Match to Sample (visual memory), Procedural Reaction Time (reaction time and working memory), and Code Substitution (delayed memory).The Simple Reaction Time subtest was completed twice, once at the beginning of the test battery and again at the end to measure reaction time before and after a period of cognitive exertion. During baseline and postconcussion testing, athletes were given instructions before completing each ANAM subtest displayed on the computer monitor. As stimuli appeared on the screen, athletes were required to respond as quickly and accurately as possible by clicking either the right or the left mouse button. A variable interstimulus interval (time between consecutive stimuli) was used throughout all subtests to decrease anticipatory responses.

Data were collected, processed, and stored on a personal computer as the ANAM battery was completed. Throughput scores were calculated as the product of speed (mean reaction time) and accuracy (percentage of correct responses) to represent the overall efficiency for each subtest.[3,8] A higher throughput score is indicative of a better performance for all the ANAM subtests.

Postural Control Assessment

Student-athletes at the University of North Carolina at Chapel Hill completed postural control testing using the SOT on the SMART Balance Master (NeuroCom International, Clackamas, OR). Shoeless athletes were positioned with a standardized foot placement relative to their height, and instructed to stand with their arms relaxed at their sides, looking straight forward, and standing as still as possible. Athletes stood on two 9 × 18-inch force plates connected by a pin joint. Both the support surface and the visual surround rotate in the anterior–posterior plane referenced to the athlete's sway and sway velocity. Center-of-pressure data were sampled at 100 Hz.

The SOT consists of six sensory conditions repeated three times for a total of eighteen 20-s trials. Each athlete was acclimated to the test by completing the first six trials in the following order: eyes opened and stationary support surface (condition 1), eyes closed with stationary support surface (condition 2), sway-referenced visual input with stationary support surface (condition 3), eyes opened with sway-referenced support surface (condition 4), eyes closed with sway referenced support surface (condition 5), and eyes opened with sway-referenced visual and support surface (condition 6). The next six trials were randomized across the sensory conditions. Once complete, the final six trials were repeated at random once more.

For each of the 18 trials, an equilibrium score was generated based on an algorithm developed for the SMART Balance Master. Percentages were computed expressing the angular differences between each athlete's displacement of his or her center of pressure in the sagittal plane and his or her theoretical limit of stability (approximately 12.5° in the sagittal plane). Less postural sway in the anterior–posterior directions results in a higher equilibrium score and, thus, indicates greater postural control. An overall composite score was computed by averaging the following 14 equilibrium scores: the mean of all condition 1 trials, the mean of all condition 2 trials, and the individual trial equilibrium scores for conditions 3–6. A higher composite score is indicative of better postural control.

Graded Symptom Checklist

The graded symptom checklist is a self-report symptom scale that assesses the presence and severity of 15 concussion-related symptoms using a seven-point Likert scale. Each athlete was asked to his or her symptoms at baseline and after concussion by indicating which of the following numbers best described the severity: not experiencing = 0, mild = 1–2, moderate = 3–4, and severe = 5–6. During the preseason baseline evaluation, athletes were instructed to rate the severity of concussion-related symptoms they regularly experienced at least three times per week. During postconcussion test sessions, athletes were asked to rate the severity of their symptoms based on how they felt at the time of testing. The graded symptom checklist has been published previously.[22] The total symptom severity score for this study is the sum of 15 severity scores for headache, nausea, vomiting, poor balance, sensitivity to noise, sensitivity to light, blurred vision, difficulty concentrating, difficulty remembering, trouble falling asleep, drowsiness, fatigue, sadness, irritability, and neck pain.

Identification of Impairments

Impairments for each injured athlete were determined by computing two postconcussion difference scores for each outcome measure as follows:

baseline difference = postconcussion score − athlete's individualized baseline score

normative difference = postconcussion score − gender-specific normative mean

The baseline difference score compared each athlete's postconcussion outcome to the athlete's individualized baseline score, whereas the normative difference scores compared postconcussion outcomes to gender-specific normative means.

Reliable change parameters were computed to provide a point range for which normal variation may occur while accounting for practice effect. We used data derived from a subset of the athletes with concussion (n = 132) included in this study and a second sample of healthy control athletes (n = 38) who completed the test battery twice, at least 2 wk apart and no more than 4 months apart. We used the standard error of the measurement from baseline (SEM_1) and session 2 (SEM_2) and the z-score associated with an 80% confidence interval (z = 1.282) to compute the predictive cutoff values for each outcome measure. This methodology was chosen because using the SE of the measurement to compute predictive cutoff values allows for some generalization across samples, it accounts for some random measurement error, and it expresses reliable change parameters in the same units as the measure.[40]

$$\mathrm{SEM}_1 = \mathrm{SD}_1\sqrt{1-r}, \quad \mathrm{SEM}_2 = \mathrm{SD}_2\sqrt{1-r}, \quad S_{\mathrm{diff}} = \sqrt{\mathrm{SEM}_1^2 + \mathrm{SEM}_2^2},$$

An 80% confidence interval predictive cutoff was used because it provides the most clinically conservative method for identifying clinically meaningful declines in performance. Reliable change parameters are presented in Table 2. Significant practice effects were observed for Simple Reaction Time Test 1, Mathematical Processing, Sternberg Memory Search, Match to Sample, Procedural Reaction Time, and Code Substitution.

Table 2. Gender-specific normative values and reliable change parameters for each outcome measure.

	RCP[a]	Male			Female		
		n	Mean	SD	*n*	Mean	SD
ANAM throughput scores							
Simple Reaction Time Test 1	43	423	230.96	30.51	226	225.82	31.71
Simple Reaction Time Test 2	62	420	232.47	33.68	224	231.87	31.26
Mathematical Processing	4	315	22.76	6.93	144	22.83	6.24
Sternberg Memory Search	26	427	74.10	16.76	226	76.79	16.74
Match to Sample	18	427	40.89	14.42	226	38.56	10.90
Procedural Reaction Time	24	426	97.89	19.55	225	98.11	17.48
Code Substitution	14	427	50.41	10.96	226	51.75	10.08
Sensory organization scores							

Composite score	8	445	79.32	6.39	226	79.73	5.98
Graded symptom scores							
Total symptom severity score	10	446	2.72	4.51	227	2.91	4.51

[a] RCP indicates reliable change parameter—the predictive cut point value for determining clinical impairment with an 80% confidence interval.

Athletes' postconcussion scores were then categorized as either "impaired" or "unimpaired" relative to their baseline score and then relative to the normative scores for each outcome measure. Athletes were identified as impaired if the difference score exceeded the reliable change parameter and unimpaired if the difference score did not exceed the reliable change score.

Statistical Analyses

Nine separate 2 × 2 McNemar tests for paired proportions were used to assess agreement on impairment status (impaired or unimpaired) between comparison methods for each of the ANAM throughput scores, the SOT composite score, and total symptom severity score. Results were considered significant at an ***a priori*** α level of 0.05. The McNemar test is a form of the χ^2 statistic that examines the differences between marginal proportions for matched pairs of data. A significant result indicates that the two marginal proportions are significantly different from each other and thus do not agree.

Results

Gender-specific normative means used for comparison are presented in Table 2. The baseline comparison method identified 2.6 times more impairments than the normative comparison method for Simple Reaction Time Test 1 ($P = 0.043$). However, the normative comparison method identified 7.6 times more impairments than the baseline comparison method for Mathematical Processing ($P < 0.001$). Disagreements between baseline and normative comparison methods were not observed for any of the other ANAM throughput scores. Likewise, no disagreements were observed for the SOT composite score and total symptom severity score. Cell frequencies and total percentages for all analyses are presented in Table 3.

Table 2. Gender-specific normative values and reliable change parameters for each outcome measure.

	RCP[a]	**Male**	**Female**

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Match to Sample	18	427	40.89	14.42	226	38.56	10.90
Procedural Reaction Time	24	426	97.89	19.55	225	98.11	17.48
Code Substitution	14	427	50.41	10.96	226	51.75	10.08
Sensory organization scores							
Composite score	8	445	79.32	6.39	226	79.73	5.98
Graded symptom scores							
Total symptom severity score	10	446	2.72	4.51	227	2.91	4.51

[a] RCP indicates reliable change parameter—the predictive cut point value for determining clinical impairment with an 80% confidence interval.

Table 3. Acute impairment disagreement and agreement frequencies (percentages of total sample) for each outcome measure

	N	Impairment Disagreements		Impairment Agreements,[a] *n* (%)	P
		Baseline Identified,[b] *n* (%)	Norm Identified,[c] *n* (%)		
ANAM throughput scores					
Simple Reaction Time Test 1	239	18 (7.5)	7 (2.9)	24 (10.0)	0.043d
Simple Reaction Time Test 2	234	13 (5.6)	9 (3.8)	15 (6.4)	0.523
Mathematical Processing	189	6 (3.2)	46 (24.3)	17 (9.0)	G0.001d
Sternberg Memory Search	239	12 (5.0)	12 (5.0)	21 (8.8)	1.000
Match to Sample	239	25 (10.5)	17 (7.1)	8 (3.3)	0.280
Procedural Reaction Time	160	9 (5.6)	3 (1.9)	2 (1.3)	0.146

Code Substitution	160	4 (2.5)	6 (3.8)	5 (3.1)	0.754
Sensory organization scores					
Composite score	166	7 (4.2)	7 (4.2)	21 (12.7)	1.00
Graded symptom scores					
Total symptom severity score	246	6 (2.4)	15 (6.1)	64 (26.0)	0.078

[a] Frequency of impairments identified by both baseline comparison when impairment was not identified by normative comparison.
[b] Frequency of impairments identified by normative comparison when impairment was not identified by baseline comparison.
[c] Frequency of impairments identified by both normative and baseline comparison methods.
[d] Significant disagreement between baseline comparison and normative comparison.

Discussion

To our knowledge, our study is the first to compare the agreement between normative and baseline comparison evaluation methods. Our results indicate that, for most postconcussion outcomes, baseline and normative comparison methods identify the same impairments.

Neurocognitive impairments

We observed two contradicting results for the Simple Reaction Time Test 1, favoring baseline comparison, and Mathematical Processing, favoring normative comparison. Although we observed significant disagreement between the baseline and normative comparison methods when identifying impairments for Simple Reaction Time Test 1, we note that only a small overall percentage of impairments occurred for this neurocognitive domain. We speculate that most of these observed impairments are false-positives. The baseline comparison method identified 18 impairments in the simple reaction time that the normative comparison did not detect. These 18 athletes achieved a mean Simple Reaction Time Test 1 throughput score of 271.3 at baseline that was well above the normative mean. In contrast, the normative comparison method identified a significantly greater number of impairments than the individualized baseline comparison method for the Mathematical Processing subtest. Unlike Simple Reaction Time Test 1, the normative comparison method identified a large overall percentage of impairments for Mathematical Processing. Because people differ in their neurocognitive capabilities, some individuals may never be able to perform to a "normative" level. Some preexisting conditions have been shown to negatively influence neurocognitive scores,[2,9] and the normative mean may have been higher than some injured athletes were able to achieve at their baseline. These athletes would always be considered impaired relative to normative values, causing

clinicians to unnecessarily hold them from play when they may have truly recovered. Therefore, using a normative comparison method may lead to a more reasonable and possibly more conservative management of an injured athlete. Normative values are available for most commonly used concussion assessment tools and are often specific to gender, age, and sometimes sport.[8,18,21,31] Clinicians who choose to use normative data should be certain to use both gender- and age-matched values to ensure a valid point of comparison. Age-specific normative means were not used in this study because our normative and concussed samples did not differ largely in age.

The results of this study suggest that sports medicine professionals, without adequate resources and time, can mostly identify the same impairments using normative neurocognitive values. Using normative values would allow clinicians to bypass the lengthy process of establishing individualized baseline measures as part of a multifaceted concussion evaluation program. Because this is the first known study to explore these two comparison methods, additional research is necessary to further explore the utility of baseline testing. For many sports medicine professionals, computerized neurocognitive testing is the most time costly and expensive aspect of baseline testing. Sports medicine professionals who do implement baseline testing should ensure that environmental distractions are minimized,[27] athletes get adequate sleep the night prior,[38] and maximal extension of effort is encouraged.[1] At a very minimum, individual scores derived from baseline testing should be closely evaluated for validity. All clinicians, regardless of whether they use a neurocognitive test battery at baseline or just after injury, must make an effort to understand and stay familiar with the psychometric properties of the neurocognitive test battery that they use to ensure proper interpretation of postconcussion scores. Sound clinical judgment must be used when interpreting neurocognitive score, regardless of which comparison methods is used.

Our results may have been influenced by our decision to use a true normative sample by excluding athletes with a history of self-reported concussion, learning disabilities, or attention-deficit disorders from our normative sample but not in our concussed sample. Our concussed sample consisted of athletes with various preexisting conditions that may have influenced both their baseline and postconcussion scores. Having said this, we believe our sample is representative of a typical college varsity athletic population. Sports medicine professionals should identify athletes with diagnosed preexisting conditions known to negatively or positively affect neurocognitive and postural control scores and obtain individualized preseason baseline for these individuals or compare these results to condition- or group-specific norms if available.

Postural Control Impairment

We did not observe disagreement between comparison methods for measures of postural control on the SOT. These findings suggest that comparing the SOT composite score to normative values is an appropriate evaluation technique for identifying postural control impairments after concussion. The SOT used in our study is a sophisticated measure of postural control that is often unavailable to sports medicine professionals; however, similar postconcussion deficits have been identified on more sideline-friendly clinical tests such as the Balance Error Scoring System (BESS).[15,32] Future research is necessary to determine whether comparing postconcussion postural control measures from other clinical balance measures, such as the BESS, properly identifies impairments.

Graded Symptom Checklist Impairment

In this study, agreement existed between the normative and the baseline comparison methods for identifying athletes who were symptomatic immediately after injury. Although most athletes present with total symptom severity scores close to the normative mean, we maintain that sports medicine professionals should continue to complete the graded symptom checklist as part of a preseason baseline screening, if resources permit.[21] The graded symptom checklist is easily administered, neither time costly or expensive, and provides an individualized measure of self-reported symptoms. In addition, total symptom severity scores are not influenced by group administration,[27] could aid clinicians in identifying other preexisting pathologic conditions, and could easily be incorporated into a standard preparticipation examination. Thus, the demand placed on sport medicine professionals is minimal. Comparing postconcussion symptom scores to normative values may be difficult if an athlete states that he or she also experienced concussion-related symptoms before injury. Interviewing an athlete about his or her preconcussion symptom severity may result in underreporting.[17] Given the subjective nature of these data, we maintain that clinicians should administer a baseline graded symptom checklist to all athletes.

Practice effects

The goal of baseline testing is to allow participants to serve as their own postconcussion controls. However, practice effects may cause score inflation during serial administration of some concussion assessment tools.[19,28,35,37] Previous studies suggest that two administrations of ANAM,[19] two administrations of the SOT,[12] and three administrations of the BESS[7] may be necessary to offset practice effects and derive a stable baseline measure to be used during concussion assessment. Although we recognize the necessity of obtaining a valid comparison, these suggestions intensify the demand already placed on sports medicine professionals who are challenged to complete baseline testing. Although comparison to normative values collected during one period presents a similar problem, an arithmetic mean of a samples' performance provides a more stable measure. Normative values derived from samples that have undergone multiple administrations of the test battery may act as the most stable comparison points for athletes with concussion who undergo serial evaluations. Using the normative comparison method in conjunction with reliable change parameters may provide the most feasible model for concussion evaluation. The purpose of reliable change parameters is to provide a point range for which normal variation may occur while accounting for practice effect. Clinicians can conclude with a given probability that the decline is due to something other than chance (e.g., concussion). Using reliable change paramaters in this study allowed us to identify impairments while accounting for practice effects.

Limitations

The present study only used a computerized neurocognitive exam (ANAM), the sensory organization test, and a 15-item graded symptoms checklist. Future research is necessary to determine whether these same results apply to other neurocognitive, postural control, and symptom severity assessment tools. Agreement analyses for some outcome measures presented with low cell counts for disagreement between comparison methods. Although we accounted for this by using a McNemar exact test, this may explain why these results were not statistically significant. Our data included postconcussion scores from 258 athletes with concussion collected during a 10-yr period. Most athletes were identified as unimpaired by both normative and baseline comparison methods for all outcome measures. Among the athletes who were impaired, we mostly observed agreement between normative and baseline comparison methods. These two factors contributed to low cell counts for

disagreement because there were low overall impairments and few disagreements on those impairments. Because we observed two contradicting results (Simple Reaction Time Test 1 (favoring baseline comparison) and Mathematical Processing (favoring normative comparison)), we chose not to emphasize one comparison method as the gold standard. Future studies that seek to determine which method is superior might consider using multivariate classifiers to determine which comparison method best identifies lingering impairments after concussion.

These results only apply to those athletes who are evaluated during the immediate stage after their concussion. Future research is necessary to determine whether the normative and baseline comparison methods identify the same impairments using different concussion evaluation tools and during evaluations that take place after the immediate stage of injury. Both our normative and concussed samples consisted of male and female collegiate athletes. It is possible that comparing postconcussion scores to normative values derived from a different sample could influence impairment identification. Future research is necessary to determine how normative and baseline comparison methods agree for high school, professional, recreational, and other collegiate athletes.

Conclusions

Comparing postconcussion scores to normative values can be used after injury as part of a multifaceted evaluation for identifying acute neurocognitive and postural control impairments. Although previous emphasis has been placed on obtaining individual baseline measurements, our data suggest that, when using these concussion assessment tools, comparing postconcussion scores to normative values provides an appropriate and feasible evaluation approach. Clinicians should recognize that, regardless of which evaluation method they may use, return-to-play decisions should never be based solely on results from concussion assessment tools. A thorough clinical evaluation is paramount to safely managing concussion.

BACK TO TOP

Surgery

Haemorrhage control in severely injured patients

The Lancet
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Summary

Most surgeons have adopted damage control surgery for severely injured patients, in which the initial operation is abbreviated after control of bleeding and contamination to allow ongoing resuscitation in the intensive-care unit. Developments in early resuscitation that emphasise rapid control of bleeding, restrictive volume replacement, and prevention or early management of coagulopathy are making definitive surgery during the first operation possible for many patients. Improved topical haemostatic agents and interventional radiology are becoming increasingly useful adjuncts to surgical control of bleeding. Better understanding of trauma-induced coagulopathy is paving the way for the replacement of blind, unguided protocols for blood component therapy with systemic treatments targeting specific deficiencies in coagulation. Similarly, treatments targeting dysregulated inflammatory responses to severe injury are under investigation. As point-of-care diagnostics become more suited to emergency environments, timely targeted intervention for haemorrhage control will result in better patient outcomes and reduced demand for blood products. Our Series paper describes how our understanding of the roles of the microcirculation, inflammation, and coagulation has shaped new and emerging treatment strategies.

This is the second in a Series of three papers about trauma surgery

Introduction

Exsanguinating haemorrhage is the most common preventable cause of death after trauma.1 It causes approximately a third of the almost six million trauma deaths per year. About half occur before the patient reaches the hospital. All civilian and military trauma systems face the challenge of ensuring that bleeding patients receive timely and effective haemorrhage control.

Key messages

- Contemporary approaches to haemorrhage control combine early control of bleeding, management of coagulopathy, maintenance of critical perfusion, and management of the inflammatory response
- Early haemorrhage control minimises genomic activation and the harmful inflammation and coagulopathy caused by shock and resuscitation
- Topical haemostatic agents and interventional radiology are useful adjuncts to surgical control of bleeding
- Several pathogenic mechanisms contribute to trauma-induced coagulopathy, and the predominant mechanism changes during the clinical course
- Blind unguided protocols for blood component therapy in haemorrhagic shock and coagulopathy have safety and logistic concerns and trials of their effectiveness are underway
- Systemic treatments for coagulopathy might reduce the reliance on and demand for blood products
- Broad-acting drugs, such as tranexamic acid, that potentially affect inflammation, coagulation, and fibrinolysis, could modify responses to shock and improve outcomes

- In the future, treatments for haemorrhagic shock will be tailored to an individual's response by use of point-of-care tests and targeted therapies

Treatment approaches to haemorrhagic shock have transformed during the past two decades. From the Vietnam War until the 1990s, patients in shock received aggressive volume resuscitation with crystalloid solutions. More recent practices emphasise early administration of blood component therapies and tolerance of moderate hypotension until bleeding is controlled. These developments, which were consolidated in the Iraq and Afghanistan wars, are affecting the role of surgery in trauma patients. Previously, inability to prevent physiological exhaustion in exsanguinating patients meant that the primary focus in the operating theatre was damage control—ie, abbreviated initial surgery followed by ongoing resuscitation in the intensive-care unit. However, improvements in early bleeding cessation and haemostatic component resuscitation resulting in less physiological disturbance mean that completion of definitive treatment is often possible in the first operation.2

Much of our understanding of haemorrhage control is based on observational studies and preclinical research, which have characterised the physiological derangements of the shock state and the effects of treatment. This piecemeal collection of evidence supports contemporary approaches that aim to minimise dysregulated immune responses and harmful systemic effects of resuscitation.

Our Series paper describes how our knowledge of the microcirculation, inflammation, and coagulation has shaped new and emerging treatment strategies

Microcirculation in haemorrhagic shock

Intravital microscopy has enabled better understanding of the crucial role that the microcirculation plays in mediation of the response to haemorrhagic shock and the inadequacy of fluid resuscitation as the only treatment Haemorrhage and resuscitation induce cellular changes that are characteristic of ischaemia—reperfusion injury—eg, production of reactive oxygen species, activation of inflammation, and apoptotic cell death.

(A) In healthy capillaries, flow is facilitated by sufficient perfusion pressure and luminal diameter, fairly quiescent endothelial cell membranes, cellular deformability, an intact marginal acellular barrier, and balance between procoagulant and anticoagulant activity. (B) In acute haemorrhage, catecholamine-mediated arteriolar vasoconstriction causes capillary hypoperfusion and hypoxia, which in turn induce changes in membrane potential and ion distribution. Intracellular water content increases, resulting in capillary endothelial swelling and disruption of tight cell—cell junctions. Reduced perfusion pressure and endothelial swelling contribute to loss of capillary lumen, and obstruction by circulating cellular elements, debris, and activated platelets further impedes capillary flow. Erythrocyte deformability is decreased by hyperosmolarity, depletion of energy stores, and activation of the complement system, and can persist for hours after resuscitation. Trauma and inflammation induce surface expression of adhesion molecules on capillary endothelial cells, promoting rolling, adhesion, and eventual transmigration of activated leucocytes. Irreversible cellular and end-organ injury is caused by tissue hypoxia and anaerobic metabolism, leucocyte activation, and initiation of diffuse

apoptosis. Critical hypoxia in arteriolar smooth muscle cells eventually causes intracellular acidosis, mitochondrial dysfunction, and ATP depletion, leading to diminished contractility and loss of vasomotor function, signalling progression to decompensated and then irreversible shock.3 (C) In crystalloid resuscitation, clotting factors and other luminal components are diluted, and interstitial oedema and leucocyte—endothelial interactions are increased. Reperfusion can exacerbate inflammation and cause further injury through delivery of new activated leucocytes and generation of harmful free radicals and reactive oxygen species. (D) In haemostatic (or damage-control) resuscitation, blood loss, metabolic derangement, and fluid resuscitation are lessened, leading to less activation and disruption of the microcirculation, and less harm from reperfusion.

The immunoinflammatory response comprises both innate and adaptive immunity. In severe shock, a large range of inflammatory mediators, cytokines, and oxidants are almost instantaneously produced and released in large quantities. This dysfunctional and exaggerated response is the presumed cause of the secondary organ damage associated with multiple organ failure and death. Further harm is caused by prolonged suppression of adaptive immunity, leading to increased risk of nosocomial infection.

Suppression of adaptive immunity was presumed to follow the proinflammatory burst as a consequence of the patient's endogenous attempt to control this burst;5 however, this presumption has been proven incorrect.6 The response to critical injury is associated with a so-called genomic storm, with substantially altered expression of as much as 75% of the entire human genome; changes to innate and adaptive immunity occur simultaneously.7 The increase in genomic activity probably starts within minutes and is greatly increased within 6 h. The difference between complicated and uncomplicated recovery is defined by the patient's inability to achieve homoeostasis. Patients with uncomplicated recovery restore their genomic expression pattern to baseline within 2—3 days, whereas patterns remain altered and dysfunctional in those who develop complications.8 Minimisation of the severity and duration of the dysfunctional microcirculatory response in the first minutes and hours after injury might prevent complications. Early control of bleeding and haemostatic resuscitation, incorporating correction of coagulopathy and minimal volume replacement, are likely to improve outcomes at least in part by facilitating recovery in the microcirculation.

Early control of bleeding

In actively bleeding patients, prompt arrest of pronounced haemorrhage is the most important intervention to prevent death and reduce the harmful consequences of inflammation and resuscitation. Immediate compression of external wounds by a first responder or paramedic can substantially reduce volume loss. Limb tourniquets can control haemorrhage without high rates of adverse limb outcomes in patients with combat-related injuries, and new devices have been designed that can effectively apply direct pressure to difficult sites such as the groin. Early immobilisation of long-bone fractures and circumferential compression of pelvic fractures can also reduce blood loss.

Although surgical techniques and operative exposures for rapid control of bleeding have changed little in recent years, an increasing number of adjunctive agents and techniques intended to improve surgical effectiveness have become available. A range of topical haemostatic agents are available for the field and operating theatre. The ideal product would be fast-acting, non-antigenic, easily applied and removed, inexpensive, stable, and transportable, and would cause few side-effects.

Topical haemostatic agents

The results of a systematic review of six clinical studies and 37 preclinical animal trials showed that newer mucoadhesive agents and factor concentrators are better than older agents in the management of arterial and venous bleeding. Liquid and aerosol fibrin sealants are often used in elective and emergency surgery, and the results of a meta-analysis of 18 trials (1406 patients) showed their use led to reduced blood loss and need for transfusions compared with controls. Other modes of delivery, such as absorbable pads, have been designed for more effective delivery of procoagulant factors (eg, fibrinogen and thrombin) to the site of major bleeding. These have been trialled in elective surgery, but their safety and efficacy in coagulopathic trauma patients are unknown.

Angioembolisation and other endovascular techniques are increasingly used for rapid haemorrhage control. In major vascular injury, temporarily placed catheters for proximal balloon occlusion might allow time for surgical access, control, and vessel repair. Endoluminal stent grafts are an alternative to surgery, especially for the aorta and its major branches, and might be associated with less bleeding and tissue damage than is surgery.

Even in hypotensive patients, pelvic-fracture-associated arterial bleeding can be effectively treated with internal iliac artery embolisation or selective angioembolisation; gluteal necrosis occurs in approximately 5% of patients. However a substantial proportion of pelvic haemorrhage arises from veins and fracture surfaces, and debate persists about whether the best primary intervention is pelvic arterial embolisation or extraperitoneal packing and external fixation with secondary angiography. In the absence of substantial coagulopathy, most pelvic venous bleeding is self-limited when timely haemostatic resuscitation is provided.

In the acute management of bleeding liver injuries, the two main indications for angioembolisation are primary haemorrhage control in haemodynamically stable patients with CT evidence of active arterial bleeding and adjunctive haemorrhage control in patients with uncontrolled suspected arterial bleeding despite emergency laparotomy. Hepatic necrosis is the main complication and occurs in approximately 10% of patients.

Patients exsanguinating from splenic injuries are usually treated with splenectomy. Angiographic techniques directed at the spleen are generally used as an adjunct to non-operative management, and a systematic review of 33 studies (10 157 patients with blunt splenic injuries) showed that embolisation of the splenic artery was associated with lower operation rates and higher rates of splenic salvage than was observation alone in patients with high-grade injuries.

Combined angiographic and surgical approaches could provide advantages for exsanguinating patients with multiple injuries and especially for management of major vascular, high-grade liver, or pelvic bleeding. A new generation of operating theatre is emerging—eg, resuscitation with angiography, percutaneous techniques, and operative repair (RAPTOR) suites, which incorporate advanced interventional radiology and resuscitation capabilityies and minimise the need to move unstable patients between hospital departments.

Management of coagulopathy

Trauma-induced coagulopathy

Coagulopathy usually accompanies severe haemorrhage in trauma patients. As many as 25% of severely injured trauma patients have an established coagulopathy when they arrive in the emergency department. The incidence and severity of coagulopathy increase in hospital as bleeding continues and additional injuries are induced by infusions, transfusions, and surgical dissections. Coagulopathy is associated with early and late mortality and increased incidence of subsequent acute lung injury, multiple organ failure, and infections, which consequently increase ventilator requirements and the length of stay in intensive-care units and hospital.

Knowledge developments in the epidemiology, mechanisms, and consequences of coagulopathy in trauma have been central drivers for changes in management. Key factors include the description of trauma-induced coagulopathy and particularly identification of the early endogenous component of the disorder—ie, acute traumatic coagulopathy. These developments have focused management of coagulopathy on the very earliest stages of care, even before the patient reaches the hospital. Elucidation of the underlying pathophysiology and discovery of new mechanisms for coagulopathy have provided a platform for a large domain of translational research in trauma.

Several pathological mechanisms contribute to trauma-induced coagulopathy. Different mechanisms occur with different patterns of injury and physiology, and the predominant mechanism changes at different times in the clinical course of the patient. Acute traumatic coagulopathy is an early endogenous coagulopathy that is present in about one in four trauma patients and characterised by systemic anticoagulation and fibrinolysis. It seems to be driven by severe shock in the presence of some degree of physical tissue trauma. Although the underlying pathological process remains unclear, studies suggest that the protein C system could have a central role. Thus, acute traumatic coagulopathy seems to be a maladaptive response to overwhelming trauma. It is established within minutes of injury and has been identified at the scene of the injury in prehospital research studies. The presence of acute traumatic coagulopathy on arrival at hospital strongly correlates with early and late morbidity and mortality.

Historically, loss or consumption of coagulation factors was thought to be the central mechanism for traumatic coagulopathy. The degree and timecourse of reduction in procoagulant factor activity in trauma-induced coagulopathy remains unclear, but initially these factors do not fall to concentrations that would affect coagulation function. Human and experimental models suggest that concentrations of fibrinogen are the first to fall, but usually these concentrations remain higher than those that would previously have provoked replacement, until substantial transfusions of red blood cells have been received. Other procoagulant factors seem even less severely affected than fibrinogen.

Dilution of clotting factors undoubtedly contributes to trauma-induced coagulopathy and possibly becomes the dominant cause during transfusion of red cells in all patients without other coagulation therapy support. In some trauma systems, prehospital administration of substantial amounts of

crystalloid or colloid solutions contributes substantially to the incidence of coagulopathy on arrival at hospital. Even in the absence of crystalloid resuscitation, some amount of autoresuscitation in hypovolaemic states might contribute to the mild reductions in coagulation factors noted at this early stage. Clear-fluid or red-cell transfusions are likely to rapidly exacerbate dilutional coagulopathy.

Systemic hypothermia and acidaemia are classically thought to be central mechanisms of trauma-induced coagulopathy because of their inhibitory effects on procoagulant enzyme function. However, acidaemia seems only to affect protease function to an extent that could be clinically relevant when it is very severe (ie, blood pH <7·2). Similarly, only severe hypothermia is associated with important functional decreases in protease activity, although platelet aggregation and overall platelet function are reduced at temperatures lower than 35°C. Hypothermia and acidaemia are probably markers of the severity of the underlying shock state and therefore markers of the endogenous coagulopathy that results from systemic hypoperfusion. In an experimental model of trauma-induced coagulopathy, correction of acidaemia alone did not restore normal coagulation. Although severe acidaemia and hypothermia are thought to be important contributors to trauma-induced coagulopathy, their role now seems less central to pathogenesis.

Several other putative mechanisms that have yet to be clearly defined could contribute to trauma-induced coagulopathy, including inflammation, platelet dysfunction, and underlying genetic variations. Because inflammatory and coagulation pathways are closely connected, coagulation is likely to be affected in some way by massive systemic activation of innate immunity in severe injury. Platelets are central components of immunity and coagulation, but little is known about their function or contribution to trauma-induced coagulopathy. Platelet counts are well preserved initially in trauma, but preliminary evidence suggests substantial dysfunction in some trauma-induced coagulopathy states. Underlying genetic variations in coagulation are known to exist in the general population but their effects on traumatic haemorrhage are not yet known. Finally, patients taking anticoagulants for premorbid disease are increasingly common; such drugs might exacerbate and complicate all mechanisms of trauma-induced coagulopathy.

Blood component therapy

Blood component therapy in the form of plasma, platelets, and cryoprecipitate is the main treatment for trauma-induced coagulopathy. Recognition that coagulopathy occurs soon after injury has led to targeted haemostatic resuscitation strategies and massive transfusion protocols that promote early and aggressive treatment.

Retrospective studies have suggested that high-dose fresh frozen plasma and transfusions of red cells might be associated with improved survival compared with low-dose protocols, and clinical trials are imminent. Some transfusion protocols call for four-to-eight times more plasma transfusions than previously given. Although evidence from previous studies is promising, these approaches raise concerns about the supply and potential adverse effects of plasma. The provision of large amounts of thawed plasma to trauma patients within minutes of hospital arrival is challenging and potentially wasteful.

Freeze-dried and lyophilised plasma are logistically attractive options that are used in some military operations. Lyophilised plasma is derived from dehydrated liquid plasma and stored as a powder at room temperature and can be rapidly reconstituted with water and used at any phase of care,

including in prehospital settings. Its use ensures that transfusions in which the ratio of plasma to packed red blood cells is high are provided early to patients needing massive transfusion. Reconstituted lyophilised plasma maintains approximately 80% the factor activity of fresh liquid plasma and is better than thawed fresh frozen plasma.

A high-dose approach has also been recommended for platelet transfusions and fibrinogen replacement therapy. This approach is supported by evidence from cohort studies, which suggest that survivors of trauma haemorrhage received higher doses of these products than did non-survivors. These studies have several sources of bias and confounding, such as the relation between the speed and severity of haemorrhage and the logistic ability to provide these products rapidly. Furthermore, the success of these high-dose plasma regimens could be at least partly because of the associated reduction in clear fluid use and subsequent reduction in iatrogenic dilutional coagulopathy.

Several compelling reasons support a move away from blood component therapy for treatment of coagulopathy. The main concerns are the safety, demand, and logistics of supply. Little evidence exists to prove that blood component therapy can effectively correct coagulopathy in trauma. Standard treatment components, such as plasma, are still dilute in terms of clotting factors, and the transfusion of packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate in an equal ratio (1:1:1:1) produces a solution containing only half to two-thirds of the active elements in whole blood (haematocrit 29%, platelet count 87 000, coagulation activity 65%, and 750 mg fibrinogen). To postulate how blood-derived products would fully reverse coagulopathy is difficult, although continuous supplementation could prevent exacerbation of an existing coagulopathy.

Some of the components in plasma might be unnecessary for the treatment of trauma-induced coagulopathy, or at least for the treatment of specific mechanisms in a particular patient. Furthermore, some aspects of trauma-induced coagulopathy, such as fibrinolysis, are not treated by these compounds. These issues have prompted the search for new therapeutics that might be used as adjuncts or replacements for blood component therapy.

Systemic treatments

Fibrinogen concentrate has generated much interest as a targeted treatment in trauma-induced coagulopathy. Its use is common in Europe, where it is often given when thromboelastography shows evidence of reduced formation of fibrin networks. However, the evidence is from case series only, and clinical trials are urgently needed to assess the roles of fibrinogen concentrate in replacement of lost fibrinogen substrate and as a potential treatment for many forms of trauma-induced coagulopathy.

Procoagulant therapy has also been of interest. The results of clinical trials of recombinant factor VIIa in unselected patients who needed transfusion showed that factor VIIa had some effects on red-cell transfusion requirements but did not affect overall mortality; the largest trial so far was stopped early because of futility. Unfortunately, these studies did not assess the effect of recombinant factor VIIa on the coagulation system. They were also done at a time when trauma-induced coagulopathy was thought mainly to be a failure of procoagulant function. Use of recombinant factor VIIa has decreased substantially since these trials were published and damage control principles became popular. Whether

some forms of coagulopathy exist that might respond optimally to recombinant factor VIIa remains unknown. Other procoagulants, in particular prothrombin complex concentrates, continue to be of interest. Prothrombin complex concentrates have a definite role in reversal of the effects of warfarin in trauma patients, but their safety and efficacy in trauma-induced coagulopathy has yet to be assessed in clinical trials.

Mechanistic evidence suggests that fibrinolysis has a central role in acute traumatic coagulopathy, although overt hyperfibrinolysis is not often apparent with thromboelastography. A large international clinical trial of the antifibrinolytic tranexamic acid showed improved survival at 30 days compared with placebo in patients deemed at risk of bleeding, when the drug was given early in the clinical course. Tranexamic acid has subsequently been incorporated into major haemorrhage protocols in many institutions and research into its efficacy and optimum use is ongoing.

Maintenance of critical perfusion

The third goal of haemorrhage control is to maintain adequate perfusion before, during, and after arrest of bleeding and thereby minimise further cellular and organ injury. Perfusion and inflammation are closely related; inflammation is a consequence of hypoxic tissue damage during low-flow states, over-resuscitation, and the generation of reactive oxygen species during reperfusion.

Restrictive fluid resuscitation is standard care in many trauma systems. Early aggressive resuscitation of haemorrhagic shock with predominately saline-based regimens is associated with increased bleeding due to displacement of established clots, cardiac dysfunction, abdominal compartment syndrome, harmful inflammation, acute respiratory distress syndrome, multiple organ failure, and increased mortality.61 Key unresolved issues affecting fluid resuscitation include the degree and duration of hypotension and perfusion that can be tolerated, which fluid to use, and the optimum management of reperfusion once bleeding is controlled.

The US Committee on Tactical Combat Casualty Care and the UK military's Clinical Guidelines for Operations do not recommend fluid resuscitation in the field unless the patient has a diminished mental status or an absent radial pulse (equivalent to systolic pressure of approximately 90 mm Hg), in which case only small volume boluses are given until a palpable pulse returns. The degree of arterial hypotension that can be tolerated is unclear, partly because capillary perfusion can vary by a factor of 100 in healthy patients, and, in the pathological state, arterial pressure correlates poorly with capillary perfusion. The results of observational studies show that the use of vasopressors to support arterial pressure in hypovolaemic patients is associated with worse outcomes, probably through exacerbation of already diminished capillary perfusion.

Ischaemic stress is determined by the degree and duration of hypoperfusion. Although overresuscitation can exacerbate systemic inflammation, dilutional coagulopathy, and rebleeding, under-resuscitation is also harmful and can result in ischaemia-mediated inflammation and coagulopathy. A combination of both approaches might be ideal. Evidence from a randomised trial in a porcine model of haemorrhagic shock with and without blast injury showed that initial saline-based resuscitation to systolic pressures of 80 mm Hg for 60 min followed by resuscitation to 110 mm Hg led

to attenuation of markers of acute traumatic coagulopathy and systemic inflammation, improved tissue perfusion, reduced metabolic acidosis, and prolonged survival compared with sustained hypotensive resuscitation. Whether a similar strategy will be effective in human beings is unknown.

Because of the tendency of isotonic crystalloids to exacerbate coagulopathy and inflammation, the search continues for safer and more effective fluids. The ideal initial resuscitation fluid should have oxygen-carrying capacity, promote capillary perfusion, and not exacerbate coagulopathy or inflammation. Hypertonic saline seems to improve tissue perfusion through restoration of circulating intravascular volume and attenuation of postinjury microcirculatory oedema. It also seems to cause sustained attenuation of harmful inflammation in patients with shock by decreasing neutrophil activation, reducing serum concentrations of tumour necrosis factor, increasing concentrations of anti-inflammatory cytokines, and lessening the shock-induced norepinephrine surge. Unfortunately these benefits have not translated to improved outcomes in clinical trials. Based on our search and update of existing reviews, we did a meta-analysis of all trials that compared types of fluids for resuscitation in haemorrhagic shock; no type of fluid was better than another in terms of mortality endpoints.

Trials involving trauma patients with acute haemorrhagic shock were pooled in a fixed-effects meta-analysis to establish relative risk and 95% CI. See appendix for forest plots and references. *Not estimable because raw data were not obtained. However, the trial reported no difference in mortality between groups receiving dextran or lactated Ringer's solution.

In many centres, and some ambulance services, plasma or blood, or both, are used as the primary resuscitation fluids. Provision of blood before hospital arrival is logistically challenging. Various preparations, including frozen blood, have been developed. Storage lesion in packed red blood cells seems associated with increased morbidity and mortality, although the age of red cells at which these effects become clinically important is unclear because of the heterogeneity and limitations of completed studies. A large multicentre trial of old versus new red-cell transfusions is underway in stable critical-care patients; an equivalent trial is needed in major trauma resuscitation.

Fresh whole blood has been associated with improved survival compared with component therapy. The potential benefits of transfusion with fresh blood over banked blood are partly because of greater red-cell deformability and subsequent restoration of functional capillary density closer to baseline levels. However, the use of fresh blood is limited by the inability to store it for more than a few days and the inherent risks of infectious diseases if comprehensive screening tests cannot be completed. Fresh whole blood is used mainly in military operating theatres when adequate blood components are not available to provide transfusions with high ratios of plasma to red blood cells, platelets are not available, or patients are not responding to damage control resuscitation.

Management of the inflammatory response

Specific treatments to attenuate the inflammatory response to haemorrhagic shock are under investigation. They show the prevailing reductionist approach to the molecular basis of disease, and research has mainly focused on isolated components of the complex immunological processes. A

wide range of mediators, including cytokines, cell-membrane lipids, enzymes, and oxidants, have all been implicated and, in most cases, have been investigated in well controlled murine models designed to mimic human disease. Unfortunately, most interventions focused on single components or limited pathways have not achieved any reproducible clinical benefits so far. Because of the extensive redundancy and parallel efficiencies of the immune system, only a multipronged approach or a sufficiently broadly effective treatment seems likely to have a measurable clinical benefit.

Several approaches merit further investigation. Replacement of rapidly depleted antioxidants in critically ill surgical patients decreases the risk of organ failure (especially adult respiratory distress syndrome), length of stay, and overall mortality. Massive doses of vitamin C decrease microvascular leak and volume requirements after burn injuries, and lyophilised plasma reconstituted with vitamin C and water is better than fresh frozen plasma for haemorrhage control, suppression of dysfunctional inflammation, and antioxidant capacity in complex multiple-injury porcine models. Whether generic antioxidants or specific combinations of agents are necessary is unclear.

By inhibiting the conversion of plasminogen to plasmin, tranexamic acid could modulate plasmin-mediated inflammation, neurotoxicity, and fibrinolysis. The interaction between coagulation and several immune pathways makes plasmin an appealing target. Other broad anti-inflammatory approaches also seem encouraging—eg, inhibitors of intracellular signalling pathways through candidates such as p38. Similarly, to reverse the detrimental suppression of adaptive immunity, restoration of interferon-γ-dependent pathways with exogenous interferon seems appropriate to explore. Finally, therapeutic hypothermia is known to provide cellular protection and mitigate the harmful effects of ischaemia—reperfusion syndrome in cardiac surgery, but so far its use in trauma has been restricted to trials of limb ischaemia and traumatic brain injury. A research agenda is planned that encompasses mechanistic studies and investigations into the effects of hypothermia alone or in combination with novel cytoprotective agents on coagulation, drug metabolism and effect, and clinical outcomes.

Early and personalised interventions

Despite improved knowledge about the microcirculation, inflammation, and coagulation, treatment options are few and therapeutic targets are still poorly understood. In particular, treatment protocols do not factor in the coagulation state of patients or their likely response to transfusion. Diagnostic tests such as prothrombin and partial thromboplastin times are inaccurate, do not indicate coagulation functional status in trauma, and are not back in time to guide treatment during active haemorrhage and transfusion. Accurate and reliable point-of-care methods to predict, diagnose, and monitor bleeding patients and responses to treatment are needed. Such tests would allow rapid administration of products to patients who are most likely to benefit from them without the risk of exposing others to unnecessary risks.

To enable early initiation of treatment, clinical prediction strategies that identify patients likely to benefit from massive transfusion in civilian and military settings or those with acute traumatic coagulopathy have been developed on the basis of injury mechanisms, vital signs, and findings after

initial assessment. These strategies are reasonably accurate (area under receiving operating characteristic [AUROC] curve >0·8), have good negative predictive values, and have positive predictive values that represent acceptable over-triage rates for initiation of treatment.

The use of thromboelastography to guide early management of coagulation has received much attention. This method has proven accuracy for diagnosis of trauma-induced coagulopathy, potentially within 5 min of collection of a blood sample. Thromboelastography is also better able to describe the functional defects in coagulopathy than are other techniques. For example, thromboelastography has shown that acute traumatic coagulopathy is mainly a problem of reduced clot strength rather than delayed initiation or propagation of clot formation. However whether this technology can identify different underlying mechanisms of trauma-induced coagulopathy or effectively guide coagulation treatment during haemorrhage is unknown. These machines are also fragile and designed for elective laboratory environments, and although they are increasingly used in trauma patients, they are not ideally suited to the robust demands of emergency settings.

Future management of trauma-induced coagulopathy and the overall inflammatory response needs to move away from the blind, unguided replacement of blood products in patients who are bleeding. Based on our understanding of the microcirculation, inflammation, and coagulation in haemorrhagic shock, a therapeutic window probably exists, during which the stimuli of harmful inflammation can be controlled and the genomic response could be altered. Control of bleeding and minimisation of resuscitation helps remove the stimulus for inflammation. Early treatment with sufficiently broad agents followed by treatment tailored to an individual's biological response should then be the goal. The finding in the CRASH-2 trial that tranexamic acid is efficacious when given within 3 h of injury but might be harmful when given later after injury emphasises the time-critical nature of some interventions.

Haemorrhage control should be prioritised in prehospital settings and upon arrival at hospital. Improved diagnostic devices are needed to characterise specific defects of trauma-induced coagulopathy and assess response to treatment. New treatments based on novel targets should reduce the dependence on allogeneic blood donation and complex logistic supply chains.

As approaches to haemorrhage control evolve, some technologies and treatments that have been available since the 1950s—eg tranexamic acid, thromboelastography, and lyophilised plasma—are now being embraced. However, with the exception of tranexamic acid, little robust evidence exists for their usefulness, serving as a reminder that future strategies should be guided by large, robust clinical trials, which in turn need strong trauma research networks and thoughtful approaches to trauma trial design by researchers and regulatory authorities.

Search strategy and selection criteria

We searched Medline, Evidence-Based Medicine Reviews, Cochrane Central Register of Controlled Trials, and Embase with the core terms “hemorrhagic shock”, “wounds and injuries”, “blast injuries”, “fluid resuscitation”, and “trauma” and the keywords “damage control”, “fluid therapy”, “hemostatic agents”, “permissive hypotension”, “blood component”, “transfusion”, and “angioembolisation”. The appendix includes a full list of

search terms. We restricted our searches of these databases to studies published in English between Jan 1, 2006, and Nov 28, 2011. We examined reference lists of relevant publications and reviews to identify further reports. 18 569 citations were screened and 501 relevant full text articles were reviewed, including 216 reviews. We preferentially cited systematic reviews rather than individual trials throughout the paper. On May 31, 2012, we updated the searches of all Cochrane systematic reviews addressing fluid resuscitation in injured patients to identify recent trials for inclusion in the meta-analyses presented.

Contributors

RLG planned the review; led writing of the paper; coordinated evidence searches, interpretation of evidence, and illustrations; and drafted the abstract and sections about early control of bleeding, early targeted treatment, the introductory and concluding comments, and summary points. KB planned the review and drafted sections about coagulopathy and early targeted treatment. MS drafted sections about management of perfusion. ZJB drafted sections about microcirculatory changes and the figure. VP coordinated evidence searches, did the meta-analyses, interpreted the findings, and drafted the tables and supplementary materials. MN drafted the section about topical haemostatic agents. RVM drafted sections about inflammation and immunity. All authors revised and edited all sections of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

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BACK TO TOP

Advances and future directions for management of trauma patients with musculoskeletal injuries

The Lancet
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Summary
Musculoskeletal injuries are the most common reason for operative procedures in severely injured patients and are major determinants of functional outcomes. In this paper, we summarise advances and future directions for management of multiply injured patients with major

musculoskeletal trauma. Improved understanding of fracture healing has created new possibilities for management of particularly challenging problems, such as delayed union and non union of fractures and large bone defects. Optimum timing of major orthopaedic interventions is guided by increased knowledge about the immune response after injury. Individual treatment should be guided by trading off the benefits of early definitive skeletal stabilisation, and the potentially life-threatening risks of systemic complications such as fat embolism, acute lung injury, and multiple organ failure. New methods for measurement of fracture healing and function and quality of life outcomes pave the way for landmark trials that will guide the future management of musculoskeletal injuries.

This is the third in a Series of three papers about trauma surgery

Introduction

Musculoskeletal injuries are the most common reason for surgery in severely injured patients after blunt trauma. More than 70% of all patients with major trauma need at least one orthopaedic surgical procedure. Survivors with orthopaedic injuries, particularly injuries of the lower limb, have poor functional outcomes and quality of life. A population-based registry for major trauma in Victoria, Australia, showed that even without other major injury, 83% of patients with fractures of the pelvis or lower limb had not returned to pre-injury function 2 years after injury, 35% had not returned to work, and 30% still had moderate to severe persistent pain.

Key messages

- Orthopaedic injuries are major determinants of resource use and long-term outcomes in multiply injured patients
- Traumatic and surgical tissue injury drives the inflammatory response through endogenous danger molecules, even without haemorrhagic shock or infection
- Individually tailored timing of major fracture fixation can maximise the benefits of timely skeletal stabilisation and minimise the risks of systemic complications
- Increased understanding of the effects of systemic inflammation on fracture healing is needed
- Biological enhancements of fracture healing that are in development could be of particular benefit for large bone defects
- The evolving definition of fracture healing will provide better endpoints for future trials
- Patient-centred outcome measures show that patients have substantial long-term disability after major orthopaedic injury, and such measures should be included in clinical trials
- Comparative effectiveness research is needed to define the benefits of modern implants on patient outcomes

Despite much progress in the science of fracture healing and substantial investment in implant and device development, research-based advances that improve outcomes for patients with major orthopaedic injuries have been constrained by two important factors. First is an over-reliance on clinical examination and radiographic endpoints and insufficient attention to patient-centred outcomes. Despite the apparent objectivity of radiographic fracture union, the radiographic appearance seems to correlate poorly with important clinical outcomes, such as pain, function, and need for further surgery. Second is the paucity of high-quality studies. Fewer than 10% of clinical studies published in the top orthopaedic surgery journals were randomised trials. Of these trials, more than 80% were methodologically limited by small sample sizes, insufficient blinding, scarcity

of allocation concealment, and no independent assessment of outcomes. Randomised trials of fracture surgery have included on average 80 patients and many have been underpowered to detect potential real differences between treatment groups. The small size and low quality of many studies of fracture management has restricted the translation of preclinical studies to patient care and left many areas unresolved.

In this paper we address advances, present challenges, and future directions in management of musculoskeletal injuries in multiply injured patients.

Systemic inflammation, fracture healing, and timing of surgery

Major transfer of mechanical energy to the body stimulates the immune system. Haemorrhage and resuscitation, cell death, bacterial invasion, and pain can release proinflammatory elements with local and systemic effects. However, even without shock, substantial soft-tissue injury leads to cellular release of danger-associated molecular patterns (DAMPs) into the circulation, which activate innate immunity and result in systemic inflammatory response syndrome. Mitochondria are the main source of DAMPs. Because mitochondria are derived phylogenically from bacteria, the DNA and peptides released from the cytoplasm of injured cells can activate polymorphonuclear leucocytes through receptor-ligand bindings, which result in intracellular calcium flux, phosphorylation of protein kinases, and degranulation. Via this mechanism, which is absent in normal post-injury apoptosis, circulating mitochondrial DAMPs can cause widespread inflammation and secondary organ injury.

Injury severity, genetic predisposition, and surgical intervention are the key determinants of the magnitude of inflammatory response, which is mediated through (1) tissue damage and hypoxia causing release from necrotic cells of intracellular trauma alarmins, such as mitochondrial DNA and nuclear HMGB1 proteins; (2) transfusion of allogenic blood and blood components; (3) pain through putative descending neurological mechanisms; and (4) fat emboli causing local hypoxia, and platelet and endothelial activation. ALI=acute lung injury. DAMPs=danger-associated molecular patterns.

Fractures cause release of lipid particles and inflammatory cytokines into the circulation. Highly acidic lipid emboli lodge in vital organs, stimulating inflammation and causing fat embolism syndrome. The marrow of fractured long bones is also a potent source of proinflammatory cytokines. Concentrations of interleukin-6 in the marrow of fractured femora are 1000-times higher than those in the femora of patients undergoing major elective surgery. Concentrations in the medullary canal of patients with femoral fractures are 40-times higher than those in their corresponding serum, independent of fracture complexity and overall injury severity; the intramedullary concentration of interleukin-6 increases further during intramedullary nailing.

The effects of intense and often excessive local and systemic inflammation on fracture healing are poorly understood; however, findings from animal studies of fractures with concomitant chest injury showed an inhibitory effect of systemic inflammation in the early phase of fracture healing. This phase is itself an inflammatory process that has many cellular and humoral components of both systemic and local inflammation. Local and marginated macrophages are pivotal to creation of a stimulating humoral environment and derivation of osteoblasts and osteoclasts. Early innate immune responses (mediated through polymorphonuclear leucocytes) and early adaptive immune responses (mediated through T

and B lymphocytes) are inhibitory to bone healing. Animal models have shown that depletion of polymorphonuclear leucocytes and a scarcity of lymphocytes (knockout models) facilitate bony union, but the clinical significance of these findings is unknown for human beings.

Better understood is remote end-organ injury, which is mediated through trauma-associated systemic inflammation and exacerbated by resuscitation and surgical intervention. Incidence of acute lung injury, sepsis, and multiple organ failure has been reported to be up to 15% in patients with polytrauma managed by reamed intramedullary nailing. A patient's susceptibility to secondary organ damage is dependent on patient factors, injury characteristics, and resuscitation and treatment after injury.

Optimisation of outcomes and avoidance of systemic complications is partly dependent on timing of procedures to when patients are least vulnerable to the consequences of accentuated inflammation. The most important concerns for timing of acute surgical intervention are fixation of long bone fractures, pelvic and spinal stabilisation, and management of open fractures. The importance of timing became evident after Bone and colleagues' 1989 trial showed that early fixation of femoral fractures within 24 h in multiply injured patients led to fewer pulmonary complications and shorter stays in intensive care and hospital than did delayed fixation. In the early 1990s, severely injured patients were often resuscitated with large volumes of crystalloid and colloid fluids, and very early fixation in patients who were physiologically compromised compounded inflammatory complications caused by injury, resuscitation, and surgical stress, which led to excessive rates of acute lung injury, adult respiratory distress syndrome, and multiple organ failure. Since then, timing of fracture fixation has been affected by improved understanding of how orthopaedic injury and surgical repair affect patients with multiple injuries.

Panel

Factors influencing secondary organ injury

Modifiable factors

Surgical intervention

- Timing of fracture fixation
- Nature of intervention and magnitude of resultant physiological insult

Resuscitation strategies that minimise physiological insult, genomic activation, and inflammation

- Timely haemorrhage control
- Judicious blood transfusion
- Minimum crystalloid resuscitation

Non-modifiable factors

- Degree of tissue injury
- Overall pattern of injury

- Initial physiological deterioration
- Age
- Comorbidities
- Genetic predisposition

Resuscitation and timing of definitive fracture fixation cannot be addressed separately. Temporary fracture stabilisation with splints, traction, or external fixation provides pain relief and minimises blood loss, fat emboli, and further tissue damage. When tolerated, timely definitive stabilisation of fractures can reduce hospital stay, facilitate recovery, prevent joint stiffness, and enable early mobilisation, which indirectly decreases the chances of deep vein thrombosis and promotes fracture healing through potential physiological loading of the injured limbs.

The concept of damage-control orthopaedics promotes initial rapid skeletal stabilisation with external fixation, followed by intramedullary nailing after the systemic inflammatory response has subsided. To aid surgical decision-making, Pape and colleagues categorised patients with femoral fractures as stable, borderline, unstable, and in extremis on the basis of the pattern and physiology of their injury. Early total care was recommended for stable patients and damage-control orthopaedics for those who were unstable or in extremis. A prospective randomised controlled trial of borderline patients showed that early total care led to a higher incidence of transient acute lung injury than did damage control, with no increase in incidence of clinically significant adverse outcomes, such as adult respiratory distress syndrome, multiple organ failure, or death. These findings are reinforced by the experience of centres that routinely provide early total care to patients with borderline physiology, and whose patients have fewer days on a ventilator, earlier discharge from intensive care, and less infectious complications than did those enrolled in the trial.

Because major fractures of the pelvic ring are high-energy injuries that are frequently associated with haemodynamic instability, neurological deficit, and urogenital or rectal injuries, timing of skeletal stabilisation is dependent on the patient's overall physiological state and the local soft-tissue environment. Non-invasive pelvic binding—which can be provided by clamped bed sheets or proprietary devices—is widely accepted during transport and imaging. In patients with shock, control of extrapelvic and intrapelvic haemorrhage takes priority, with staged fracture management consisting of external fixation and subsequent definitive internal fixation. However, patients with fracture patterns amenable to minimally invasive internal fixation can safely undergo definitive skeletal stabilisation, alongside haemostatic resuscitation and rewarming, within hours of admission. Furthermore, early stabilisation of unstable thoracolumbar spine injuries in multiply injured patients is associated with reduced ventilator and intensive-care needs, shorter hospital stay, and less respiratory morbidity than late stabilisation, irrespective of neurological deficit.

Timing of surgery in open fractures has always been regarded as important to minimise the risk of infection, with most orthopaedic surgeons trained to aim for debridement and surgical stabilisation within 6 h of injury. However, findings from studies of patients with isolated fractures have not shown an association between precise timing of initial surgical debridement and incidence of deep infection, or delayed union or non union, provided surgery occurs within 24 h and antibiotic coverage is adequate. Little relevant data exists for polytrauma patients with open fractures, but initial debridement should be done as soon as the patient is taken to the operating room for other injuries.

Overall, research supports basing of the timing of acute long bone fixation on patient physiology and injury pattern, rather than on arbitrary timeframes. Pape and colleagues' physiological categories should be regarded as severity scores in which the score for any patient can be affected by clinical interventions. Modern resuscitation strategies that restrict fluid administration before haemorrhage control and simultaneously administer balanced blood and clotting factors help to reverse physiological deterioration in borderline patients. This approach leads to safe early total care in most major trauma patients with long bone fractures. Early does not necessarily mean immediate, it means as early as the patient's resuscitation makes total care possible, usually in 4—24 h. Frequent reassessment of the patient's physiology, including blood gases and coagulation status, is an essential part of physiological optimisation.

Biological enhancement of fracture healing and major bone defects

Biological enhancements of fracture healing are potentially useful in major musculoskeletal trauma in which high-energy transfer and soft-tissue injuries can result in large segments of exposed or devascularised bone. These fractures are at high risk for delayed union, non-union, and infection. Critical bone defects, defined as those that will not heal spontaneously, often need secondary interventions and subsequent surgery. According to Giannoudis' diamond concept, the core components of bone regeneration have four pillars: osteogenic cells, growth factors, osteoconductive scaffolds, and the mechanical environment.

Although growth factors or cell-based approaches in isolation could be used to manage small bone defects, large defects need the structural integrity that osteoconductive scaffolds provide. An ideal osteoconductive scaffold should have surface properties that optimise attachment, have a highly porous interconnected network in three dimensions that facilitates nutrient and metabolite transport and cellular proliferation and differentiation, have sufficient strength to achieve stable biomechanical conditions and vascularisation, and permit continuous tissue remodelling. Furthermore, to prevent failure, osteoconductive scaffolds should be biocompatible and biodegradable at rates that correspond to the formation, remodelling, and maturation of new tissue.

Prominent options for tissue engineering options for bone regeneration are emerging. The osteoconductive scaffolds can be adapted with osteoinductive properties by addition of cells, such as mesenchymal stem cells, periosteal cells, and osteoblasts, or with growth factors, such as bone morphogenic proteins. Mesenchymal stem cells are multipotent progenitor cells that can be isolated from mesenchymal tissues—eg, bone marrow, periosteum, and fat. These cells can expand in vitro and differentiate into various musculoskeletal tissues using defined growth factors or cytokines and specific culture conditions. Mesenchymal stem cells from the bone marrow are fairly easy to harvest by aspiration and have high osteogenic potential. Although these cells have been investigated extensively in vitro and in vivo in preclinical studies for their osteogenic capacity and potential for treatment of critical bone defects, this assessment has yet to be done in human beings. The bone morphogenic protein family of growth factors have high osteogenic potency and are already used to stimulate bone healing in small defects. Genetic treatments can be used to deliver growth factors with techniques that have reached clinical trials of arthritis management, but have not yet reached such trials of fracture healing. Bone formation can be induced by a recombinant adenovirus vector carrying complementary DNA that encodes the full amino acid sequence of human bone morphogenic protein-1. Autologous cells with large amounts of complementary DNA that encodes human bone morphogenic protein-2 were successfully used to reliably and rapidly heal a femoral segmental defect in rats. However, with clinical applications come potential risks of cancer stimulation and ectopic bone formation.

Because no in-vivo animal models are similar to human beings, investigations are underway with different species, various anatomical locations, bone enriched with growth factors, biomaterials, applied cells, and bioactive agents (eg, bone morphogenic proteins, platelet-rich plasma, and bone marrow). Although preclinical studies have increased understanding of cell biology and biomaterials for bone regeneration, the preclinical models still have to be optimised and piloted in human beings before the results can be broadly applied in patients with large bone defects.

Other new laboratory-based approaches to fracture healing might have application for large bone defects. Several pharmacological drugs target cell signalling cascades. Intermittent parathyroid hormone stimulates bone formation, but so far, no improvement in union rates have been noted in a murine model of open fracture. Teriparatide—a synthetic small-fragment recombinant human parathyroid hormone—has been used for fragility fractures in human beings, and low doses seem to shorten healing time compared with placebo, but this effect has not been noticed at higher doses. Other potential therapeutic targets are components of the Wnt signalling pathway, such as sclerostin or Dickkopf-1, which inhibit progression of osteoblast lineage and thus bone formation. Antisclerostin and anti-Dickkopf-1 antibodies have been developed and shown to promote callus mineralisation and improve mechanical properties, but more work is needed to confirm the biology and safety of these experimental treatments. Control of motion during bone healing might likewise affect healing efficiency. Findings from studies of advanced imaging technologies have shown that in a large bone-defect model, rigid bone fixation is preferable to early mechanical loading because early motion is associated with inhibited vascular invasion into the defect and reduced bone formation. The effects of low-intensity ultrasound, high-intensity focused ultrasound, and extracorporeal shockwave treatments on fracture healing have been assessed in 12 small and clinically heterogeneous trials that to date provide insufficient evidence for the routine use of vibrational treatments.

Adjuvant anabolic strategies might have a role in osteoporotic fractures, which are becoming increasingly common because the average age of major trauma patients is 10 years older than it was 30 years ago. In osteoporotic bone, fixation is less reliable, stiffness mismatch between the implant and bone greater, and patients have less capacity for specific treatment (eg, partial weight bearing) than do patients with normal bone density. Comminution in osteoporotic bone is particularly challenging, especially in elderly patients and in regions of decreased vascularity, which take longer to heal than do well-vascularised regions. For comminuted periarticular fractures in osteoporotic bone (especially around the elbow and knee), which can be impossible to reconstruct, prosthetic replacement might better facilitate functional recovery.

Improvements to the evidence base for clinical research of orthopaedic trauma

Limitations in clinical research of orthopaedic trauma have not prevented innovation and uptake of new techniques and devices. For example, plates with locking screws that provide angle-stable fixation and stabilised fracture fragments have fundamentally changed strategies for surgical treatment in the past decade. An increasing inventory of anatomically contoured, low-profile, fragment-specific plates is available to aid minimally invasive techniques of insertion through incisions away from the fracture, and anatomical restoration of the joint surface in complex periarticular fractures with optimum reconstruction of the length, axis, and rotation of the joint block.

Although modern plates, locking screws, and percutaneous insertion techniques are popular, few randomised trials have investigated their effectiveness compared with alternative techniques. Published trials have not shown statistically significant or clinically important benefits or harms from locking plates compared with intramedullary nailing of the femur and tibia, or compared with other approaches, including closed reduction

and casting of distal radius fractures. The remaining published literature does not show a clear benefit of locked plates compared with alternative methods of fixation.

As implants continue to evolve and new products emerge, comparative effectiveness research will be needed to define which treatment works best, for whom, and in what circumstances. In the USA, substantial investment in such research is based on the need for decisions about costly or potentially harmful interventions to be informed by evidence about benefits and harms compared with existing alternatives. The research should include pragmatic and well-powered trials in diverse practice settings, better post-market monitoring of intended and adverse outcomes than exists presently, and a focus on clinically meaningful endpoints.

Endpoints of fracture healing

Some patients need reoperation for delayed fracture union or non-union, especially in cases of severe open fracture or large bone defects with postoperative fracture gap; however, definitions of delayed union and non-union have varied greatly. Determination of fracture union is most commonly based on serial clinical and radiographic assessments, and healing is often appraised by assessment of orthogonal radiographic views for bridging by fracture callus, absence of fracture lines, and cortical continuity across the fracture ends. Radiographic fracture healing is often defined as the presence of bridging callus on at least three of the four cortices (anterior, posterior, medial, and lateral).

How good plain radiography is at showing actual bone healing is dependent on the correlation between radiographic findings and other meaningful measurements. Experimental data suggests that the number of cortices bridged by callus is a strong predictor of union strength at maximum torque (correlation coefficient *r* 0·80), and that moderate correlation exists between radiographic healing and stiffness at the fracture site (*r* 0·59). Reliability of radiographic assessment—ie, the ability of independent clinicians reviewing the same radiographs to agree on the level of healing of a fracture—has improved with standardised scales, such as the Radiographic Union Scale for Tibial Fractures (RUST), which assesses the anteroposterior and lateral views of the fracture. The extent of callus bridging and visibility of the fracture line is scored for each of the four cortices, with total scores ranging from four points (no healing) to 12 points (complete healing). RUST has shown high interobserver and intraobserver agreement (intraclass correlation coefficient *r* 0·86 and 0·88, repsectively) at several different stages of fracture healing.

Fracture micromotion is a useful indicator of healing, but is largely undetectable with plain radiography. Radiostereometric analysis, also known as roentgen stereophotogrammetric analysis, improves the precision of radiographic assessments with highly accurate three-dimensional measurements in vivo over time with sequential radiographs. Micromotion varies on average between 1·5 mm and 3·2 mm during the healing of distal radius fractures and tibial osteotomies, and between 6 mm and 12 mm during that of trochanteric fractures. Widespread use of fracture micromotion to assess healing is limited by present scarcity of the necessary technology.

Although radiographic approaches, whether conventional or radiostereometric analysis, are the usual basis for assessments of fracture healing, they are insufficient without supportive clinical correlates. Clinical assessment of fracture healing is largely subjective with no gold standard, and is an amalgam of radiographic and clinical impression. In a review of 77 clinical studies that used clinical criteria to define fracture union, the three most common criteria were absence of pain or tenderness when weight bearing, or on palpation or examination, and the ability to bear weight.

Weight bearing could be an objective measure of healing of tibial fractures that are treated by external fixation because weight-bearing ability increases with time after fracture and correlates well with bone stiffness.

The Functional Index in Trauma (FIX-IT) score provides a simple standardised approach to assess weight bearing and pain in lower-limb fractures. FIX-IT is a 12-point functional score (minimum zero, maximum 12 points) with two primary domains: weight bearing status (six points) and pain at the fracture site (six points). Early assessment of this score by five content experts showed high face and content validity, and high overall inter-rater reliability (0·88, 95% CI 0·83—0·92). FIX-IT correlates well with validated measures of physical function, such as the 36-item Short Form Health Survey (SF-36) physical component summary score (*r* 0·68—0·77).

Patient-centred outcomes

Declining mortality after major trauma, recognition of the need to measure quality of survival, and poor correlation between clinical or radiographic findings and patient-reported outcomes, such as pain, have resulted in a recent shift to definition and measurement of patient-centred outcomes—ie, outcomes that are most important to patients. WHOs International Classification of Functioning, Disability and Health (ICF) and the List of All Deficits (LOAD) framework describe individual, social, and societal effects that are relevant to major trauma patients with orthopaedic injuries, and provide guidance about domains that are important to measure.

Many patient-reported outcomes that are specific to body region and relate to items of the ICF and LOAD frameworks are available for orthopaedic injury, but interpretation of these outcomes in patients with multiple injuries is challenging. Such outcomes—eg, shoulder and wrist scores—usually have some items that are related to activities of daily living, pain, work, and social and leisure activities, but are designed to contain items that are relevant to only disease or region. The key advantage of this specificity is sensitivity to even small changes, and therefore, an increased ability to detect any differences between treatment groups. However, use of specific outcomes is complicated in patients with multiple trauma for whom measured disability might be partly caused by injuries to other body regions. To distinguish the effect of specific orthopaedic injuries from other orthopaedic and non-orthopaedic injuries (eg, head injury) with measures of disease-specific or region-specific outcomes might not be possible.

General health-related quality of life or health-status measures, such as SF-36 or SF-12, WHO's Disability Assessment Schedule II (WHODAS II), and the EuroQol Group's EQ-5D, are less specific than outcome measures related to disease or region, but might be overall more relevant to patients with multiple trauma because they are designed to be generic methods and include items related to social, mental, and role functioning. These methods capture patients' experiences and expectations of their injuries, and broad aspects of health and wellbeing. Because the measures should be collected from the patient themself, they are of restricted use in patients with pre-existing or injury-related cognitive and communication deficits. Nevertheless, their widespread use for different disorders allows for the comparison of outcomes and cost-effectiveness of interventions between many types of injury or disease.

When best to measure patient-reported outcomes is dependent on the time course of recovery to the point of return to pre-injury function or plateau. Little consensus exists about the timing of follow-up of patients with multiple injuries. Some studies have reported no improvement in

major trauma outcomes at 12-months after injury and others have shown that major trauma patients with orthopaedic injuries continue to improve beyond 12 months. Whereas orthopaedic injuries have been associated with poor outcomes 10 years after major trauma, the time at which outcomes stabilise cannot be ascertained in studies that measure outcomes at one time point alone. Little evidence exists for the need to follow-up patients with orthopaedic trauma beyond the short to medium term (1—2 years after injury), and in research, investigators should consider the effect of long-term follow-up on follow-up rates, responder bias, and resources.

Several studies have emphasised the prolonged effect of spinal column and lower-limb injuries on function and health-related quality of life, particularly up to 10 years after injury. Emerging data from the population-based Victorian State Trauma Registry showed that the presence of any orthopaedic injury reduced the odds of functional recovery 1 year after injury. In patients with head injuries, the odds of any functional improvement in the first year were reduced by 30% if orthopaedic injuries were present. In patients with no head injury who had sustained lower-limb injuries, with or without spinal column injury, the age-adjusted and sex-adjusted physical health scores on SF-12 were well below than the population norms and only marginally better than for spinal cord injury.

Sows the pooled standardised mean differences (95% CI) of the Short Form (SF)-12 physical and mental-health summary scores at 24 months after injury for each major trauma group, excluding patients with head injury. Mean differences show the degree of deviation from the population norm by adjustment of scores for age and sex. A difference of zero suggests no difference to population norms; less than zero represents SF-12 scores lower than population norms. Data are from the Victorian State Trauma Registry 2007—2010, which includes information about 2409 major trauma patients without head injury who survived to hospital discharge; 68% of patients had sustained orthopaedic injuries and 80% were followed-up at 24 months. Major trauma is defined as patients with an Injury Severity Score of less than15; those who died after injury; those who had urgent surgery for intracranial, intrathoracic, or intra-abdominal injury, or fixation of pelvic or spinal fractures; and those who were admitted to intensive care for more than 24 h and needed mechanical ventilation. PCS=physical component summary score. MCS=mental-health component summary score.

Standardised outcome measures and routine collection of patient-reported outcomes are needed to monitor and assess present and new treatment approaches and to support clinical trials and evidence-based care. Collection should continue throughout recovery to increase understanding of when outcomes stabilise, and to inform trial and study design.

The future of research in polytrauma patients with orthopaedic injuries

Patients with multiple injuries present substantial challenges for coordination of clinical care. Orthopaedic injuries are important determinants of short-term and long-term patient outcomes, as are treatment decisions made by the orthopaedic surgeon. Modern orthopaedic and trauma care entails each patient receiving the best treatment at the right time. As the range of potential treatment options expands, surgeons will be increasingly dependent on research that addresses important questions, is sufficiently powered to answer them, and uses meaningful primary outcome measures.

The benefits of more individualised approaches to the timing of surgery and adjuvant treatments might soon become apparent, taking into account injury patterns, specific aspects of physiological compromise, the immune response, and genetic polymorphism. For example, clinical decision-making has not routinely incorporated information about the immune response with inflammatory markers that are associated with injury severity, the magnitude of surgical interventions, and clinical outcomes. Collaborative research networks, and further research about fracture healing, immune monitoring, genetic mapping, DAMPs, and shock resuscitation will be central to such advances.

Furthermore, the novel innovations and laboratory-based experimental treatments discussed in this paper will only become available for routine clinical use via the sorts of robust trials that have already transformed specialty areas, such as cardiovascular medicine, osteoporosis, and critical-care medicine. Dedicated surgeon-scientists, development of global networks and coordinating centres for trauma and fracture trials, improved availability of centres for coordinating trauma trials, and improved funding sources are setting new benchmarks in surgical research. Large trials of fracture management, such as the Study to Prospectively evaluate Reamed Intramedullary Nails in Tibial fractures (SPRINT), which analysed 1226 patients, and the study of Fluid Lavage of Open Wounds (FLOW), which aims to analyse 2280 patients, are challenging the dogma that surgical trials are inevitably small single-centre initiatives. Innovative studies of novel systemically-administered biological agents are underway to optimise outcomes in fracture healing, function, and quality of life. These and other important trials will transform the care of trauma patients with musculoskeletal injuries in the next decade by informing practice with sound actionable evidence.

Search strategy and selection criteria

We searched Medline, evidence-based medicine reviews, Cochrane Central Register of Controlled Trials, CENTRAL, and Embase from Jan 1, 2006 to March 31, 2012, using the core terms “orthopedics”, “fracture”, “orthopedic procedures”, and “surgery” in combination with keywords for the following topics: fracture healing, tissue engineering and orthobiologics, timing of fracture fixation, open fractures, periarticular fractures, pelvic fractures, spine fractures, large bone defects, osteoporotic fractures with major trauma, orthopaedic trauma implants, orthopaedic trials, and outcomes. We focused on English-language articles. We scanned reference lists of relevant publications and reviews to identify further relevant citations. 18 102 citations were screened, 4102 were reviewed in abstract and full text, and 423 were relevant; representative publications were chosen to substantiate our interpretation of this evidence. We preferentially referred to systematic reviews when available.

Contributors

ZJB planned the review, selected topics, interpreted evidence, and drafted the abstract and key messages, sections relating to inflammation, fracture healing and timing of surgery, the panel on secondary organ injury. MKR performed search and selection of citations, co-ordinated referencing, and drafted sections relating to biology of fracture healing. RLG planned and coordinated the review and the evidence searches, drafted sections relating to introduction and future directions, and led content editing. PMK drafted sections on new laboratory-based approaches to fracture healing and table 2. IAH drafted sections on implants, surgical techniques and timing of surgery in open fractures. MAS drafted sections on major bone defects and osteoporotic bone fractures. BJG drafted sections on patient centred outcomes. MB drafted sections on fracture healing endpoints, fracture trials and challenges in orthopaedic trauma research. All authors revised and edited all sections of the manuscript.

The course of fracture healing consists of overlapping stages of interplay between tissue formation and resorption and other progresses, including initial haematoma and inflammation, subsequent repair processes, intramembranous and endochondral bone formation, and remodelling (left side, top to bottom). The initial proinflammatory response of the haematoma is characterised by hypoxia and low pH and involves several inflammatory cell types at the fracture site. During the subsequent repair process mesenchymal stem cells are recruited to the fracture site by growth factors and cytokines. These cells mainly derive from the periosteum, but are likewise recruited systemically and derive from surrounding tissues (eg, muscle). Beginning ingrowth of a vascular network is important for proper vascularisation of the fracture gap. Mesenchymal stem cells start proliferating and differentiating into osteoblast lineages, which build woven bone (collagen type 1), and chondroblast lineages, which build cartilage (collagen type 2). The final stage of remodelling is characterised by a balance of hard callus resorption by osteoclasts and lamellar bone deposition by osteoblasts. The right side of the figure lists available clinical interventions, which target distinct mechanisms during bone repair, disturbed bone healing, and management of critical bone defects.

Conflicts of interest

MB has received research funding and fees for consultancy from Smith and Nephew, Stryker, DePuy, Amgen, and Eli Lilly. All other authors declare that they have no conflicts of interest.

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BACK TO TOP

Transforming growth factor beta1 inhibits bone morphogenic protein (BMP)-2 and BMP-7 signaling via upregulation of Ski-related novel protein N (SnoN): possible mechanism for the failure of BMP therapy?

BMC Medicine

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Background

Bone morphogenic proteins (BMPs) play a key role in bone formation. Consequently, it was expected that topical application of recombinant human (rh)BMP-2 and rhBMP-7 would improve the healing of complex fractures. However, up to 36% of fracture patients do not respond to this therapy. There are hints that a systemic increase in transforming growth factor beta1 (TGFbeta1) interferes with beneficial BMP effects. Therefore, in the present work we investigated the influence of rhTGFbeta1 on rhBMP signaling in primary human osteoblasts, with the aim of more specifically delineating the underlying regulatory mechanisms.

Methods

BMP signaling was detected by adenoviral Smad-binding-element-reporter assays. Gene expression was determined by reverse transcription polymerase chain reaction (RT-PCR) and confirmed at the protein level by western blot. Histone deacetylase (HDAC) activity was determined using a test kit. Data sets were compared by one-way analysis of variance.

Results

Our findings showed that Smad1/5/8-mediated rhBMP-2 and rhBMP-7 signaling is completely blocked by rhTGFbeta1. We then investigated expression levels of genes involved in BMP signaling and regulation (for example, Smad1/5/8, TGFbeta receptors type I and II, noggin, sclerostin, BMP and activin receptor membrane bound inhibitor (BAMBI), v-ski sarcoma viral oncogene homolog (Ski), Ski-related novel protein N (SnoN) and Smad ubiquitination regulatory factors (Smurfs)) and confirmed the expression of regulated genes at the protein level. Smad7 and SnoN were significantly induced by rhTGFbeta1 treatment while expression of Smad1, Smad6, TGFbetaRII and activin receptor-like kinase 1 (Alk1) was reduced. Elevated SnoN expression was accompanied by increased HDAC activity. Addition of an HDAC inhibitor, namely valproic acid, fully abolished the inhibitory effect of rhTGFbeta1 on rhBMP-2 and rhBMP-7 signaling.

Conclusions

rhTGFbeta1 effectively blocks rhBMP signaling in osteoblasts. As possible mechanism, we postulate an induction of SnoN that increases HDAC activity and thereby reduces the expression of factors required for efficient BMP signaling. Thus, inhibition of HDAC activity may support bone healing during rhBMP therapy in patients with elevated TGFbeta serum levels.

BACK TO TOP

UK Paraplegic Woman First to Take Robotic Suit Home

Reuters
Chris Wickham
4 Sep 2012

A British woman paralyzed from the chest down by a horse riding accident has become the first person to take home a robotic exoskeleton that enables her to walk.

The exoskeleton is activated by the wearer tilting their balance to indicate the desire to take a step. It supports the body's weight and also allows the person to go up or down stairs, as well as sit or stand up independently.

Although bionic exoskeletons have been used in hospitals and rehabilitation centers, Claire Lomas is the first to take the ReWalk suit home for everyday use.

Lomas earlier this year used the suit to complete the London Marathon in 17 days, raising about 200,000 pounds ($317,900) for research into spinal damage, and she was recently given the job of lighting the Paralympic cauldron in Trafalgar Square.

But she said more routine activities are equally gratifying.

"One of the best experiences was standing at a bar," she said. "To be stood up in this means everything to me."

Larry Jasinski, chief executive of Argo Medical Technologies, the company that developed the suit, told Reuters he was initially nervous about backing the marathon bid because the suit was still being tested but Lomas said it held up well.

"The suit was really reliable in the worst weather and I got there 17 days later," she said.

It costs 45,000 pounds ($71,500) and although clinical studies are ongoing that could back a case for health authorities to fund purchases of the device, the developers argue that savings on the treatment of ailments related to inactivity could offset the cost.

Paralyzed people are prone to pressure sores and a loss of bone density, as well as problems linked to poor posture. Jasinski said estimates on the cost of treating these range from $500,000 to $3 million over a patient's life.

The company estimates that of the SIX million wheelchair users in the U.S. and Europe, around 250,000 could be suitable for using the ReWalk device.

A report in 2010 by U.S. firm ABI Research forecast the market for this technology could be worth $320 million within 10 years.

In the meantime, says Jasinski, the U.S. and Israeli military have shown an interest for use by injured soldiers.

Research into exoskeletons goes back 50 years but advances in software management systems and sensors have only recently made them practical.

Argo, which is backed by Israeli venture capitalists SCP Vitalife and Israeli Healthcare Ventures, is working on a similar device for quadriplegics, as well as a brain interface that could allow more intuitive 'thought control' of the exoskeleton.

Although Jasinski says this is still years away, scientists have recently unveiled devices that can be controlled in real time by thought using advanced brain scanning.

Others are working on materials that can interact with human nerves and tissue that could eventually lead to prosthetics that are fused with the body and controlled directly by the nervous system.

In June, a team at Maastricht University in the Netherlands unveiled a device that uses functional magnetic resonance imaging, which monitors blood flow in the brain, to allow people to spell out words simply by thinking of each letter.

Another experiment reported in July saw fMRI used by a man at Bar-Ilan University in Israel to control the movements of a robot thousands of miles away at Beziers Technology Institute in France.

Lomas said that after her accident, she rejected pleas from doctors to give up on the idea of using her legs, saying that as a young, active woman before her 2007 accident, "I didn't want to have a big stomach and spindly legs."

Since the accident she has got married, had a child, and next year plans a London-to-Paris bicycle ride using a so-called Functional Electrical Stimulation bike that artificially stimulates the paralyzed rider's own muscles to propel it along.

BACK TO TOP

Cognitive Dysfunction and Anxious-Impulsive Personality Traits Are Endophenotypes for Drug Dependence

American Journal of Psychiatry
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Objective Not everyone who takes drugs becomes addicted, but the likelihood of developing drug addiction is greater in people with a family history of drug or alcohol dependence. Relatively little is known about how genetic risk mediates the development of drug dependence. By comparing the phenotypic profile of individuals with and without a family history of addiction, the authors sought to clarify the extent to which cognitive dysfunction and personality traits are shared by family members—and therefore likely to have predated drug dependence—and which aspects are specific to drug-dependent individuals.

Method The authors assessed cognitive function and personality traits associated with drug dependence in stimulant-dependent individuals (N=50), their biological siblings without a history of drug dependence (N=50), and unrelated healthy volunteers (N=50).

Results Cognitive function was significantly impaired in the stimulant-dependent individuals across a range of domains. Deficits in executive function and response control were identified in both the stimulant-dependent individuals and in their non-drug-dependent siblings. Drug-dependent individuals and their siblings also exhibited elevated anxious-impulsive personality traits relative to healthy comparison volunteers.

Conclusions Deficits in executive function and response regulation as well as anxious-impulsive personality traits may represent endophenotypes associated with the risk of developing cocaine or amphetamine dependence. The identification of addiction endophenotypes may be useful in facilitating the rational development of therapeutic and preventive strategies.

Figures in this Article

Drug dependence is a major contemporary public health issue (1) involving harmful effects not only for the affected individuals but also for their families, communities, and society as a whole (2). Community-based family studies indicate that relatives of drug-dependent individuals have eight times the risk of developing drug abuse disorders themselves (3), but the role of preexisting vulnerability in addiction remains poorly understood.

Twin and adoption studies have produced compelling evidence for genetic influences in the development of drug dependence (4–7) but have also shown that the high prevalence of drug dependence within families may be caused by environmental factors or interactions between environmental and genetic influences (8, 9).

The concept of endophenotypes offers a useful strategy for elucidating the underlying factors that render an individual vulnerable to drug dependence. Endophenotypes have been defined as quantitative traits that are intermediate between the predisposing genes (genotype) and the clinical symptoms (phenotype) of a complex disorder. According to the criteria outlined by Gottesman and Gould (10), endophenotypes are quantifiable traits that are 1) associated with the disorder; 2) genetically determined; 3) largely state independent (i.e., they should manifest in periods of health and during acute illness); 4) cosegregate with the disorder within families; and 5) overrepresented in nonaffected family members relative to the general population. The identification of familial vulnerability markers for drug dependence may provide a scientific basis for the development of effective preventive and therapeutic strategies for individuals at risk.

In our study, we used an endophenotype strategy to identify putative cognitive, emotional, and personality markers of stimulant dependence vulnerability. Addiction is largely subserved by brain circuits that have also been associated with executive control (11, 12), specifically response inhibition (13, 14), mental planning (15, 16), working memory (17–19), and attentional control (20–22). These neural networks were possibly dysfunctional before the stimulant abuse, rendering individuals vulnerable for addiction. Alternatively, cognitive function may also deteriorate in response to chronic stimulant abuse, a proposal supported by preclinical studies showing that prolonged stimulant abuse leads to deficits in neuropsychological function (23, 24). Moreover, interactions between both predisposing and neurotoxic effects on cognitive function are equally conceivable.

Stimulant dependence often co-occurs with anxiety and affective disorders (25, 26), and affect-related psychopathologies are also common in families with substance abuse problems (27). Depressive symptoms have been associated with both intoxication and withdrawal from various addictive drugs (28, 29), possibly resulting from drug-induced changes in monoamine neurotransmission (29, 30). Growing evidence also points to the role of personality traits, attitudes, and demographics in elevating the risk of drug dependence (31, 32). Both impulsivity (33, 34) and sensation-seeking (35) traits have been prospectively associated with a higher risk of drug abuse and addiction. Psychological constructs such as self-efficacy (36, 37), which describes the confidence in being able to achieve a certain outcome or the perceived control that a person has over life events (38–40), may mediate the risk of problem drug abuse.

We compared the cognitive and emotional functioning and the personality traits of stimulant-dependent individuals, their non-drug-dependent siblings, and healthy unrelated comparison volunteers. The rationale for the focus on stimulants is based on relatively high heritability estimates for stimulant dependence (41). The recruitment of sibling pairs was pragmatically advantageous, but the design has limited power for making inferences about the etiology of personality and cognitive abnormalities evident in both the dependent individuals and their siblings when compared with a twin design. We can say that these represent abnormal familial vulnerability factors (i.e., they are shared by members of the

same family), but we cannot discriminate genetic from common environmental causes for their emergence. Nevertheless, the distinction this affords between predisposing factors and drug-induced changes is still valuable. We hypothesized that deficits in executive control function and impulsive personality traits represent an endophenotype for drug dependence and would therefore be identified not only in the drug-dependent individuals but also in their siblings.

Participants

Participants were recruited from treatment services and media advertisements; recruitment figures and participation details are shown in the data supplement that accompanies the online edition of this article. Sibling pairs were included if three conditions were met: 1) they had the same biological parents; 2) one sibling satisfied DSM-IV-TR criteria for cocaine or amphetamine dependence; and 3) the other sibling had no personal history of substance dependence (other than nicotine). All participants who enrolled in the study underwent a screening that included semistructured interviews to ascertain history of drug use, physical health (including signs of acute intoxication and withdrawal), mental health as assessed with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (42), and demographic characteristics.

Exclusionary criteria, applied for all groups, were a lifetime history of a psychotic disorder or a history of a neurological illness, neurodevelopmental disorder, or traumatic head injury. Healthy comparison volunteers did not have a personal or family history of drug or alcohol dependence. Participants had to be 18–55 years old and able to read and write in English. The study protocol was approved by the Cambridge Research Ethics Committee and written informed consent was obtained from all volunteers before study enrollment.

All drug-dependent individuals (N=50) met DSM-IV-TR criteria for stimulant dependence (94% for cocaine and 6% for amphetamines). The majority (76%) were currently enrolled in a drug treatment program, and all but five were actively using stimulant drugs as verified by urine screens. On average, they had been using stimulants for 16 years (SD=6.4) starting at age 16 (SD=2.8), and they last used them 3 days before testing began (SD=4.7; range=0.5–28 days); without the five drug users who were abstinent, stimulants were last used 1.7 days before testing (SD=2.0), which is consistent with the 72-hour detection window for stimulants. On the Obsessive-Compulsive Drug Use Scale (43), participants indicated moderate levels of stimulant-related compulsivity (mean score=23.7; SD=9.5). Half of the drug-dependent sample also met DSM-IV-TR criteria for dependence on other substances (54% for opiates, 24% for alcohol, and 8% for cannabis). The drug-taking experiences and the use of alcohol were notably low in the sibling and comparison groups, as reflected by low scores on the Drug Abuse Screening Test (DAST-20; 44) and the Alcohol Use Disorders Identification Test (AUDIT; 45); these results are summarized in Table 1.

Details about the comprehensive assessment of cognitive function and personality traits are summarized in the online data supplement. The neurocognitive tests were selected on the basis of their known cortico-striatal and medio-temporal neural substrates, which are brain systems that have been associated with the pathophysiology of drug dependence. Personality measures were included because of their hypothesized associations with drug dependence. Measures of trait-anxiety, stress-sensitivity, and trauma history were used as markers of psychological stress

or vulnerability. All participants were assessed and tested in a fixed order with the same cognitive battery at a clinical research facility, and they were allowed breaks as needed.

Data Analysis

Data were analyzed using SPSS, version 13, using a five-step strategy:

We performed data reduction by Cambridge Neuropsychological Test Automated Battery (CANTAB) domains to control for the number of tests by calculating summary mean scores from z-transformed test variables within the cognitive domains.

We tested the specificity of cognitive effects by performing repeated-measures analyses of covariance (ANCOVAs) with group as the between-subject factor and domain as the within-subject factor. Where Mauchly tests showed violation of the sphericity assumption, Greenhouse-Geisser corrections were used. Nonsignificant group-by-domain interactions were compatible with the null hypothesis that all cognitive impairments are attributable to deficits in general intelligence.

We used ANCOVA models for group comparisons for each cognitive domain, which were controlled for multiple comparisons using the Bonferroni correction.

We made post hoc comparisons for each significant domain using paired t tests to control for relatedness of siblings and drug-dependent individuals and independent t tests for comparisons between unrelated pairs.

We used permutation statistics for familiality testing for each domain impaired in the sibling pairs relative to healthy comparison volunteers. The within-pair variance between the biological sibling pairs was compared with a permuted distribution of random pairs of drug-dependent-individuals and unrelated siblings (46).

Additionally, we conducted exploratory analyses at the subdomain level of individual tests using ANCOVA models, followed by post hoc comparisons using the Bonferroni correction. Gender was included as a covariate in all analyses to control for the significant group differences of gender. To obviate the confounding effects of dysphoric mood on cognitive performance (47), a participant score on the Beck Depression Inventory-II was also included as a covariate in the analysis of the cognitive data. ANCOVA models were applied to compare the results for individuals with and without parental drug or alcohol abuse separately within the drug-dependent and sibling groups; verbal IQ was included as a covariate to control for IQ differences between these subgroups. The affective and personality domains were defined according to the questionnaire constructs, and we followed the same analysis methods as outlined above. Independent t tests were used to compare cognitive and personality profiles of drug-dependent individuals with and without comorbid opioid dependence. The Padua Inventory–Washington State University Revision and the Perceived Stress Scale (version 14) total scores were square-root transformed to reduce skew, as described by

Howell (48). For the group differences in demographic characteristics, ANCOVA models, chi-square tests, or Fisher's exact tests were applied as appropriate for the analysis of categorical data. Pearson correlations were estimated where appropriate using the Bonferroni correction. All tests were two-tailed, and we set a significance level of 0.05. Because of technical problems, Rapid Visual Information Processing, One-Touch Stockings of Cambridge, and stop-signal data for one drug-dependent participant were unavailable.

The groups were matched for age, verbal intelligence, and duration of formal education (Table 1), but they differed with regard to gender, as the majority of drug-dependent individuals were men. The shared familial environment in the sibling pairs, which lasted in most cases into adolescence, was notably different from the childhood familial environment reported by healthy volunteers; the sibling pairs had larger household sizes, a higher incidence of parental divorce and of parents with addiction problems, and more frequent experiences of childhood abuse.

Cognitive Domains

Task performance differed significantly over the four cognitive domains (executive function, visual memory, attention control, and response control) across the three groups, as reflected by a highly significant domain-by-group interaction ($F=6.7$, $df=2.6, 371.7$, $p<0.001$), refuting the null hypothesis that all cognitive impairments were attributable to deficits in general intelligence. No significant main effects of domain were found, but there was a significant main effect of group ($F=9.6$, $df=2, 142$, $p<0.001$). To investigate the nature of the interaction, we compared the groups separately on each domain, revealing significant results for the domains of executive function ($F=16.0$, $df=2, 144$, $p=0.004$) and response control ($F=5.9$, $df=2, 144$, $p=0.012$). Figure 1A shows that the difference between groups in terms of visual memory and attention did not reach significance. Post hoc comparisons revealed that both siblings and drug-dependent individuals differed significantly from healthy volunteers in executive function ($tsibs=2.6$, $p=0.012$; $tdrug=8.8$, $p<0.001$) and from each other ($t=5.9$, $p<0.001$). In response control, the sibling pairs differed significantly from healthy volunteers ($tsibs=4.0$, $p<0.001$; $tdrug=3.6$, $p<0.001$) but not from each other. Parental drug or alcohol abuse was associated with aggravated performance in executive function and visual memory only in drug-dependent individuals but not in their siblings.

aPanel A shows performance profiles in four cognitive domains in healthy comparison volunteers, unaffected siblings, and drug-dependent individuals. Panel B shows characteristic profiles in affective, psychosocial, and personality domains.

Affective and Personality Domains

The difference between sibling pairs and healthy volunteers reached significance in executive function and response control. We compared the within-pair variance between the biological sibling pairs in these two measures with the variance between random sibling pairs (46). The observed variance on response control was significantly smaller within the biological pairs compared with the randomly permutated distribution ($p=0.006$), indicating that impairment in response control is a shared trait between family members. For executive function, variances in biological pairs did

not significantly differ from those in random sibling pairs, suggesting that impairments in executive function are not familial. Biological sibling pairs also differed significantly from unrelated healthy volunteers in emotional function, impulsivity-compulsivity traits, and self-evaluation, but the variances within these biological pairs did not significantly differ in any of these domains from variances within randomly permutated pairs. Comorbid dependence on opioids was not related to a different cognitive or personality profile in the current sample.

The sibling pairs reported significantly higher levels of childhood trauma compared with unrelated healthy volunteers (Table 1). We used a composite variable across all of the three types of abuse (49) to explore the relationship within the sibling pairs' traumatic childhood and the cognitive and personal domain measures. Executive function ($r=-0.3$, $p<0.05$) and impulsive-compulsive traits ($r=0.3$, $p<0.05$) were significantly associated with the degree of childhood abuse in the sibling pairs. The significant relationship between childhood abuse and emotional function, however, did not survive correction for multiple comparisons.

Cognitive Profiles and Indexes of Drug Abuse

Correlational analyses between last stimulant use, duration of stimulant abuse, and cognitive or personality domain measures did not reach significance. Compulsive pattern of stimulant use was significantly associated with emotional functioning ($r=-0.5$, $p<0.05$) and self-evaluation ($r=0.5$, $p<0.05$). Relationships between alcohol use (as reflected by the AUDIT score) and cognitive/personality measures did not survive correction for multiple comparisons. No statistically significant relationships were observed between cognitive performance and the duration of cannabis use or the age at onset. Trait impulsivity and anxiety traits were associated with each other in all volunteers ($r=0.5$, $p<0.05$). Cognitive and personality domains correlated with each other; a full correlation matrix can be found in the online data supplement.

Discussion

By comparing the characteristic phenotypes of drug-dependent individuals with those of their unaffected siblings and unrelated healthy volunteers, our study identified candidate endophenotypes for drug dependence. We found shared abnormalities in the sibling pairs in domains of executive cognitive and response control, emotional function, impulsivity-compulsivity traits, and self-evaluation; the detailed results are summarized in Table 2.

The siblings' cognitive profile was characterized by deficits in executive function such as working memory and mental planning. The impairments became especially apparent when the rapid suppression of an ongoing, well-established response was required. The siblings showed a general slowing in response speed, and this was even slower in drug-dependent individuals (Table 2). Similar profiles of impaired response regulation have been reported in adults with a family history of alcohol dependence (50) and in children with drug-dependent parents (51, 52). We believe that the cognitive deficits identified in both drug-dependent individuals and their siblings represent a shared trait in family members that predates

the exposure to stimulant drugs and may be a predisposing risk factor for the development of drug dependence. This proposal is supported by a longitudinal study in boys with and without a family history of alcoholism: poor inhibitory control, as indicated by prolonged stop-signal response time, predicted the onset of substance abuse in all children, but most strongly in those with alcohol-dependent parents (53).

Contemporary models of the pathogenesis of drug dependence suggest that immaturity of the regulatory control systems in the prefrontal cortex renders adolescents vulnerable to the initiation of drug abuse (54). The progressive breakdown of inhibitory control implemented by this circuitry, however, has been attributed to the repeated abuse of drugs, possibly paving the way for the development of drug dependence (55). Impaired regulatory abilities in those siblings without a history of chronic drug abuse might indicate a developmental dysfunction of prefrontal control. We recently showed that impaired stop-signal performance in the nondependent siblings of drug-dependent individuals was associated with reduced fractional anisotropy in diffusion tensor imaging scans of frontal white matter, which is compatible with disrupted anatomical connectivity of the inferior prefrontal cortex (56) (see Figure 2). The low within-pair variation in response control performance between the sibling pairs further supports the familial risk for impaired inhibitory control in people with stimulant dependence and their first-degree relatives. Yet, despite this higher familial risk of addiction, some of the siblings have experimented with drugs but never made the transition to addiction. Thus, occasional exposure to drugs, such as the recreational use of cannabis and social drinking, did not produce addiction in these high-risk individuals. The potentially protective factors against addiction in at-risk individuals are incompletely characterized and merit further study.

As shown by our preliminary data, the sibling pairs reported significantly higher levels of trait impulsivity than did the healthy comparison volunteers (57). Our data further indicate reduced emotional functioning in the sibling pairs, as reflected by high levels of trait anxiety and stress sensitivity (Table 2). Anxious-impulsivity trait has previously been described by Newman and Wallace (58) as a breakdown of inhibitory control in situations when the escape from aversive consequences appears impossible. More recently, a similar concept of negative urgency has been proposed that describes a personality trait of impulsive actions in response to intense negative affect (59). The higher levels of anxious-impulsivity in the sibling pairs suggest underlying deficits in emotion regulation, an ability that develops through the maturation of the fronto-limbic brain systems (60, 61). Developmental imbalances between these systems generally emerge during adolescence. Emotion systems in limbic structures mature before control systems in the prefrontal cortex (60), possibly laying the foundation for individual differences in emotion regulation or psychopathologies (62, 63). The concept of self-evaluation includes individuals' beliefs and perceptions about themselves that influence their mental and social well-being (64). Low levels of self-efficacy and self-perception in relation to other people, as shown in the present sample (Table 2), have been associated with addictive behaviors (65).

Relationships between childhood trauma and executive function as well as impulsivity have been reported in stimulant-dependent individuals (66). These relationships are not just restricted to dependent individuals but also affect their nondependent siblings. Our results are therefore consistent with the contemporary literature, suggesting that abuse experiences during childhood have long-lasting effects on cognitive function and behavior in adulthood (67–69).

Dysfunction Associated With Chronic Drug Abuse

As hypothesized, and in keeping with previous studies (15, 18, 70), cognitive function in drug-dependent individuals was significantly impaired on all tests. Impairments in executive function were significantly exacerbated in drug-dependent individuals compared with their siblings, suggesting that neurotoxic or other ancillary effects of chronic drug abuse may account for the scale of the impairments. However, we did not find significant correlations between the duration of stimulant abuse and cognitive performance, indicating that the relationship is more complex than for a simple exposure hypothesis. The fact that almost all drug-dependent individuals tested positive for stimulants at the time of testing may also have affected performance to some degree (71, 72). We did not find any relationships between the time of last stimulant use and performance in the measured cognitive domains. Although chronic drug abuse has a negative influence on cognitive performance, some cognitive deficits also exist in first-degree relatives in the absence of drug abuse. Cognitive dysfunction may thus be considered as a stable trait predating drug-taking that is independent of the states of intoxication or withdrawal.

Consistent with our preliminary data (57), higher levels of sensation- and reward-seeking personality were observed only in drug-dependent individuals but not in their siblings (Table 2), suggesting that the need for excitement is specific for individuals with chronic stimulant drug exposure. Levels of anxious-impulsivity were also higher in drug-dependent individuals than in their siblings, indicating that chronic drug abuse further increases both anxiety and impulsive traits. The significantly higher levels of stress-sensitivity in drug-dependent individuals are consistent with the notion that the system implicated in stress overlaps with brain circuitries associated with addiction (73, 74).

Strength and Weaknesses

The strengths of the study include the relatively large sample size and well-characterized participants in terms of personality and demographic variables. The neuropsychological tests we used have been validated in terms of their neural substrates (75). The test battery was theoretically focused on cognitive mechanisms of special relevance to drug dependence and demonstrated excellent sensitivity for the detection of cognitive endophenotypes in sibling pairs. The drug-dependent individuals were recruited from a variety of sources, enhancing the generalizability of the results. From its relatively novel perspective, our study confirmed and extended several findings using other approaches, suggesting that male gender, stressful life events, dysfunctional family structure, anxious personality, and impulsivity are associated with a heightened risk for drug dependence (32). Although the siblings shared many of these risk factors with their drug-dependent brothers and sisters, they did not engage in drug abuse. Their average age of 33 years suggests that they may have had many opportunities to initiate drug abuse and develop dependence, which makes them ideal candidates for the study of endophenotypes.

Potential limitations of the study include the use of a sibling design instead of a twin design; the latter would have allowed the disentangling of genetic from environmental influences, but it would have been prohibitively difficult to complete. However, we used permutation statistics to test

the familiality of salient markers as well as correlational analyses to explore the relationships with childhood trauma and the candidate endophenotype markers. Longitudinal studies are now warranted in order to clarify whether abnormalities that are not shared between the sibling pairs reflect a more selective higher “dose” of genetic or environmental risk factors in those individuals who become dependent. In contrast to previous research suggesting that the genetic influence on opioid abuse is specific and not shared with other drugs (8), we did not find differences in the cognitive and personality profiles of drug-dependent individuals with and without opiate dependence or between their siblings. However, further research is also needed to clarify whether these findings reflect a specific vulnerability to stimulants or to drug dependence more generally. Finally, our study does not directly address the important question of why some individuals with familial risks do not become dependent on drugs. This shortcoming lies in the endophenotype concept itself, which defines “intermediate markers of genetic risk,” not of resilience. Presumably, the nondependent siblings have benefited from some resilience or protective factors to offset the risks they shared with their dependent siblings, but it is not clear what these protective factors might be.

BACK TO TOP

Other

The Incidence and Risk of Celiac Disease in a Healthy US Adult Population

The American Journal of Gastroenterology
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Abstract

OBJECTIVES: Celiac disease (CD) is an increasingly common disease that may affect as many as 1% of the North American population. Recent population-based data suggest a substantial increase in the prevalence of CD over the last several decades. Several factors are hypothesized as possible disease triggers including intercurrent illnesses, such as gastroenteritis, surgeries, and trauma. We used the active duty US military, a unique healthy worker population with essentially complete medical diagnostic coding, as an opportunity to describe trends in CD and deployment-related risk factors.

METHODS: Using electronic medical encounter data (1999–2008) on active duty US military (over 13.7 million person-years), a matched, nested case–control study describing the epidemiology and risk determinants of CD (based on ≥2 ICD-9 medical encounters) was conducted. Incidence

and duration of CD-related medical care were estimated, and conditional logistic regression was utilized to evaluate CD risk following infectious gastroenteritis (IGE) occurring within 3 years before CD diagnosis while controlling for other risk factors.

RESULTS**:** A total of 455 incident cases of CD were identified and age, gender, and time matched to 1,820 controls. The incidence of CD increased five-fold from 1.3 per 100,000 in 1999 to 6.5 per 100,000 in 2008, with the highest rates of increase among those over 34 years of age (average annual increase of 0.8 cases per 100,000). A total of 172 IGE episodes, predominately of "viral etiology" (60.5%), were documented. In multivariate models, a significant association between IGE and CD was found (Odds ratio (OR): 2.06, 95% confidence interval (CI) 1.43, 2.97). Risk generally increased with temporal proximity to, and non-viral etiology of, exposure. Other notable risk factors for CD in multivariate models were Caucasian race (OR: 3.1, *P*<0.001), non-Army service (OR: 1.5, *P*=0.001), and greater than a high-school education (OR: 1.3, *P*=0.05).

CONCLUSIONS: Incidence of CD diagnosis in the US military is increasing, particularly among those in the fourth and fifth decades of life and appears higher than other population-based estimates. An association between antecedent IGE and risk of CD was noted, but the potential for exposure misclassification cannot be ruled out and further study is needed to link pathogen-specific exposure to incident CD anti-gluten antibody development or symptom onset.

Introduction

Celiac disease (CD) is an increasingly common disorder that may affect as much as 1% of the North American population. It is known to affect all ages, including young adults, and may be more prevalent in Caucasians. The rate of diagnosis in other racial groups is largely unknown. However, due to the broad spectrum of clinical presentation, and, until recently, the unavailability of sensitive and specific diagnostics, most affected individuals are never diagnosed. The consequence of the disease may be diverse in terms of issues such as bone fragility, depressed resistance to bacterial and fungal infections, reduced ability to respond to vaccinations, and a variety of other nutritional, immunological, and inflammatory comorbidities. The majority of CD patients have 1 of 2 HLAs encoded by genes that are also found in approximately one-third of the North American population. Considering that virtually the entire population consumes food containing significant amounts of the primary exogenous trigger (i.e., gluten), yet only 1% of the population may get the disease, research has been conducted to identify other factors triggering disease onset, or associated with increased CD risk among genetically susceptible individuals. Several factors have been suggested including early introduction or large consumption of gluten early in life after weaning and childhood,[3] and infant infections.[4] Other triggers include the seasonality of birth and risk of disease. In addition, intercurrent illnesses, such as surgeries, and trauma, are potential triggers. The role of infection early in life, especially in those that overlap with the introduction of high-dose gluten follow-on formulas that are often used after weaning, may be particularly likely to increase the rate of disease.

Recent population-based data suggest a substantial increase in the prevalence of CD over the last several decades. This increase is unlikely to be due to a change in human genetics or population changes in wheat consumption, but may reflect a change in other environmental factors. It has

also recurred in adults, a phenomenon that may be more marked in North America than in Europe. In this study, we aim to explore the recent incidence and risk factors of CD in one of the largest and best documented adult populations in North America of active service personnel. This population includes substantial diversity of race and ethnicity and education level.

Methods

Database Information

Data were obtained from the Defense Medical Surveillance System, the main repository for medical data of Department of Defense beneficiaries maintained by the Armed Forces Health Surveillance Center. All subjects were active duty US military personnel who served between 1999 and 2008. Medical information was derived from ambulatory and inpatient claims data for care provided within the Military Health System. Demographic data were derived from personnel information; deployment data were derived from deployment rosters and deployment health assessments. Included data were linked at the individual level and compiled into a single de-identified data set, which was provided to the study investigators. The study was reviewed and approved by the Naval Medical Research Center Institutional Review Board in compliance with all applicable regulations governing the protection of human subjects.

CD Case Identification and Control Selection

A CD case was identified when the service member had at least two ICD9-CM (579.0) specific medical encounters for a CD diagnosis within 6 months. Subsequent medical encounters were determined to be related to the CD if the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) code was included in any of the diagnostic positions. Each case was matched by time (a medical encounter within 1 calendar year), sex, and age (within 1 year) with up to four controls with an unrelated diagnosis randomly selected from the population that produced the cases (i.e., active duty military personnel). Baseline medical encounters for the control subjects included vaccinations, procedures, or other unrelated diagnoses. Incident CD was defined as the first documented ambulatory or inpatient medical encounter with the ICD9-CM code listed above. Given that the military generally would not enlist or commission a service member with known CD, it is unlikely that many of the incident CD diagnoses would include individuals who have a prior diagnosis of CD, though undiagnosed disease could be prevalent among both cases and controls selected.

Exposure

The primary exposure variable of interest was infectious gastroenteritis (IGE) at any time before a diagnosis of an incident CD (cases) or censure (controls). An IGE exposure was defined by ICD9-CM codes for specific pathogens and non-specific infectious enteritis as previously reported. Non-specific IGE codes were included due to the lack of routine microbiology performed on patients with IGE in similar health-care settings. Both specific and non-specific codes were utilized to classify an exposure as a specific bacterial, non-specific bacterial, protozoal, or viral etiology. We also evaluated exposures at 24, 18, 12, and 6 months before CD diagnosis or censure (controls) to assess the temporal relationship between exposure and outcome. While previous studies have evaluated associations of exposure up to 1 year, we chose to extend exposure windows up

until 24 months to account for potential in diagnostic delay due to patient's care seeking behavior and/or provider diagnosis, and we saw no significant changes in effect estimates with differential exposure windows. Due to similarities in clinical presentation between the primary exposure (IGE) and symptoms of the CD outcome of interest, we evaluated a 6-month diagnostic delay window whereby exposures occurring within 6 months before CD diagnosis (or censoring for controls) were excluded. In addition to IGE exposure, other demographic variables available in the data were evaluated, including race, military rank, educational attainment, marital status, and branch of service.

Analysis

CD incidence was estimated using the number of incident cases in a given year and the total number of active duty service members for that same year. The associations between CD, IGE, and covariates were initially explored by univariate methods. All analyses evaluated each CD independently. Univariate and multivariate conditional logistic regression models were used to evaluate the relationship between IGE, other covariates, and CD. For multivariate models, a backwards elimination approach was used, whereby all variables were initially added to the models. The variable with the largest insignificant *P* value was removed, and the models were refit. This process was continued iteratively until all variables retained in the models were significant at the $\alpha = 0.15$ level. Effect modification was assessed statistically utilizing a multiplicative approach. The association of psychological comorbidity among cases and controls was also evaluated, but limited to concomitant diagnosis for initial CD visit of incident diagnosis and at censure visit for controls.

Statistical analyses were performed using SAS v. 8.2 for Windows (SAS Institute, Cary, NC). Two-tailed statistical significance was evaluated using an α of 0.05.

Results

As shown in Table 1, a total of 455 cases of incident CD were identified in active duty US military personnel between 1999 and 2008 with an overall incidence of 3.55 per 100,000 person-years (p-yrs) (95% confidence interval (CI): 3.24, 3.90; Table 1). Rates were higher in females (7.70 per 100,000 p-yrs) compared with males (2.78 per 100,000 p-yrs) ($P<0.001$). Incidence for CD was noted to rise from 1.32 per 100,000 p-yrs in 1999 to 6.54 per 100,000 p-yrs in 2008, and this rise was highest in the older age strata (Figure 1). While incidence increased at a higher rate per annum in whites, those classified as other race (i.e., non-white and non-black) also showed year-over-year increases of ~0.8 per 100,000 per year.

The majority of cases and controls were male (65.9%), white (66.4%), and married (69.4%). Cases were noted to have education beyond high school (54.7%), which was higher than controls (45.8%) ($P<0.001$). The three major branches of the US Military Armed Forces (Army, Navy, and Air Force) comprised the majority (88.6%) of the study population, with most classified as enlisted personnel, though a higher proportion of officers were noted among CD cases compared with controls (32.5 vs. 22.1%, $P<0.001$). Overlap with functional and other gastrointestinal disorders were assessed among cases and included dyspepsia (8/455, 1.8%), constipation (10/455, 2.2%), irritable bowel syndrome (20/455, 4.4%), and

functional diarrhea (4/455, 0.9%). There was no overlap with gastroesophageal reflux disease. Overall, 38 (8.4%) had one or more visit associated with these gastrointestinal disorders. One-hundred seventy-two subjects had one or more IGE exposures with etiological category distributed as follows: bacterial pathogens (*n*=4, 2.3%), protozoal (*n*=2, 1.2%), viral (*n*=104, 60.5%), and other (*n*=74, 43.0).

Among incident CD cases followed, the median number of visits was two (interquartile range: 2, 4) with no significant difference based on exposure. Data were not available on the proportion of CD cases that resulted in discharge from medical service, though this is often known to occur in these cases (personal communication, Brooks Cash, US Navy).

Initial univariate analyses found that the following covariates were independently associated with an increased risk of CD: Caucasian race, non-Army branch of service, greater than high-school education, and previous IGE episode. Prior deployment to Operation Iraqi Freedom deployment had lower risk of CD compared with non-Operation Iraqi Freedom deployers. The odds ratio (OR) for incident CD following an antecedent episode of IGE increased as the time frame allotted for exposure decreased. When limiting the IGE episodes to only those of non-viral origin in the 24 months before censure, the associated OR increased for CD. In a multivariate model, after controlling for the other covariates, being married, having less than a Bachelor's Degree, being in the Army, having an episode of IGE in the 24 months before censure significantly increased the risk of each functional gastrointestinal disorder (FGD). In contrast, being in the Marines appeared to be protective (Navy referent). Being classified as non-Caucasian decreased the risk of CD.

Discussion

This study demonstrates a substantial increased incidence and diagnosis rate of CD in a large, generally healthy young adult population for which there is excellent capture of diagnosis and ready access to health care. This rise in incidence is consistent with what has been reported in other western industrialized population-based studies and likely represents a combination of both increased diagnoses due to increased suspicion but also may reflect a true increase in incidence possibly related to environmental changes in cereal processing including wheat genetics, bread processing, and enzymatic modification of wheat prolamins resulting from changes in industry processes. It is interesting that this increase in incidence seemed to be more marked in individuals in the third, fourth, and fifth decades in life, among those who would have already been in the military service for many years, suggesting that this is a true new onset of disease or the emergence of longstanding silent disease. We did not have data available on secular trends for number of serological CD tests performed, which should be done to inform the potential bias associated with increased testing that could partially explain the increased incidence (studies planned).

Clearly, environmental, genetic, and immunological factors have a role in the pathogenesis of CD. It is well accepted that the common HLA genotype encoding HLA types DQ2 or DQ8 is necessary for CD to occur. However, as almost 30% of the Caucasian population carries these genotypes, and virtually all eat gluten, there must be other factors including genetics, immune dysfunction, and environmental exposures that trigger the disease. Extensive genetic analysis has revealed a large number of other genes that all have very small attributable risks that cumulatively only add 10% of risk. The balance of genetic and environmental influences in risk of disease is also supported by the 75% concordance in monozygous twin studies. Although the only well-documented environmental trigger is gliadin, it has been proposed that the

clinical expression of CD can be modulated by environmental factors. It is possible that in genetically susceptible patients, an infectious insult may contribute to trigger overt CD through increased intestinal permeability, or adjuvant effects of infection or inflammation, latent CD may be unmasked.

Given the potential for infections to act as triggers for developing gluten intolerance through molecular mimicry or other immune modulation mechanisms, efforts to identify an infectious association have be made. However, to date, there is no compelling evidence for such an association. Neonatal infections have been associated with increased risk of CD, and the role of adenovirus 12 virus remains controversial. Based on the 12 amino-acid homology sequence of adenovirus type 12 E1B protein and α-gliadin, it has been suggested that exposure to adenovirus type 12 E1B may sensitize individuals to gliadin and trigger CD. However, it is difficult to establish a causative relationship between adenovirus type 12 E1B and gliadin, because adenovirus type 12 E1B is also highly prevalent in the duodenal tissue of normal individuals. CD is epidemiologically associated with other viral infections, such as chronic hepatitis C, non-viral disorders including insulin-dependent diabetes, thyroid disease and cardiomyopathy, and HIV. This suggests that the association may involve chronic immune stimulation, which in turn triggers an autoimmune reaction.

In the present study, we found an increased odds ratio of exposure to prior IGE twice as high among CD cases compared with matched controls (OR: 2.0, 95% CI: 1.4, 2.8). Non-viral IGE exposure odds were relatively higher (OR: 3.0, 95% CI: 1.9, 4.8), and odds of exposure were higher when looking at temporal proximity to CD diagnosis. Unfortunately, we do not have specific pathogen etiologies associated with these infections, and while these results are intriguing, the potential for misclassification of exposure given the conflated symptomatology of infectious diarrhea and CD confounds the potential association in this study. While much is known about the pathogenic adaptive and innate immune responses associated the disease process, less is known about the initiating steps that are involved in disease onset. As demonstrated in animal models of gluten sensitivity, gastrointestinal infection may trigger or facilitate the onset of clinical CD, either by increasing intestinal permeability or by enhancing uptake and dysfunctional anti-gliadin immune response in the genetically susceptible host. It is reasonable to suspect that acute gastrointestinal infections could result in the translocation of luminal antigens, including incompletely digested gluten peptides, which in the background of pro-inflammatory anti-bacterial responses could trigger a maladaptive immune response. *Campylobacter jejuni*, a leading cause of enterocolitis worldwide, has been shown experimentally to permit the translocation of normal, non-invasive microflora via novel processes that implicate epithelial lipid rafts and M-cell transport and induce a pro-inflammatory response. Thus, similarly to the epidemiological studies observing Campylobacter and Salmonella infections as a trigger of inflammatory bowel disease it is possible that such infections could also trigger luminal antigens, including gluten peptides, across the intestinal barrier, and in certain susceptible individuals prime a mucosal immune response toward such antigens resulting in loss of tolerance to these antigens due to an inappropriate inflammatory response.

With regard to what is known about infectious diarrhea as a trigger for CD there are a few anecdotal reports and case series suggesting an association whereby some patients with CD often attribute the onset of classic symptoms to a stressful episode or gastroenteritis, and cases of CD have been reported as presenting as persistent travelers' diarrhea when no infectious cause could be documented. It has also been described that exposure to three or more IGE events in young children at or around the time of introduction of follow-on formula was associated with a substantial increased risk of childhood diagnosis of CD. In addition, a birth cohort followed in Denver suggested that rotovirus infection in the first year of life

was associated with subsequent risk for CD. More recently, a case of a healthy subject who developed sudden irritable bowel syndrome-like symptoms after a confirmed episode of *C. jejuni* enteritis was subsequently diagnosed with new onset CD. It is interesting that in this study, we found a higher risk of CD in subjects who were diagnosed with a "non-viral" IGE episode. While the ICD-9-based diagnosis is non-specific, it would suggest that bacterial infections could be more associated with subsequent diagnosis of CD. In total, the results we found lend support to the infectious trigger hypothesis, though this study relied on non-specific (and potentially misclassified) infectious gastrointestinal exposures, which needs confirmation through studies evaluating risk after pathogen-specific exposures.

While CD is known to predominantly affect Caucasians, less is known about the incidence of CD in non-Caucasians. As this cohort of active military service personnel incorporates large numbers of individuals who are non-Caucasian, with unhindered access to medical care, the low incidence seen in non-Caucasians likely reflects a true difference in biologic predisposition, although rates increased during the study period that may implicate secular trends in environmental influences which has been seen in inflammatory bowel disease rates among non-whites. It is unlikely that there would be significant differences in environmental exposures or diet due to common food and preparation and provision with the military service, though it is possible that there may be inherently lower suspicion for CD by the medical personnel caring for individuals who are non-Caucasian. Future active surveillance study should be considered including sampling of non-Caucasians to verify that incidence is truly lower and not simply undiagnosed. Other US military population specific differences were noted. The association of CD with officer rank and higher educational level begets the positive association with socioeconomic status. This has been suggested in an epidemiologic study from Finland wherein there is a higher rate of CD in the more developed population of Finland than the adjacent less developed population. It is, however, possible that educational levels may have lead to increased awareness of this diagnosis, and also there may be a negative association with smoking for which we could not control.

Interestingly, we found that deployment decreased the risk of CD that may be counterintuitive given the known high risk of infectious exposures, including gastrointestinal infections, and stress while deployed. Unfortunately, capture of deployment-related illness and injury into the Defense Medical Surveillance System (DMSS) medical encounter databases is not complete; therefore, assessment of deployment-related illness effects (particularly minor ones) is incomplete. Furthermore, military members with underlying medical illness may not be deployed resulting in a type of "healthy worker" effect, which might also explain the lower rate of CD in deployed personnel compared with their non-deployed counterparts. Surgical stress has been described to trigger CD, and future studies should be designed to capture these data to further evaluate deployment-related infectious and non-infectious exposures of interest.

This study has several limitations. First, an important limitation is that CD diagnoses were based on a medical encounter database, and while we believe our strategy for determining case status is robust based on prior experience with other complex diseases it is not possible to review individual medical records to confirm. Additional studies are needed (and being planned) that use clinical procedure codes associated with upper endoscopy and histology, as well as serological evidence from linked Department of Defense serum repository specimens. Furthermore, given our reliance on clinically diagnosed CD, our incidence estimates should be considered as a gross underestimate of the true incidence in the population, though we feel the secular trends and differential rates among demographic subgroups are relevant observations. Second, as mentioned, the precise identification of enteropathogens associated with IGE visits was not described, due to the fact that laboratory work-up of

these infections is infrequently carried out in US military as well as in civilian clinics and emergency rooms. Furthermore, our stratification of IGE into viral and non-viral categories is imprecise. It is further possible that these gastroenteritis episodes that were called IGE may actually have represented short-lived symptom events associated with subsequently diagnosed CD. To assess for such an effect, we utilized a 6-month exposure exclusion period before initial CD diagnosis (or control censoring) to prevent misclassification of initial CD presentation as an episode of IGE, and we did not see such effect (data not shown). However, if the duration between exposure and disease onset is short, then we may have underrepresented the true association biasing the results toward the null. Additionally, to minimize potential misclassification, this study excluded functional gastrointestinal disorders among controls and did not include such medical encounter visits before onset of incident CD. While not directly addressing this potential source of bias, excluding CD cases with functional gastrointestinal disorders co-diagnoses in this study did not change in the primary effect estimate of any IGE exposure (adjusted-OR: 2.00, 95% CI: 1.37–2.90). Finally, this study cohort does not address CD in the elderly or in the very young, and indeed individuals with chronic ill health are generally not admitted into military service; hence, this study may underestimate the true incidence in the general population.

In summary, our study shows a substantial increase in the rate of CD diagnosis in adult healthy Caucasian population with a much lower but increasing incidence in non-Caucasians. The disease is more likely to be diagnosed after a proximate IGE event of a non-viral nature and contribute to the emerging body of data that warrants further prospective or seroepidemiological studies linking pathogen-specific infectious diarrhea exposure attribution to incident CD. Studies that aim to evaluate the instigating exposures and mechanisms of CD-related antibody development, or initiation of disease in those who were previously asymptomatic but with pre-existence of positive celiac serology are needed (planned).

BACK TO TOP

From Sick Care to Health Care- Reengineering Prevention into the U.S. System

New England Journal of Medicine
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Although the United States pays more for medical care than any other country, problems abound in our health care system. Unsustainable costs, poor outcomes, frequent medical errors, poor patient satisfaction, and worsening health disparities all point to a need for transformative change. Simultaneously, we face widening epidemics of obesity and chronic disease. Cardiovascular disease, cancer, and diabetes now cause 70% of U.S. deaths and account for nearly 75% of health care expenditures. Unfortunately, many modifiable risk factors for chronic diseases are not being addressed adequately. A prevention model, focused on forestalling the development of disease before symptoms or life-threatening events occur, is the best solution to the current crisis.

Disease prevention encompasses all efforts to anticipate the genesis of disease and forestall its progression to clinical manifestations. A focus on prevention does not imply that disease can be eliminated but instead embraces Fries's model of "morbidity compression," in which the disease-free life span is extended through the prevention of disease complications and the symptom burden is compressed into a limited period preceding death. Thus, a prevention model is ideally suited to addressing chronic conditions that take decades to develop and then manifest as life-threatening and ultimately fatal exacerbations.

Although the need for a prevention model was highlighted during the recent health care reform debate, efforts to expand prevention continue to be thwarted by a system better suited to acute care. A century after the Flexner report, the acute care model and its cultural, technological, and economic underpinnings remain securely embedded in every aspect of our health care system.

The organizational structure and function of our medical system is rooted in fundamental changes made at the beginning of the 20th century that emphasized an acute care approach and marginalized prevention and public health. Breakthroughs in laboratory sciences led by Koch and Pasteur provided powerful tools for mechanistically understanding and treating infectious diseases. Bolstered by philanthropy and the Flexner report, U.S. medicine became reliant on laboratory research. This strategy made sense 100 years ago, given the prominence of acute infectious diseases in a young population; it makes little sense now.

With the aging of the population, the shift in the burden of disease toward chronic conditions has accelerated. The most prevalent preventable causes of death are now obesity and smoking, which result in delayed but progressive disease. Even in the developing world, increases in the prevalence of chronic disease are outstripping reductions in acute infectious diseases. Such epidemiologic evolution demands a focus on public health and prevention.

Yet economic and technological factors dating from the early 20th century remain strong barriers to effective disease prevention. A key feature of U.S. health care is its use of a piecemeal, task-based system that reimburses for "sick visits" aimed at addressing acute conditions or acute exacerbations of chronic conditions. Economic incentives encourage overuse of services by favoring procedural over cognitive tasks (e.g., surgery versus behavior-change counseling) and specialty over primary care. The current model largely ignores subclinical disease unless risk factors are "medicalized" and asymptomatic persons are redefined as "diseased" to facilitate drug treatment. These mismatched economic incentives effectively preclude successful prevention through health maintenance.

Moreover, our reliance on ever newer, more advanced technology has perpetuated an expensive system in which costly new technology is widely adopted in the absence of comparative advantage. When combined with economic incentives for patenting devices and drugs, these technological factors become self-reinforcing. Although many preventive strategies may be cost-effective, they unfortunately have limited potential for wide adoption because they cannot be patented or made profitable. Therefore, the primacy of patentable therapies impedes research on prevention and diffusion of prevention approaches that could cost-effectively address the burden of chronic disease.

The cultural and social underpinnings of our system also inhibit optimal disease prevention. Faith in reductionism, which was infused into medicine in the 20th century, has empowered medical research to pursue only isolated problems and to yield targeted, immediately deployable solutions. Consequently, the model for treating acute infectious disease is being misapplied to the treatment of chronic disease. For example, cancer chemotherapy is modeled after antibiotic therapy, and coronary revascularization is modeled after abscess incision and débridement. Societal

expectations of a “magic bullet” and a focus on symptom relief also reflect and reinforce the reductionist approach. These scientific and societal values emphasize discovering a “cure” for the major causes of death. With the advent of direct-to-consumer advertising for pharmaceuticals and surgical procedures, these cultural expectations of immediate, simplistic solutions have been bolstered by consumerism and fully exploited to generate demand for therapies that are marginally indicated and potentially unsafe. Our very culture thus devalues disease prevention.

Changing the system requires recognition of these cultural, technological, and economic obstacles and identification of specific means for overcoming them through alterations in medical education, medical research, health policy, and reimbursement. For example, to combat the primacy of technical knowledge and the profit-based system for medical technology, medical schools must teach prevention strategies alongside treatment approaches and emphasize motivational interviewing with a focus on lifestyle modification. Payers and the federal government must fully reward use of appropriate nonpatentable therapies and support research on the development and dissemination of prevention strategies.

To change our reductionist way of thinking, we must teach aspiring physicians about systems science that addresses psychological, social, and economic determinants of disease. Taking a patient-centered, whole-person approach focused on long-term functional status will also help to address the current fragmentation of care and allow for standardization of prevention strategies.

Medical school curricula should emphasize homeostasis and health, rather than only disease and diagnosis, and provide training in the science and practice of cost-effective health promotion. In turn, payers will need to reimburse for health maintenance and prevention activities, primary care physicians will have to act as health coaches, and all health care professionals will need to embrace a coordinated multidisciplinary team approach. Systematic steps must also be taken to change the culture of medicine so that primary care is valued. Renewing primary care will require increasing ambulatory care training in community settings and reallocating funding for residency training away from hospitals to reimburse appropriately for innovative models such as medical homes. Furthermore, we must compensate primary care physicians for their work as care coordinators by establishing reimbursement parity for cognitive and procedural care and accounting for long-term costs and benefits.

The new approach to medicine endorsed by the Flexner report succeeded because it was based on sound science and a radical restructuring of the way medicine was taught, organized, and practiced. Today, we face a similar challenge that requires another fundamental reordering of our health care system. Although the need for acute care will remain, centering our efforts on prevention is the only way to thwart the emerging pandemic of chronic disease.

Current health care reform efforts will bring incremental improvement, but reengineering prevention into health care will require deeper changes, including reconnecting medicine to public health services and integrating prevention into the management and delivery of care. Though change is painful, the successful transformation of medicine at the turn of the last century shows that it is possible. Ultimately, embedding prevention in the teaching, organization, and practice of medicine can stem the unabated, economically unsustainable burden of chronic disease.

BACK TO TOP

Engaging Physicians and Leveraging Professionalism: A Key to Success for Quality Measurement and Improvement

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INCREASING COSTS AND GROWING EVIDENCE OF GAPS IN quality have led to a health care environment emphasizing accountability to purchasers and patients. Physicians and hospitals are expected to demonstrate the value of the services they provide by measuring the quality of care, reporting to payers, and increasing public transparency. Patients and payers increasingly expect public input in the formation and evaluation of medical evidence and the inclusion of patient experience and clinical outcomes when evaluating quality of care.

Trends over the past decades have contributed to strengthening this context for medical care. One is the expanding science of health care quality and the ability to develop meaningful measures of clinical quality, safety, and patient experience. The second is increasing awareness of the importance of quality improvement science and high-reliability organizations as learned from other industries.1 Organizations such as the Institute for Healthcare Improvement have applied the science of quality research from other industries to health care. This transformational thinking has led health care to use industrial engineering models to reduce or eliminate defects in process, increase reliability, and reduce waste. The third trend has been the increasing adoption of electronic health records, stimulated by the creation of the meaningful-use incentive program. The proliferation of quality measures in this context have increased attention to accountability and led to the formation of the National Quality Forum (NQF) to encourage consistency and endorse measures being used to improve quality. This background highlights the importance of the need for insurance payers to actively engage physicians and other clinicians and to lever- age professionalism in quality programs.

Maintenance of Certification

The medical profession is responding to these same realities and is increasingly aware of its own responsibility to demonstrate value and improve quality. For the profession, this awareness resulted in advancing the concept of Maintenance of Certification (MOC) through the American Board of Medical Specialties. For nearly a century, specialty board certification had been a mark of distinction and a way of differentiating the competencies of specific medical specialties. For most physicians, this meant passing an examination of knowledge at the end of training after which certification remained valid for the rest of their life. In the 1970s, a few proactive specialties limited the validity of certificates so that to remain board certified, physicians would have to recertify periodically (eg, every 6-10 years). By 2002, all 24 specialty boards had agreed to the necessity for peri- odic recertification.2 The number of grandfathered physi- cians not required to recertify has decreased over time and is the minority in major specialties. For instance, among all physicians who are currently board certified by the Ameri- can Board of Internal Medicine, approximately 23% of those younger than 70 years are not required to and have chosen not to recertify. In addition, the percentage of physicians who have never been board certified is declining.

The move toward recertification was in response both to the ever-changing nature of medicine and the primacy of public accountability within their ethical framework of pro- fessionalism. In response, the boards developed a consis- tent framework for MOC, which in addition to demonstrat- ing up-to-date knowledge in a specific field, also included actual assessment of performance consistent with measure- ment, accountability, and quality improvement science. This movement had momentum and extended to physicians within the osteopathic specialty framework.

Beginning to Pay for Quality

With the proliferation of quality measurements and report- ing, reward systems emerged. The reporting systems led to report card–type reports on physicians using the measures available. Insurance companies began to use models of pay for performance that had been tested in the United King- dom. The Centers for Medicare & Medicaid Services (CMS) began developing this idea, called value-based purchasing, outlining the need to move from fee-for-service payment to purchasing based on value. The CMS completed its hospi- tal value-based purchasing report to Congress in 2007, which became 1 of the first value-based purchasing programs.3 The CMS started the physician quality reporting program in 2007, which has evolved over time, and rewards physicians for re- porting approved quality measures such as blood pressure measurement and control, cholesterol measurement and con- trol, and many process of care measures. As a result, phy- sicians were increasingly expected to report certain quality measures to payers other than CMS and separately to their specialty boards for board certification.

CMS and Physician Quality

Despite the rapid changes in specialty certification and qual- ity-related payment programs in the past 5 to10 years, there is an increasing concern that the results of pay-for- reporting and pay-for-performance programs and public re- porting have not driven health system change as quickly as desired. Quality improvement has occurred in select areas, but the pace and scale of improvement need to increase. Im- portantly, smaller physician groups and solo practitioners have had lower successful reporting rates.4 The relatively small payments outlined in congressional statute did not typi- cally offset the additional work that went into collecting and transmitting this information.

Therefore, CMS reviewed the major physician program, the Physician Quality Reporting System, in 2011. The aims of the review were to align measures with the National Qual- ity Strategy5 released by the Department of Health and Hu- man Services outlining national goals, ease the burden of reporting to reach a goal of the majority of physicians in the United States participating by 2013, strategically engage the physician community in improving the program over time, and focus on measures with maximum effect on achieving the National Quality Strategy goals of better health, better care, and reduced costs through improvement. The review also focused on how to leverage other collection mecha- nisms, such as registries and specialty quality measure- ment efforts, to increase participation in the Physician Qual- ity Reporting System. In addition, the review focused on aligning reporting requirements, including leveraging the electronic health record incentive program so a physician could ultimately report once to receive credit for multiple programs.

This review resulted in implemented changes that fo- cused on measure alignment and engaging the clinician com- munity in the stage 2 meaningful use rule proposed in early 2012 and in the CMS physician fee schedule rule proposed in July 2012. These changes are the beginning of imple- menting this longer-term strategy. The stakes of quality and cost measures for physicians were raised further by the con- gressional mandate for CMS to implement a physician value modifier that will adjust payments to all physicians by 2017 based on performance.

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MOC, Clinician Engagement, and CMS

Physician engagement in MOC has been better than ex- pected, even though its requirements in many specialties are greater than many payer programs. Many physicians have reported quality data through the boards for several rea- sons: board certification remains a valuable professional cre- dential, increasingly valued not only by physicians but by employers, patients, and potential patients. In addition, the process of certification is familiar to physicians and in- cludes aspects such as evaluation of knowledge and com- prehensive and clinically relevant quality measures that re- turn data back in a timely fashion and require improvement as part of the process. Maintenance of certification is often required for privileging with the clear aim to improve qual- ity rather than simply to increase payment. The compre- hensiveness of the MOC approach makes sense to physi- cians and is consistent with the clinical flow of their practice.

These observations suggest that closer alignment for phy- sicians who choose to use their MOC-related assessments with CMS programs for quality reporting and value-based purchasing could lead to more meaningful information avail- able to consumers, as well as greater opportunities for mean- ingful quality improvement as a result. The CMS is engag- ing with the specialty boards to make this vision a reality over time. Participation in MOC would still be voluntary but for physicians who participate, they might reap addi- tional benefits in terms of participation and quality report- ing that meets CMS requirements. This is part of a broader strategy in which CMS aims to engage clinicians of all types in quality measurement and improvement through spe- cialty and professional societies. A fully integrated system of data collection and data reporting to both payers and spe- cialty boards is possible. Although much work remains, col- lectively leveraging professionalism and continuous learn- ing are needed to improve the health system.

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BACK TO TOP

Tattoo Ink–Related Infections — Awareness, Diagnosis, Reporting, and Prevention

New England Journal of Medicine
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Tattoos have become increasingly popular in recent years. In the United States, the estimated percentage of adults with one or more tattoos increased from 14% in 2008 to 21% in 2012.1 The process of tattooing exposes the recipient to risks of infections with various pathogens, some of which are serious and difficult to treat. Historically, the control of tattoo-associated dermatologic infections has focused on ensuring safe tattooing practices and preventing contamination of ink at the tattoo parlors — a regulatory task overseen by state and local authorities.2 In recent months, however, reported outbreaks of nontuberculous mycobacterial infections associated with contaminated tattoo ink have raised questions about the adequacy of prevention efforts implemented at the tattoo-parlor level alone. The Food and Drug Administration (FDA) is reaching out to health care providers, public health officials, consumers, and the tattoo industry to improve awareness, diagnosis, and reporting (through the MedWatch program) in order to develop more effective measures for tattoo ink–related public health problems.

In late January 2012, the FDA was notified, through MedWatch adverse-event reports,3 of a cluster of patients in New York who had contracted nontuberculous mycobacterial infections manifested by red papules on the gray-colored areas of recently acquired tattoos (see photoPapules Associated with Tattoo Ink–Related Nontuberculous Mycobacterial Infection. and the article by Kennedy and colleagues in this issue of the Journal, pages 1020–1024). The FDA collaborated with local and state health departments and the Centers for Disease Control and Prevention to investigate the outbreak. Efforts to identify additional cases nationwide revealed that there were other outbreaks of tattoo ink–related nontuberculous mycobacterial infection that were associated with multiple brands of ink, occurred in other states, and involved multiple species of mycobacteria (e.g., chelonae, fortuitum, and abscessus).

Previously published reports of tattoo-related nontuberculous mycobacterial infections suggested that tap water or distilled water used to dilute inks at tattoo parlors was a likely source of contamination.4 Findings from the recent outbreak investigations, however, suggested that the inks were contaminated before distribution. During the response to the New York outbreak, the outbreak strain of mycobacteria was isolated from an unopened ink container. Thus, contamination could have occurred at various points in the ink-production process — for instance, from unsanitary manufacturing processes or the use of contaminated ingredients such as water, glycerin, or pigments.

Under the Federal Food, Drug, and Cosmetic Act, tattoo inks are considered to be cosmetics,5 whereas the pigments used in the inks are color additives that require premarketing approval. This law requires that cosmetics and their ingredients not be adulterated or misbranded, which means, among other things, that they cannot contain poisonous or deleterious substances or unapproved color additives, be manufactured or held in unsanitary conditions, or be falsely labeled. Furthermore, cosmetic manufacturers are supposed to ensure the safety of a product before marketing it.

However, the FDA does not have the authority to require premarketing submission of safety data from manufacturers, distributors, or marketers of cosmetic products, with the exception of most color additives (dyes, pigments, or other substances used to impart color). The FDA does have the authority to take other actions to protect the public health. For example, the agency can conduct investigations, request that a manufacturer recall violative products, and issue advisory letters. The agency can also request that the Department of Justice conduct seizures, enjoin a firm or person from manufacturing or distributing products, or file criminal charges against a firm or responsible persons on behalf of the FDA.

Several features of nontuberculous mycobacteria make it particularly important to increase awareness about these types of tattoo ink–related infections. Nontuberculous mycobacterial infections may be difficult to diagnose and treat. Commonly reported symptoms of such infections associated with tattoo ink include lesions consisting of red papules solely in areas where the contaminated ink has been applied. Symptoms can be difficult to recognize, since other conditions (e.g., allergic reactions) may present with similar findings. Recovery of mycobacteria may be challenging, often requiring a skin biopsy, and special culture mediums may be required for diagnosis. Depending on the medium used, it can take up to 6 weeks to identify the organism. Because of these diagnostic challenges, infections may initially be misdiagnosed and patients may receive ineffective treatments. Antibiotic choices are limited by the susceptibility profile of the organism, and prolonged treatment may be necessary to clear the infection. Moreover, complications such as coinfection with pathogens such as methicillin-resistant Staphylococcus aureus may pose a further challenge to a patient's full recovery. Many of the persons affected by the recent tattoo-associated outbreaks of mycobacterial infection who received medical treatment were given macrolide therapy, to which they had a favorable response. Health care providers need to be aware of the symptoms associated with nontuberculous mycobacterial infections from tattoo ink, the challenges involved in diagnosing and treating them, and their own essential role in reporting such cases to MedWatch.

Even if a person receives a tattoo at a tattoo parlor that maintains the highest standards of hygienic practice, there remains a risk of infection from the use of contaminated ink. People who get tattoos must be made aware of this risk and should seek medical attention if lesions consisting of red papules or a diffuse macular rash develop at the tattoo site. Consumers should patronize artists who use sanitary tattooing practices and who can confirm that their inks have undergone a process that eliminates harmful microbial contaminants.

In light of the recent tattoo ink–related outbreaks of nontuberculous mycobacterial infection, the FDA is committed to pursuing educational and outreach efforts to health care providers, public health officials, consumers, and the tattoo industry. Our messages seek to raise awareness, improve diagnosis, and encourage adverse-event reporting, with the intent of preventing future infections. The FDA encourages health care providers, public health officials, consumers, and tattoo artists to use MedWatch to report to the FDA any tattoo-related infections and any other adverse events related to tattooing.3 The agency will continue to collaborate with other public health partners in investigating reported adverse events, identifying root causes, and taking the actions necessary to prevent future illnesses.

BACK TO TOP