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The Uses of Heparin To Treat Burn Injury

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Dr. Young is affiliated with the Henderson Research Center, which has interests in Heparin. Drs. Oremus, Hanson, Whitlock, Gupta, Dal Cin, and Raina have no financial interest in this field, nor does Ms. Archer.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov**.

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Structured Abstract

Objectives: To assess the evidence for using heparin in the treatment of burn injury or the complications of burn injury in adults and children.

Data Sources: The following databases were searched: MEDLINE® (1966-current), EMBASE (1980-current), Cumulative Index to Nursing & Allied Health (CINAHL) (1982-current), The Cochrane Central Database of Controlled Trials (1995-current), Web of Science (1976-current), and BIOSIS (1976-current). Additional data sources included the U.S. and European Patent Offices, technical experts, the partner organization, and reference lists.

Review Methods: Studies identified from the data sources went through two levels of title and abstract screening. Passing studies advanced to full text screening. Studies that met the full text screening criteria were abstracted. Criteria for abstraction included publication in any language, human patients of any age, and burns of any type, grade, or total body surface area. All formulations of heparin, and all application methods (e.g., topical, subcutaneous), were eligible for inclusion in the report. Abstracted studies required a comparison group. Outcomes of interest included mortality, pain, length of stay in hospital, thrombosis and emboli, psychiatric adjustment, and adverse effects (e.g., bleeding).

Results: Nineteen articles from 18 unique studies were abstracted and included in this report. In these articles, there were multiple uses of heparin to treat burns (e.g., wound healing, inhalation injury, sepsis, pain). However, the overall quality of the articles was weak. Examples of weakness included unclear or inappropriate treatment allocation, no blinding, no control of confounding, poorly defined burn characteristics (e.g., thickness), unclear duration of treatment, incomplete description of heparin treatment, and use of inadequately described or invalid outcome measures. Overall, the evidence from these weak articles was insufficient to determine whether the effectiveness of heparin to treat burn injury was different from the effectiveness of other treatments, or whether treatment effectiveness varied according to (a) the method of applying heparin to (b) burn etiology.

Four studies mentioned contraindications to using heparin to treat burns. These contraindications were bleeding diathesis, bleeding history, active bleeding or associated trauma with potential bleeding, active intestinal ulcer, thrombocytopenia, liver disease, renal disorders, or allergy to heparin.

Conclusion: There is no strong evidence in the 19 abstracted articles to suggest that heparin should be used in the treatment of burn injury on account of its non-anticoagulant properties. However, since the lack of evidence is largely a function of the poor quality of the articles, further research is needed to investigate the potential uses of heparin in the treatment of burn injury.

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Appendixes are provided electronically at http://www.ahrq.gov/clinic/tp/heparntp.htm

Executive Summary

Introduction

The non-anticoagulant effects of heparin and related molecules form the rationale for using heparin in the treatment of burns. Recent basic science literature suggests heparin may have a biological role as an anti-inflammatory, anti-angiogenic, and anti-metastatic agent. More importantly, at the molecular level, heparin may be an enhancer of wound healing, which has enormous implications for the treatment of acute and chronic burn wounds. In the immediate post-burn setting, the benefits of heparin's postulated anti-inflammatory and enhanced wound healing properties could include reduced pain (hence better compliance with dressing changes or physiotherapy), infection, length of hospital stay, and mortality. The long-term benefits of this expanded range of uses of heparin in the treatment of burn injury could include improved function and range of motion of extremities, reduced scarring, and possibly decreased psychiatric or psychosocial sequalae.

An expanded range of treatment options for burn injury is desirable given that 1.25 million people on average are treated annually for burns in the United States. Four percent of these people will require hospitalization and specialized burn care. Approximately 25 percent of people with severe burn injuries (greater than 75 percent of total body surface area) will die even after receiving advanced treatment at specialized burn centers. The morbidity from burn injury is also great. Short term morbidity includes the pain of the injury and subsequent surgical therapy. Over the medium to long term, the psychosocial impact of disfigurement, and the potential for post-traumatic stress disorder, can have lasting ill effects on patients and patients' loved ones.

This report was commissioned to address two key questions about the uses of heparin in the treatment of burn injury:

1. What is the evidence for the benefits and harms of heparin use in thermal injury care?
    a. Does the method of application make a difference?
    b. Do the outcomes vary by the type or degree of burn?
    c. How do the outcomes of burn treatment with heparin compare to current treatment without heparin?

2. What are the contraindications of heparin use in burns?

Addressing these questions will serve to identify the strength of the evidence for using heparin to treat burns and gaps in existing research. As well, answering these questions will facilitate the establishment of future research priorities.

Methods

A comprehensive search of the literature was conducted to capture all relevant, published studies on the topic of heparin and burns. The following electronic databases were searched:

1. MEDLINE® (1966-current);
2. EMBASE (1980-current);

3. CINAHL (Cumulative Index to Nursing & Allied Health) (1982-current);
4. The Cochrane Central Database of Controlled Trials (1995-current);
5. Web of Science (1976-current); and
6. BIOSIS (1976-current).

In addition, literature in the U.S. and European Patent Offices was searched for relevant studies, members of the TEP and the partner organization were asked to supplement the database search with additional references of published and unpublished studies, and the reference lists of articles that passed full text screening were also searched for relevant studies.

Inclusion/exclusion criteria. A list of inclusion/exclusion criteria was developed to screen studies for this evidence report. The criteria were:

Language. There was no language restriction. Studies published in any language could be included in the report.

Study Design. Studies required a comparison group for inclusion. Case series, case reports, editorials, letters, comments, opinions, abstracts, animal experiments, and conference proceedings were excluded from the report.

Population. Human patients of any age, with burns of all types, grades, and total body surface area (TBSA) involvement, could be included in the report.

Outcomes. Studies with the following outcomes could be included:

- Need for surgical procedure (e.g., grafting, debridement, fasciotomy, quality of graft take [percentage], re-grafting, reconstructive surgery);
- Pain;
- Mortality (prior to, or after, discharge from hospital);
- Length of stay in hospital;
- Scarring (size, hypertrophic scarring);
- Decrease in range of motion, function, or activities of daily living;
- Respiratory measures (e.g., length of intubation);
- Thrombosis and emboli;
- Complications (e.g., bleeding, infection);
- Rehabilitation;
- Quality of Life; and
- Psychiatric adjustment (e.g., post-traumatic stress disorder [PTSD], anxiety, depression).

Data Collection and Reliability of Study Selection

A team of raters was trained to apply the inclusion/exclusion criteria. Standardized forms were developed for this purpose, as well as for data abstraction. The forms were created and stored online using Systematic Review Software (SRS; TrialStat Corp., Ottawa, Ontario).

For title and abstract screening, two independent raters evaluated the citations that were obtained from the literature search. Articles that met the inclusion/exclusion criteria, or for which there was insufficient information to determine if they met the criteria, were retrieved for further assessment. Once retrieved, the entire text of the article was screened to determine if the inclusion/exclusion criteria were satisfied. At this stage, an article could be excluded from further review only if both raters agreed that it did not satisfy the inclusion/exclusion criteria. In

cases of disagreement, the raters met to arrive at a consensus. Articles that successfully passed the full text screening phase went on to full data abstraction.

Quality assessment of abstracted studies. The quality of the studies that passed full text screening was assessed using the Effective Public Health Practice Project, Quality Assessment Tool for Quantitative Studies. Two raters, either a local expert or a MU-EPC staff member, conducted the quality assessment for each article. Differences were resolved by consensus.

Results

The search strategy yielded 471 citations. Of these, 132 proceeded to full text screening and 19 (representing 18 unique studies) advanced to the data abstraction phase. The countries of origin for the 19 abstracted articles were: U.S. (n = 8), Soviet Union (n = 2), India (n = 2), Bulgaria, Italy, United Kingdom, China, Japan, El Salvador, and Mexico (n = 1 each for the last seven countries). Sample sizes ranged from 6 to 327, with a mean of 62. The samples were composed of patients who presented to hospital burn units or emergency rooms with burn injuries. Nine articles contained reports of the breakdown of patients by sex; males formed the majority in eight articles. Mean ages were reported in seven articles. In the five articles with adult populations, the lowest mean age was 30 years and the highest mean age was 57 years. In the two articles with pediatric populations, the lowest mean age was 3.2 years and the highest mean age was 8 years. The etiology of burn, reported in eight articles, included flame, inhalation injury, and 'thermal' injury. One article contained patients with any burn etiology. Eight articles also contained information about the degree of burn.

Key Question 1. What is the evidence for the benefits and harms of heparin use in thermal injury care?

Does the method of application make a difference? There were insufficient data in the abstracted articles to answer this question. None of the articles contained comparisons of systemic heparin (intravenous or subcutaneous) or topical heparin in the treatment of burn injury.

Do the outcomes vary by the type or degree of burn? There were insufficient data to answer this question. None of the abstracted articles contained analyses of heparin stratified by the type or degree of burn. In fact, the abstracted articles were characterized by vague reports of the etiology, type, or degree of burn in the samples.

How do the outcomes of burn treatment with heparin compare to current treatment without heparin? Multiple roles for heparin in the treatment of burns were examined in the abstracted articles. These roles included wound healing and pain control, as well as the treatment of sepsis, inhalation injury, and venous thrombosis. However, there was insufficient data available to answer the key question. This was because only 10 of the abstracted studies contained clinical outcomes (the remaining nine were primarily laboratory studies that did not contain clinical outcomes), publication dates spanned three decades, and the research was conducted in a multitude of different countries with varying standards of burn care. Thus, the available evidence was severely limited with respect to its relevance and applicability to current treatment standards in many locales. Another issue concerned the many methodological

deficiencies of the abstracted articles. These deficiencies hampered the ability to judge the reported effectiveness of heparin in burn treatment. Deficiencies included:

1. Poorly defined burn etiology and degree;
2. Unclear method of treatment allocation;
3. Unclear duration of treatment, especially the point at which heparin was first administered;
4. Outcome variables that were vague and unlikely to be reproducible; and
5. Use of descriptive statistics only (no comparative statistics).

Key Question 2. What are the contraindications of heparin use in burns?

Four of the abstracted articles listed contraindications to the use of heparin in burn patients. These contraindications were bleeding diathesis, bleeding history, active bleeding or associated trauma with potential bleeding, active intestinal ulcer, thrombocytopenia, liver disease, renal disorders, or allergy to heparin. The authors of two of these articles wrote that these contraindications served as study exclusion criteria, while the authors of the other two articles wrote that none of the patients in their studies had any of these contraindications.

Quality Assessment of Abstracted Articles

The overall quality of the 19 abstracted articles was poor. Selection bias could not be ruled out for many of the articles because the authors did not report on patient recruitment or participation rate. Similarly, non-reporting was a problem in the area of study design: only one article contained a specific description of how treatments (exposures) were allocated amongst study participants. None of the authors discussed blinding. For confounding, half of the articles had reports of potential differences between treatment groups on important confounders, and no attempts were made in any of the articles to control for possible confounding. Statistical methods (when reported) were simple between-group comparisons. Many authors did not mention the type of statistical test used in the comparisons, nor did they provide p-values. In some instances, no statistical comparisons were performed.

Limitations

There was insufficient evidence from the abstracted articles to answer the first key question. Although the authors of some of the articles claimed that heparin had benefits for outcomes such as pain, cosmesis, and wound healing, this evidence was of limited clinical utility because of the poor quality of the research. Some articles were beset by vague descriptions of study participants, burn etiology, or treatment regimen. Articles without these deficiencies had problems regarding the use of invalid comparison groups or invalid outcomes. The major issue with comparison groups was the use of controls that were treated at earlier points in time, or at different hospitals, than people who received heparin. In both cases, different treatment protocols could have confounded the observed associations between treatment and outcome. Regarding outcomes, an important one in burn injury – pain – was never examined using a validated measurement instrument such as the McGill Pain Scale. Instead, surrogate measures

(e.g., amount of pain medication used during hospitalization) were employed to estimate the degree of pain relief in heparin versus control patients. For cosmesis, pictures were used to demonstrate the benefit associated with heparin use, but there were no apparent standards employed to govern the timing, photographic angles, or interpretation of the pictures. Confounding was not controlled in any of the abstracted articles. Furthermore, confounding could not be ruled out for the randomized controlled trials because none of the authors mentioned how subjects were randomized to treatment.

The evidence from the abstracted articles was not applicable to all clinical contexts. This was because the treatment protocols employed in the articles did not demonstrate a common standard of burn care. Reasons for the absence of commonality were temporal, i.e., the research was done before current standards were adopted, or contextual, i.e., the research was country-specific and standards of burn care differ between countries.

Conclusions

There is no strong evidence in the 19 abstracted articles to indicate that the non-anticoagulant properties of heparin improve clinical outcomes in the treatment of burn injury. The lack of evidence is largely a function of the poor quality of the articles. However, some data in these poor quality articles suggest the possibility of clinical benefit, so the authors of this evidence report recommend future research into the use of heparin to treat burn injury.

Future Research

Two sets of studies are recommended for future research. The first set would investigate heparin's wound healing properties. One randomized trial would involve the application of topical heparin to donor areas (commonly the upper leg) after skin graft in adult and adolescent populations. Comparisons would be done with controls who receive standard treatment for the donor areas. Outcomes would include the healing time of the donor area, pain, itching, and scarring. In addition, research of this type may have an impact on factors that contribute to the psychiatric morbidity associated with burn injuries and their care, especially morbidity in relation to skin grafting and the pain and discomfort of donor sites. Psychiatric outcomes that would be evaluated include Acute Stress Disorder (ASD) and PTSD. If heparin is shown to promote wound healing of the donor area, then the next study would involve people (adults, adolescents, and children) with bilateral extremity burns to the arms, hands, or legs. People would serve as their own controls: topical heparin plus standard treatment would be applied to one extremity and standard treatment alone would be applied to the other extremity. Outcomes would be the same as in the first study, plus there would be an evaluation of quality of life.

The second study would consist of a randomized controlled trial to investigate the use of aerosolized heparin in the treatment of burn-related inhalation injury. The study would be conducted in both the adult and pediatric populations. The objectives regarding treatment of inhalation injury would be to decrease the reintubation rate, and length of stay in the intensive care unit (ICU). Other objectives would be to reduce the incidence of acute respiratory distress or atelectasis. As with the first set of studies, there should be an investigation of psychiatric outcomes. In addition to ASD, PTSD, and quality of life, the ICU context of the inhalation injury trial requires the inclusion of two additional psychiatric outcomes, i.e., ICU psychosis and delirium.

All these studies would have to be organized at multiple sites to ensure that adequate numbers of patients are recruited to achieve high statistical power (≥ 80%). A general list of potential outcomes includes:

- Mortality;
- Incidence of medical procedures following initial treatment with heparin or standard therapy (e.g., reintubation, excision, grafting);
- Functional performance (e.g., thumb opposition score, fingertip-to-palm distance, prehensile score);
- Pain (measured using the McGill Pain Scale);
- Scarring (measured using the Vancouver Scar Scale);
- Itching (measured via the amount of anti-pruritic medications used [e.g., Benadryl®])
- Quality of Life (measured using the Health Outcomes Burn Questionnaire for children and the Burn-Specific Health Scale for adults); and
- Post-traumatic Stress Disorder (measured using the Child Stress Disorders Checklist for children and a selected range of measurement methodologies for adults).

Evidence Report

Chapter 1. Introduction

Heparin

Heparin belongs to a family of polyanionic polysaccharides called glycosaminoglycans (GAGs). The structure of GAGs is described in terms of their prevalent repeating disaccharide sequences, which consist of alternating uronic acid and amino sugar residues. Heparin is a highly sulfated polysaccharide composed of hexuronic acid and D-glucosamine residues joined by glycosidic linkages.[1]

Heparin is a polydisperse compound with a molecular weight ranging from 3,000 to 30,000 Da (Daltons) (mean weight, approximately 15,000 Da). Commercial heparin, or unfractionated heparin (UFH), is isolated from mammalian tissues rich in mast cells. Heparin acts as an anticoagulant by activating antithrombin and accelerating the rate at which antithrombin inactivates clotting enzymes, particularly thrombin (factor IIa) and factor Xa. UFH also enhances the inhibition of factor IXa, factor XIa, and factor VIIa bound to tissue factor by antithrombin. Heparin binds to antithrombin through a high affinity pentasaccharide, which is present on about one-third of heparin molecules. Binding of heparin to antithrombin via its unique pentasaccharide sequence causes a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa, but not with thrombin. For inhibition of thrombin, heparin must bind to both the coagulation enzyme and antithrombin. This bridging effect requires a heparin chain that contains at least 18 saccharides. By inactivating thrombin, heparin not only prevents fibrin formation, but also inhibits thrombin-induced activation of platelets and factors V and VIII.[2]

Besides binding to antithrombin, heparin also binds to a wide range of other proteins via electrostatic interactions. These proteins include heparin cofactor II, receptors, and growth factors. The relative strength of binding depends on the sulfation pattern, charge density, and molecular weight.[2]

Low Molecular Weight Heparins

During the last decade, low molecular weight heparins (LMWHs) have gradually replaced UFH for some clinical indications. LMWH is prepared from UFH by controlled enzymatic or chemical depolymerization. Like heparin, LMWHs are polydisperse and comprise heparin chains from 1,000 to 10,000 Da. The mean molecular weight of LMWHs is between 3,600 and 6,500 Da. About 15 to 20 percent of LMWH chains contain the antithrombin-binding pentasaccharide sequence. At least half of the pentsaccharide-containing chains of LMWH are too short to bridge thrombin to antithrombin. For this reason, LMWHs have reduced ability to inactivate thrombin. In contrast, the smaller molecular weight chains retain their ability to inactivate factor Xa because bridging between antithrombin and factor Xa is less critical. Compared to UFH, LMWHs exhibit a better subcutaneous bioavailability, a more predictable anticoagulant response, and a longer half-life.[3] More recently, synthetic analogs of the antithrombin-binding pentasaccharide sequence have been developed.[4]

Non-Anticoagulant Effects of Heparin

Heparin possesses both a flexible structure and a high anionic charge that permits electrostatic interactions with a variety of different molecules. While heparin has been used largely for its anticoagulant effects, there is evidence that heparin and related molecules also possess anti-inflammatory and antiangiogenic properties, as well as a capacity for wound healing. These effects are discussed separately below.

Anti-Inflammatory Effects

Although the mechanisms responsible for the anticoagulant effects of heparin are well understood, the mechanisms underlying heparin's anti-inflammatory activity are not. The evidence that heparin possess anti-inflammatory properties comes mainly from cell culture and animal studies. The anti-inflammatory and immunomodulating effects are far-reaching and include influencing monocyte, T-cell and neutrophil activity, nitric oxide production, chemokine and cytokine activity, complement activity, platelet activation and aggregation, and smooth muscle cell proliferation.[5]

Antiangiogenic and Antimetastatic Effects

There is increasing interest in a potential role for heparin and related molecules in the management of cancer patients.[6] LMWHs have generated particular interest because they have been validated in both the treatment and prevention of thromboembolic disease in patients with malignancy. More interestingly, the benefits of LMWH therapy appear to be independent of any anticoagulant properties, which suggests that direct effects on tumor cell biology can help to explain the mechanism. Possible mechanisms include the inhibition of selectin-mediated cell-cell interactions, heparanase inhibition, binding of proangiogenic growth factors (e.g., basic fibroblast growth factor [bFGF] and vascular endothelial growth factor [VEGF]), and stimulation of tissue factor pathway inhibitor (TFPI) release.[7]

Wound Healing Effects

A persistent inflammation with the accumulation of large numbers of neutrophils is characteristic of chronic wounds. Secretory products released from these cells, such as elastase, cathepsin G, and proteinases, are detrimental to wound healing because they degrade the extracellular matrix and growth factors and further recruit neutrophils to the wound area. Heparin and related molecules are thought to inhibit the action of these secretory products via electrostatic interactions.[8,9]

Clinical Uses of Heparin

Since its discovery in 1917, heparin preparations have been used as an effective anticoagulant for thromboembolic prophylaxis and treatment.[10-13] With over half a century of use, other roles for heparin have been elicited, including angiogenesis regulation, lipoprotein lipase modulation, maintenance of endothelial competence, and inhibition of vascular smooth

muscle proliferation after injury.[14] This section will focus on clinically proven and accepted applications of heparin.

Heparin is the most widely used parenteral antithrombotic in clinical medicine due to its ease of administration and titration, availability, cost, known side-effect profile, and demonstrated clinical efficacy. Other parenteral antithrombotic agents available include heparinoids such as fondaparinux or direct thrombin inhibitors such as hirudin and bivalirudin. These drugs are more expensive, not as easily titrated and reversed, and have been studied in fewer clinical applications relative to heparin. Numerous guidelines define the role of heparin in thrombosis prevention and treatment; the American College of Chest Physicians (ACCP) guidelines are perhaps the most frequently cited. See Baglin et al. for a review of these guidelines.[15] Clinical indications for heparin have been divided into (1) thrombosis prevention and (2) thrombosis treatment (See Tables 1 to 3 below).

Thrombosis Prevention

Subcutaneous heparin has been demonstrated to reduce the incidence of venous thromboembolism in several clinical scenarios. Table 1 summarizes both the clinical indications and level of evidence for using heparin in this treatment area. Grades of evidence from Tables 1 to 3 are explained in Table 4.

Table 1. Accepted indications for heparin prophylaxis

Indication for Heparin Prophylaxis	Grade of Evidence	Literature Reference
Major non-orthopedic surgery	**Grade A**	**Clagett & Reisch 1988[16]**
Major elective orthopedic surgery	**Grade A**	**Nurmohamed et al. 1992,[17] Koch et al. 1997[18]**
Hip fracture	**Grade A**	**Handoll et al. 2002[19]**
Medical patient at high risk of VTE	**Grade A**	**Mismetti et al. 2000,[20] Leizorivcz et al. 2004[21]**
Major trauma with no contraindications	**Grade B**	**Upchurch et al. 1995,[22] Geerts et al. 1996[23]**
Lower limb plaster immobilization	**Grade B**	**Lassen et al. 2002[24]**

Thrombosis Treatment

Heparin, in the absence of heparin induced thrombocytopenia (drop in platelet number), is the initial anticoagulant of choice for treating thrombotic processes (blood clots) involving veins and arteries. Tables 2 and 3 contain generic summaries of clinical scenarios where therapeutic heparin is indicated for treating thrombotic processes.

Table 2. Accepted indications for heparin treatment – venous

Indication for Treatment: Venous	Grade of Evidence	Literature Reference
Deep vein thrombosis (DVT) and pulmonary embolism (PE)	Grade A	Barritt & Jordan 1960,[25] Douketis et al. 1998,[26] Gould et al. 1999[27]
Cerebral venous sinus thrombosis	Grade B	Bousser et al. 1985,[28] Einhaupl et al. 1991[29]
Intraabdominal venous thrombosis	Grade C	Abdu et al. 1987[30]
Superficial vein thrombosis (SVT)	Grade C	Wichers et al. 2005[31]

Table 3. Accepted indications for heparin treatment – arterial and other

Indication for Treatment: Arterial and Other	Grade of Evidence	Literature Reference
Acute myocardial infarction post-lysis with any of: Anterior Q wave , LV dysfunction, CHF, history of PE or systemic embolism, mural thrombus, atrial fibrillation	Grade A	Collins et al. 1996,[32] Hirsh & Raschke 2004[33]
Acute coronary syndrome	Grade A	Oler et al. 1996,[34] Magee et al. 2003[35]
Peripheral vascular surgery	Grade C	Thompson et al. 1996[36]
Central venous and arterial catheters	Grade C	Merrer et al. 2001[37]
Hemodialysis	Grade A	Lim et al. 2004[38]
Cardiopulmonary bypass surgery (CPB)	Grade A	Beijering et al. 1997[39]

As shown above, in the realm of thromboembolic pathology, heparin plays a major role in clinical medicine.

Table 4. Grades of evidence

Grade of Evidence	Explanation
A	Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk
B	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
C	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain

Source: Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. Chest 2006;129(1):174-181.

Burn Injury

Approximately 1.25 million people are treated annually for burn injuries in the United States. Four percent of these people require hospitalization and specialized burn care. High-risk populations for burn injuries include children, elderly, physically or mentally disabled, and people in military service.[40,41]

Definition and Description of Burn Injury

Burn injuries are either partial thickness or full thickness in nature. Partial thickness burns involve the epithelium and various depths of the underlying dermis. These burns are diagnosed both clinically and temporally. Partial thickness burns can be divided into superficial or deep partial thickness burns.

Superficial partial thickness burns appear as an erythema (first degree) or blistering (second degree) on the skin. Very superficial burns correlate with injury to the epithelial layer of skin and usually heal without medical intervention or scarring (except for possible hyperpigmentation, which is usually temporary in nature [e.g., sunburn]). Superficial partial thickness burns heal within 7 to 14 days.

A superficial partial thickness burn may also involve the superficial aspect of the dermis (second degree), which can result in blistering and scarring of the skin. The presence of varying shades of foci of pallor indicates deep partial thickness burns that heal within six weeks. However, healing may be incomplete. These burns scar the skin and frequently require surgical debridement and grafting.

Full thickness burns result in injury and loss of the entire epithelium and dermis (third degree). A full thickness burn may also involve injury to underlying structures such as muscles, nerves, tendons, or bones (fourth degree). If left on their own, without surgical intervention, these burns would take well in excess of six weeks, or even months, to heal. These burns may cause significant scarring and, if present around joints, may severely limit the range of motion .[42]

Partial Thickness
First degree → superficial (erythema)
Second degree → deep (blister, pallor)

Full Thickness
Third degree → white, tan, beige, red, etc. skin color
Fourth degree → involves tendon, bone, etc.

Burn injuries may also be classified according to the type of noxious agent causing the burn (e.g., flame, scald, flash, contact, smoke inhalation, electrical). Scald injuries, the most common burn injury in civilian populations, are secondary to contact with hot liquids. Hot water is the most common cause of scald injury, but other agents can include coffee, tea, soup, sauces, hot grease, or oil. Burns secondary to contact with tar and asphalt are also considered scald injuries. Intentional scalding of children is a common method of child abuse.

Flame burns are secondary to contact with a source of open flame. House fires, careless smoking, automobile accidents, inappropriate use of flammable materials, and ignition of clothing are common factors associated with flame burn injury. Flame burns are associated with

a serious and potentially fatal condition known as smoke inhalation injury. Inhalation injury is due to the exposure of the respiratory tract to steam and toxic inhalants from the smoke of a fire.[43]

Flash burns are secondary to exposure to explosions of combustible or flammable materials. Contact burns are secondary to skin contact with hot items such as metal, glass, chemicals, plastic, or coals. Electrical burns are thermal injuries that occur when electrical energy is converted into heat upon contact with the skin.[44] Electrical burns can severely affect deeper structures such as nerves or bones even when there is minimal damage to the overlying skin.

Burn Care

In the past three decades, North American burn care has undergone significant transformation, and this has led to markedly improved survivability.[45-47] The North American health care system has developed a sophisticated approach to hospital burn care that is predicated on a network of specialized burn treatment centers. These centers are well equipped and professionally staffed to treat local injuries and to handle the transfer and treatment of serious burn injuries from more distant locales. This transformation of burn care reflects advancements in multiple areas of medicine, including critical care, wound infection control and antimicrobial therapy, surgical therapy (e.g., early excision and grafting), specialized burn care research, and coordinated methods of burn patient transfer (e.g., air ambulance and accompanying medical support services).[45] Early excisional therapy of deep partial thickness or full thickness burns is a common component of the North American standard of care for burn injury.[46,47] Burns that heal within three weeks commonly do well and are less likely to produce hypertrophic scarring or functional impairment. Burns that require more than three weeks to heal are commonly associated with hypertrophic scarring or functional impairment. For patients with small to moderate burn injuries where the healing time will exceed three weeks, early excision and grafting is the recommended course of treatment. The benefits of early excision and grafting include decreased hospitalization, early return to work or school, enhanced functional status, and improved physical appearance. However, properly estimating the time to healing for a burn remains an important clinical challenge.[44] Risk factors associated with mortality in burn injury include total body surface area (TBSA) greater than 40 percent, age over 60 years, and inhalation injury.[48] Temporary or permanent disabilities are common in patients with significant burn injuries who are admitted to specialized burn care facilities.[49] Reconstructive surgery and long-term rehabilitation are routine components of extended care for disabled burn patients.

Psychosocial Aspects of Burn Injury

The morbidity associated with burn injury is not limited to physical conditions such as pain or scarring. Psychiatric and psychosocial morbidities form important and often overlooked aspects of burn injury. Psychiatric and psychosocial morbidities are classified into pre- and post-injury conditions.[50,51] Pre-injury psychiatric conditions in adults may include depression, suicidality, substance abuse, and personality disorders. In children, pre-injury conditions may include behavioral disorders such as conduct disorder or attention deficit hyperactivity disorder.[50,51]

In the post-injury phase, hospitalization and acute burn care can lead to psychiatric and psychosocial stresses for patients.[50,51] Common psychiatric conditions include delirium, acute

stress disorder (ASD), post-traumatic stress disorder (PTSD), and depression. Psychological suffering (i.e., PTSD) may also be manifest in the parents of children or adolescents with burn injury.[52]

The first year post-burn injury may be particularly psychologically stressful for patients,[51,53] but most adult[50,51] and pediatric[54] burn patients do not suffer long-term, burn-related, psychiatric sequelae.

For a minority of burn injured patients, altered patterns of socialization may develop, especially for men with visible disfigurement. In women, decreased levels of sexual satisfaction are a frequent long-term result of burn injury.[51]

Heparin and Burns

The non-anticoagulant effects of heparin and related molecules form the rationale for the use of heparin in the treatment of burns. This report will address two main questions related to heparin and burns:

1. What is the evidence for the benefits and harms of heparin use in thermal injury care?
   a. Does the method of application make a difference?
   b. Do the outcomes vary by the type or degree of burn?
   c. How do the outcomes of burn treatment with heparin compare to current treatment without heparin?

2. What are the contraindications of heparin use in burns?

Addressing these questions will serve to identify both the strength of the evidence for using heparin to treat burns and gaps in existing research. As well, answering these questions will facilitate the establishment of future research priorities.

Chapter 2. Methods

Analytic Framework

An analytic framework is a schematic representation of the strategy for organizing topics for review and guiding literature searches. Figure 1 illustrates the inter-relationships between the questions being asked in this evidence report. The key areas addressed are the use of heparin to treat burns, heparin's method of application (e.g., topical, intravenous), the clinical outcomes and contraindications of said treatment, and a comparison of heparin to other burn treatments. Heparin can be applied topically (e.g., cream or dressing material impregnated with heparin), subcutaneously, by infusion, via aerosol, or by a combination of any of the aforementioned methods. Burns are described by degree (first, second, third), total body surface area (TBSA) involvement, and type (flame, scald, flash, contact, smoke inhalation, electrical, or any combination of these types). The clinical outcomes are separated into early and late outcomes. Early outcomes include the need for acute hospitalization and surgery (e.g., grafting, debridement, and fasciotomy), quality of graft take (percentage), pain, mortality (prior to discharge from hospital), length of hospital stay, scarring (size, hypertrophic scarring, contractures), rehabilitation outcomes (decreased range of motion), intensive care unit (ICU) admissions and respiratory measures (e.g., length of intubation), incidence of thromboses and emboli, complications such as bleeding or infection, and acute psychiatric adjustment (delirium, acute stress disorder [ASD] and post-traumatic stress disorder [PTSD]). Late outcomes include rehabilitation, re-grafting, reconstructive surgery, quality of life, psychiatric adjustment (anxiety, depression), and mortality (after discharge from hospital). The three major contraindications to heparin use are thrombocytopenia, bleeding, and osteoporosis (after long term use). The benefits of heparin use in burn care, compared to other burn treatments without heparin, will be explored in the results and discussion sections of this report.

Topic Assessment and Refinement

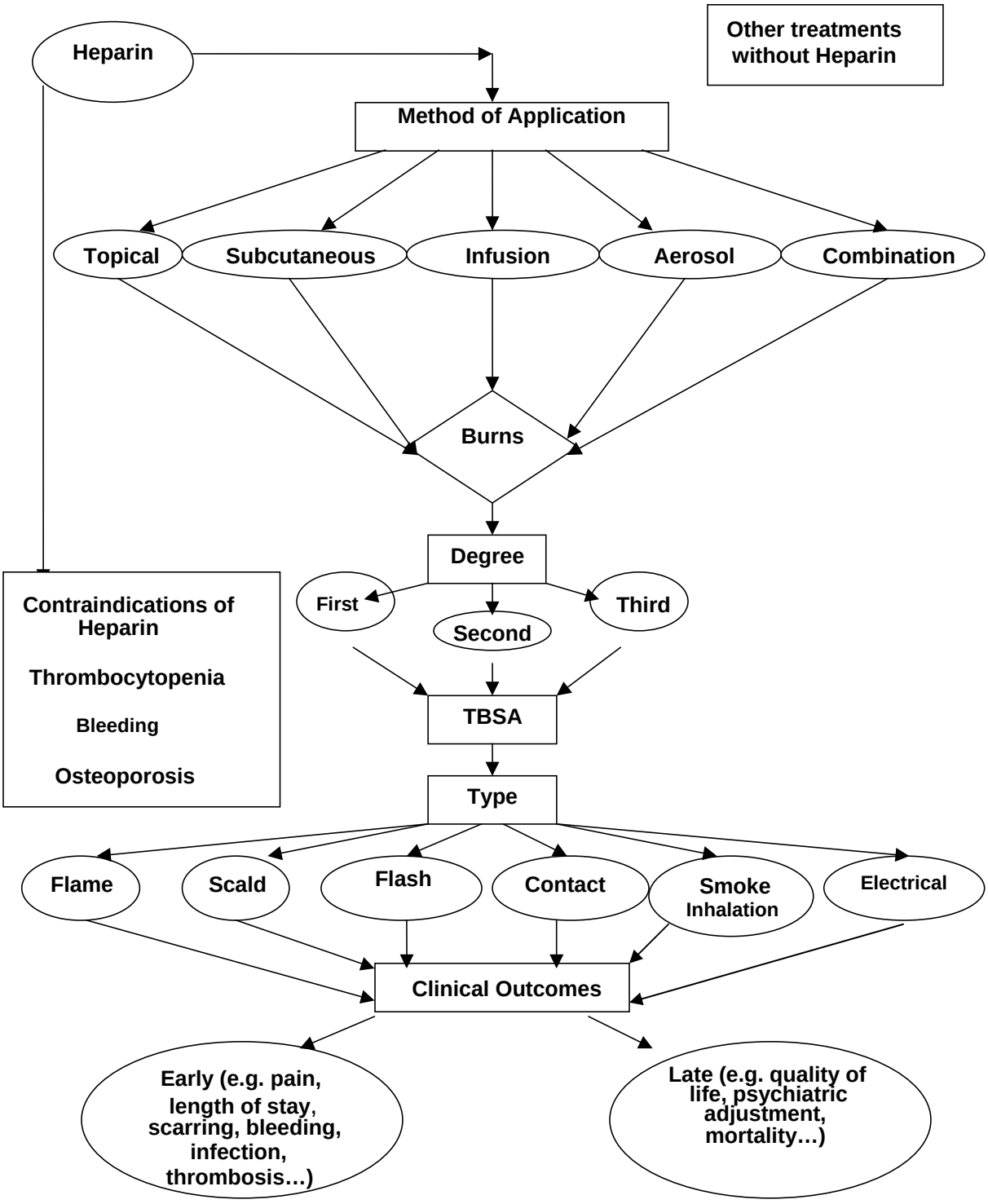
Research Team

A multidisciplinary, local research team ('local experts') with expertise in epidemiology and systematic reviews (M. Oremus, PhD; P. Raina, PhD), pediatric psychiatry and pediatric burn injury consultation (M. Hanson, MD), clinical chemistry (E. Young, PhD), and surgery (R. Whitlock, MD; A. Dal Cin, MD) was assembled at the McMaster University Evidence-based Practice Center (MU-EPC) to plan an approach to completing this evidence report in a thorough, timely, and efficient manner. This team had regular meetings to reach consensus on key methodological issues.

A 'kick-off' teleconference with the partner organization (Saliba Burns Institute), the Agency for Healthcare Research and Quality (AHRQ) Task Order Officer (TOO), the local experts, and MU-EPC staff was held at the start of this project to define the magnitude of the topic and refine and clarify the preliminary research questions for this evidence report. A Technical Expert Panel (TEP), composed of internationally recognized experts in the field of burns, was assembled to provide high-level content expertise on heparin use and burns. Members of the TEP were

requested to participate in teleconferences on an as-needed basis throughout the data refinement and data abstraction phases of this evidence report.

Figure 1: Analytical Framework



Technical Expert Panel Teleconference Calls

The first TEP teleconference took place on November 29, 2005. Technical experts participating included Dr. Bishara Atiyeh (Clinical Professor Of Surgery, Plastic And Reconstructive Surgery, American University of Beirut Medical Center, Beirut, Lebanon), Dr. Leo Klein (Head, Department of Burns Medicine, Charles University and Teaching Hospital, Prague, Czech Republic), Dr. Jan Koller (Slovak Society of Plastic and Aesthetic Surgery, Bratislava, Slovakia), and Dr. Glenn Warden (Editor, Journal of Burn Care and Research, Salt Lake City, Utah) (see Appendix A[*]). A second TEP teleconference took place on February 3, 2006. Several topics were discussed during both calls, including the definition and scope of the key questions, search strategies, inclusion and exclusion criteria, and the composition of the screening and data abstraction forms.

General Methods

Key Questions

The original set of key questions for this evidence report was revised by the local experts and discussed during the TEP teleconferences. Additional discussants included the partner organization and the TOO.

The revised key questions are:

1. What is the evidence for the benefits and harms of heparin use in thermal injury care?
    a. Does the method of application make a difference?
    b. Do the outcomes vary by the type or degree of burn?
    c. How do the outcomes of burn treatment with heparin compare to current treatment without heparin?
2. What are the contraindications of heparin use in burns?

Literature Search Strategy

We conducted a comprehensive search of the literature to capture all relevant, published studies on the topic of heparin and burns. The following electronic databases were included in the search:

1. MEDLINE (1966-current);
2. EMBASE (1980-current);
3. CINAHL (Cumulative Index to Nursing and Allied Health) (1982-current);
4. The Cochrane Central Database of Controlled Trials (1995-current);
5. Web of Science (1976-current); and
6. BIOSIS (1976-current).

In addition, literature in the U.S. and European Patent Offices was searched for relevant studies, members of the TEP and the partner organization were asked to supplement the database search with additional references of published and unpublished studies, and the reference lists of

[*] Appendixes are provided electronically at http://www.ahrq.gov/clinic/tp/heparntp.htm.

articles that passed full text screening were also searched for relevant studies. Please see Appendix B for a detailed description of the search strategies used for this review.

Inclusion/exclusion criteria. A list of inclusion/exclusion criteria was developed to screen studies for this evidence report. The criteria are as follows:

Language. There was no language restriction. Studies published in any language could be included in the report.

Study design. Studies required a comparison arm for inclusion. Case series, case reports, editorials, letters, comments, opinions, abstracts, animal experiments, and conference proceedings were excluded from the report.

Population. Human patients of any age, with burns of all types, grades, and TBSA involvement, could be included in the report.

Outcomes. Studies with the following outcomes could be included:

1. Need for surgical procedure (e.g., grafting, debridement, fasciotomy, quality of graft take [percentage], re-grafting, reconstructive surgery);
2. Pain;
3. Transfusion rate;
4. Mortality (prior to, or after, discharge from hospital);
5. Length of stay in hospital;
6. Scarring (size, hypertrophic scarring);
7. Decrease in range of motion, function, or activities of daily living;
8. Respiratory measures (e.g., length of intubation);
9. Thrombosis and emboli;
10. Complications (e.g., bleeding, infection);
11. Rehabilitation;
12. Quality of life; and
13. Psychiatric adjustment (e.g., PTSD, anxiety, depression).

Appendix C* contains the list of excluded studies.

Data Collection and Reliability of Study Selection

A team of research assistants was trained to apply the inclusion/exclusion criteria. Standardized forms were developed for this purpose, as well as for data abstraction (see Appendix D). The forms were created and stored online using Systematic Review Software (SRS; TrialStat Corp., Ottawa, Ontario).

For title and abstract screening, two independent raters evaluated the citations that were obtained from the literature search. Articles that met the inclusion/exclusion criteria, or for which there was insufficient information to determine if they met the criteria, were retrieved for further assessment. Once retrieved, the entire text of the article was screened to determine if the inclusion/exclusion criteria were satisfied. At this stage, an article could be excluded from further review if both raters agreed that it did not satisfy the inclusion/exclusion criteria. In cases of disagreement, the raters met to arrive at a consensus.

* Appendixes are provided electronically at http://www.ahrq.gov/clinic/tp/heparntp.htm.

Articles that survived the full text screening phase went on to full data abstraction. Either a local expert or a MU-EPC staff member abstracted the data. Local experts who were responsible for addressing the key questions in the results chapter reviewed the abstractions to confirm the accuracy of the work.

Quality Assessment of Abstracted Studies

The quality of the studies that passed the full text screening was assessed using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies (EPH Tool [see Appendix E*]).[55] The EPH Tool was developed for systematic reviews of the effectiveness of public health interventions.

The EPH Tool can be utilized with observational studies or clinical trials. It is divided into several sections, including selection and allocation bias, confounding, blinding, validity and reliability of data collection instruments, analysis (e.g., use of appropriate statistical methods), and intervention integrity (e.g., percentage of participants who actually received the allocated intervention or exposure). Each section contains from one to seven questions; algorithms[56] are used to transform question responses into a qualitative score for each section. The score options are weak, moderate, or strong.

Two raters, either a local expert or a MU-EPC staff member, conducted the quality assessment for each article that passed the full text screening phase. Differences were resolved by consensus.

Summary of Findings: Descriptive and Analytic Approaches

Descriptive approaches were used to summarize the characteristics of abstracted articles and answer the key questions. The local experts judged that a meta-analysis was not feasible because the abstracted articles were far too heterogeneous with respect to study participants, study design, treatment modalities, and outcomes. Instead, data were collected on the characteristics of study participants, methods of diagnosis, treatments, and outcomes. The quality of this information was judged and the findings were summarized in both text and tables. This evidence report provides a greater understanding of the effectiveness of using heparin in burn treatment, identifies gaps in existing research, and suggests a plan for future research.

Peer Review Process

The partner organization, local experts, and members of the TEP were asked to identify potential peer reviewers from relevant professional organizations, consumer organizations, and purchasers of care. A list of potential reviewers was compiled by the MU-EPC and submitted to AHRQ for approval prior to the circulation of the draft report. The reviewers were asked to review the report and provide feedback on clinical and methodological content, as well as on the readability and presentation of information. Their comments and suggestions will be incorporated into the report where possible.

* Appendixes are provided electronically at http://www.ahrq.gov/clinic/tp/heparntp.htm.

Chapter 3. Results

Literature Review and Screening

The literature search yielded 470 citations. A search of the reference lists of abstracted articles yielded one additional citation of interest, which passed through all levels of screening and went on to be abstracted. In total, 339 citations were excluded from further review following the two initial levels of title and abstract screening; 132 citations proceeded to full text screening. Of these 132 articles, 112 were excluded from further review and 19 advanced to the data abstraction phase. One article could not be retrieved despite persistent inter-library loan requests and attempts to contact the authors and publishing journal. Figure 2 depicts the flow of articles through the screening process. The remainder of this chapter contains a description of the general characteristics of the abstracted articles, a section addressing how the abstracted articles answer the two key questions, and a quality assessment of the abstracted articles.

General Characteristics of the Abstracted Articles

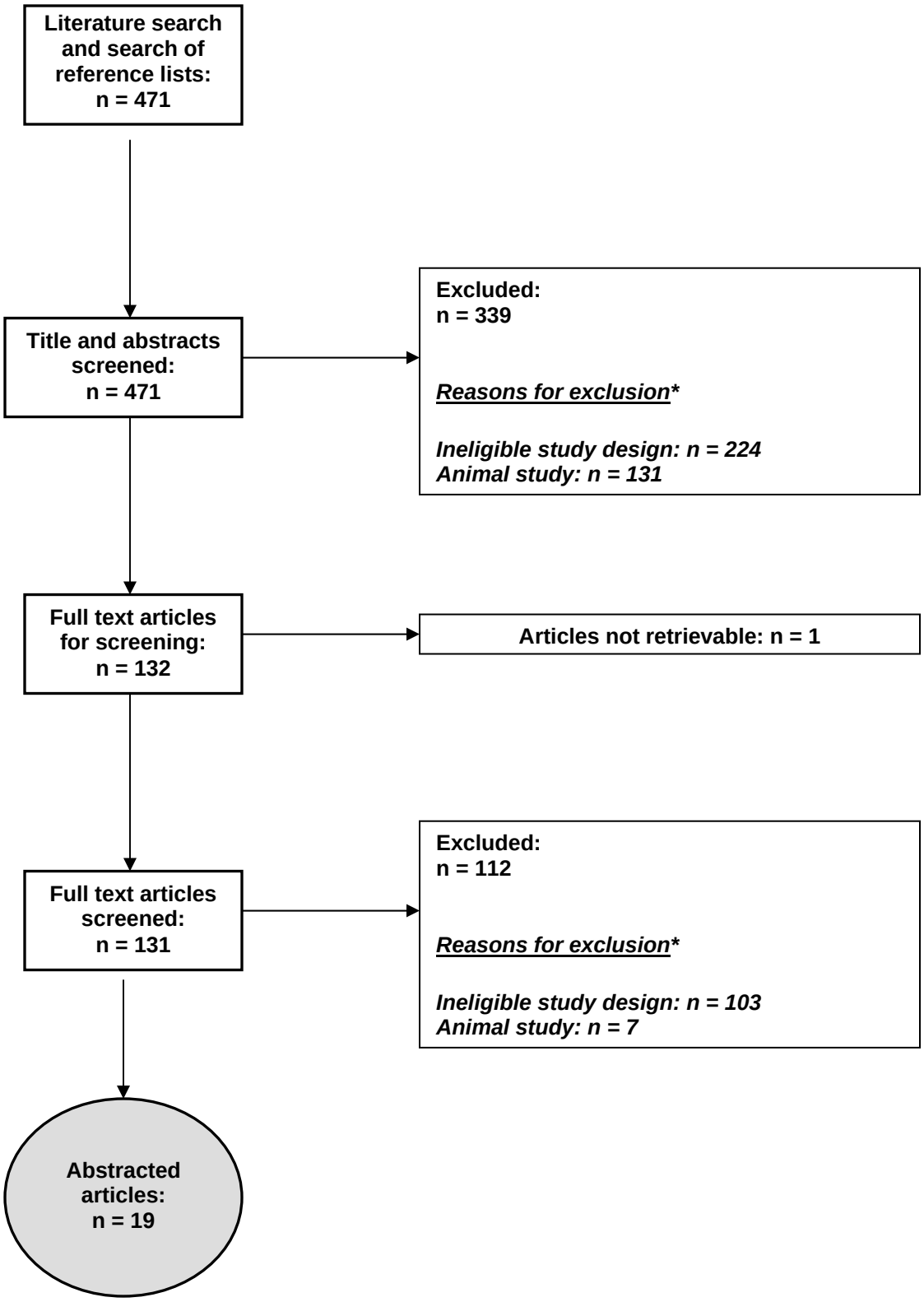
Nineteen articles describing 18 unique research projects contained data on the use of heparin to treat burns (Table 5). In two articles from the University of Michigan, the same group of patients was used to assess outcomes related to deep vein thrombosis.[57,58] Eight of the abstracted articles were based on research conducted in the U.S..[57-64] The remainder were from the Soviet Union,[65-68] United Kingdom,[69] China,[70] Japan,[71] India,[72,73] El Salvador,[74] and Mexico.[75] Sample sizes ranged from 6[64] to 327.[63] The sample size was not reported in one article.[62] The mean sample size, counting the Michigan articles as one, was 62. Samples were composed of patients who presented to hospital burn units or emergency rooms with burn injuries.

In eight of nine articles where the complete breakdown of patients was reported by sex, the majority of patients were male.[58,63,66,68,70,72-75] The largest proportion of males was 0.95 (19/20)[70] and the smallest proportion of males was 0.49 (49/100).[72]

The authors of seven articles reported the mean age of patients.[58,59,63,68,70,74,75] In the five articles with adult populations, the lowest mean age was 30 years[75] and the highest mean age was 57 years.[68] In the two articles with pediatric populations, the lowest mean age was 3.2 years[74] and the highest mean age was approximately 8 years.[59] Age ranges, reported in ten articles,[58,63,64,66-68,72-75] were as wide as 21 to 77 years[68] and as narrow as 0.25 (3 months) to 8 years.[74]

The etiology of burn, reported in eight articles,[58-60,63,66,72,74,75] included flame,[58,72,74,75] scald,[72,74] inhalation injury,[58,59,66] and 'thermal'.[60] One article contained patients with any burn etiology.[63] Eight articles also contained information about the degree of burn.[59,63,65,67,69,72,74,75] Patients with first degree burns were included in two articles,[65,69] second degree in six articles,[63,65,67,72,74,75] and third degree in six articles.[59,63,65,73-75]

Figure 2. Flow diagram showing the final number of articles meeting the eligibility criteria



*Articles may have been excluded for more than one reason.

Total body surface area (TBSA) involvement was reported by the authors of 17 articles (exceptions were the authors of the Bulgarian[67] and British[69] articles). Reporting was in the form of a range (e.g., 8.5 to 90 percent TBSA),[59,60,64,66,68,72] mean TBSA (e.g., 65.8 ± 13.7 percent),[57,58,62,63,70,74,75] or the upper or lower bound of TBSA that would be required for a patient to be included in a research project (e.g., TBSA > 30 percent).[61,65,71,73] No common level of TBSA involvement marked the articles. For example, one article included patients with TBSA involvement between 8.5 and 90 percent.[60] Other articles included patients with TBSA > 30 percent[61,71] or TBSA in the range of 50 to 60 percent.[59,62]

Key Questions

Question 1. What is the Evidence for the Benefits and Harms of Heparin Use in Thermal Injury Care?

The 19 abstracted articles did not contain strong evidence for the efficacy of heparin in treating burns. Three of the articles were randomized controlled trials (RCTs) in adult and pediatric burn patients. The first, by Srivastava et al., was a comparison of heparin and standard therapy to standard therapy alone. Heparin use was found to improve the following outcomes: mortality, infection rate, graft healing, and eschar separation.[73] For mortality, three out of 25 people died in the heparin group, while 11 out of 25 people died in the control group. Infection rates were lower in the heparin group, with 20 people having wound infection versus all 25 people in the control group. Grafts healed 11 days faster on average in the heparin group and eschar separation was a mean of 9 days faster in the heparin group. The study had a clear monitoring protocol for adverse effects and no increases in bleeding were found as a result of heparin use. Despite the encouraging results, these findings must be weighed against the study's limitations. The authors described the study as randomized, but they did not discuss the allocation method. If allocation was improper, then healthier patients may have been disproportionately assigned to the heparin group. The authors also failed to address blinding, did not clearly define the clinical outcomes, and only reported descriptive statistics. Lastly, the treatment regimen was a combination of systemic and topical heparins, so any potential therapeutic benefits could not be attributed to one route of administration over the other.

The second RCT showed that topical heparin significantly reduced primary scarring in 37 heparin-treated adults and children.[67] These people were compared to 27 controls who received standard therapy. However, the method of treatment allocation was not described in the publication and the outcome measures were not validated in burned patients. Thus, it is difficult to attribute the favorable outcome to heparin alone.

The third RCT, an unpublished study by Venkatachalapathy et al., was conducted to examine the effect of topical heparin on clinical outcomes in people with second degree burns (age range:15 to 35 years).[72] Control patients received usual treatment, which included topical antimicrobial cream, debridements, and skin graftings in the early post-burn period. Outcomes included length of hospital stay, mortality, and number of skin grafts. The authors found a significantly ($p<0.001$) shorter length of hospital stay in the heparin-treated patients (all 50 heparin-treated patients had lengths of stay ≤ 40 days, while 28 of 50 control patients had stays of 40 to 50 days). There was also less mortality (0 heparin versus 5 controls) and fewer skin grafts (4 heparin versus 10 controls) in the heparin group. However, it was unclear how patients

were allocated to treatment. The authors simply described the process as "randomly selected." Indeed, there was an imbalance in the study groups: the control group had more patients with a larger burned surface area (a major predictor of morbidity and mortality in burns). If the controls were sicker, then that fact alone (not the use of heparin) could explain the better outcomes in the heparin group.

Two articles contained investigations of heparin's use in adult-only burn populations. The first, by Reyes et al., was a non-randomized, comparative (cohort) study of nine patients who were injured in a thermal disaster.[75] Four patients received topical heparin immediately after hospital admission and they were reported to have better pain relief, less swelling, fewer fasciectomies, a shorter length of hospital stay, and earlier burn revascularization than five control patients who did not receive topical heparin until 5 days after hospitalization. While the results were positive for heparin, they must be interpreted cautiously due to two study limitations. First, the important outcome of pain relief was measured using doses of pain medication. Besides the fact that the degree of patient pain is not necessarily associated with doses of pain medication, patients' impressions of pain were never directly assessed in the study. Second, two patients in the control group received daily subcutaneous heparin before day 5 of hospitalization. This 'contamination' of the control group diminishes the ability to conclude that inter-group differences were due to the use versus non-use of heparin. The observed differences may have occurred because of random chance owing to the small sample size. Or, given that the heparin and control groups were not treated at the same hospital, subtle variations in institutional practice patterns (e.g., protocols for administering medications) could have led to the observed differences.

The other article about heparin use in adult burn patients was written by Acharya, who compared the effects of three therapies: 1) topical heparin, 2) topical heparin with topical steroid and antibiotic, and 3) topical steroid and antibiotic alone.[69] In the article, the type and degree of burn were poorly defined (e.g., "superficial burn") and the outcomes (e.g., pain and reduced inflammation) were vague and poorly validated. The study showed no difference between treatment groups, but the author failed to use statistical hypothesis tests and instead relied on descriptive statistics (e.g., number of patients in each group with "speedy" relief of pain) to make inter-group comparisons.

Three studies focused on the use of heparin to treat burns in pediatric populations. Desai et al. conducted a non-randomized trial (cohort study) to examine the effect of aerosolized heparin with acetylcysteine for 7 days on inhalational burn injuries in children.[59] The heparin/acetylcysteine group ($n = 47$) had significantly less reintubations, less atelectasis, and a lower mortality rate than the standard therapy group ($n = 43$, $p < 0.05$). However, the results were beset by two major limitations. First, the standard therapy group was a historical cohort whose members received treatment between 1 and 5 years before the first members of the active treatment group received heparin/acetylcysteine. If there were changes in the protocols for managing pediatric burns during this 5 year period, then the observed differences could have been due to these changes, rather than to any possible effect of heparin. Second, heparin and acetylcysteine were tested together, so the impact of either active agent cannot be separated from the other.

Another pediatric study was a 20-year chart review of burned children who developed renal vein thrombosis (RVT).[64] Six such children were identified in the review; three received heparin and three did not. The three children who did not receive heparin died within 5 days of developing RVT, while the children who received heparin survived. The authors conclude by

recommending heparin therapy for burned children with RVT, but the comparison upon which this recommendation is based may be invalid. Although the historical cohort and small sample size are problematic, the main difficulty is that the controls may not have had the same exposure opportunity as the treated patients. Even if there were no contraindications to heparin in the controls, they were diagnosed with RVT within 24 hours of death (n = 2) or at necropsy (n = 1). Thus, the controls may not have had the chance to receive heparin, and they may have been sicker than the children who were treated with heparin.

The final pediatric article was an unpublished cohort study to compare nine children undergoing standard burn therapy in 1998 to 10 children undergoing standard therapy plus heparin (intravenous followed by topical) in 1999.[74] The authors reported lower mortality (four versus eight deaths) and less pain in the heparin group. The mortality result must be interpreted carefully because the study groups were different with respect to co-morbidity. All nine children in the 1998 (control) group had sepsis, while three children in the 1999 (heparin) group had sepsis. The treatment for sepsis was not well described and may have changed over time, thereby accounting for the difference in mortality. The authors measured pain using subjective, observational criteria like patient behavior (e.g., crying, struggling) and a decrease in the "noisy din and distressing emotional ambience" of the hospital ward. These observations were not measured in a systematic, quantitative fashion and therefore should not be taken as indicative of a treatment effect.

Several abstracted articles met the inclusion criteria at the screening phase, but upon data abstraction they were found to contain little or no clinical data on the use of heparin to treat burns. Four such studies contained no presentation of clinical outcomes, with the focus instead on laboratory outcomes such as autologous red blood cell survival,[62] fibrin degradation products,[61] platelet aggregation,[60] and blood coagulation.[65] Another three studies examined treatment modalities such as continuous renal replacement and had mentioned heparin in passing, but no outcomes were presented based on heparin therapy.[68,70,71] One study contained treatment regimens that included heparin, but it was not possible to separate the effect of heparin from concomitant therapies such as nicotinic acid, contrical, thrental, phytin, and alpha-tocopherol.[66] Three studies focused on the possible risk factors for, and incidence of, deep vein thrombosis/pulmonary embolism (DVT/PE) in burn patients.[57,58,63] Each study identified the number of patients with DVT/PE who had been on heparin prophylaxis, but reported no other outcomes by this grouping.

Given the above discussion (summarized in Table 6), some of the abstracted studies contain evidence that heparin has potential clinical benefits in the areas of reducing mortality,[59,72-74] reducing pain,[72,75] improving cosmesis, [67,73,75] and alleviating lung injury in inhalational burns.[59] However, these studies suffer from numerous limitations (see above and the quality assessment section below). In light of these limitations, the evidence supporting the use of heparin in burn injury cannot be considered strong.

The a priori defined sub-questions to be answered by this review are:

1. Does the method of application make a difference?
2. Do the outcomes vary by the type or degree of burn?
3. How do the outcomes of burn treatment with heparin compare to current treatment without heparin?

Does the method of application make a difference? As illustrated above, there are insufficient data available to determine if the method of application of heparin in burn patients makes a difference with respect to clinical outcomes.

The following gaps exist within the literature. Four published studies[67,69,73,75] and two unpublished manuscripts[72,74] comparatively examined (e.g., treatment versus control) clinical outcomes in the use of heparin to treat burns. Another study had clinical outcomes, but the effect of heparin could not be separated from concomitant therapy.[59] In these studies, no comparisons were made of systemic heparin (intravenous or subcutaneous) or topical heparin applications to the burn site.

Do the outcomes vary by the type or degree of burn? There are insufficient data available to answer this question. None of the abstracted studies contained analyses where the effectiveness of heparin was stratified by type or degree of burn. In fact, the abstracted studies were often characterized by vague reports of the etiology, type, or degree of burn in the samples.

How do the outcomes of burn treatment with heparin compare to current treatment without heparin? Multiple roles for heparin in the treatment of burns were examined in the abstracted studies. These roles included wound healing and pain control, as well as the treatment of sepsis, inhalation injury, and venous thrombosis. However, there were insufficient data available to answer the key question. This was because the abstracted studies were conducted in eight different countries with varying standards of burn care and published over a time span of three decades. Thus, the studies simply did not encompass any standard, current burn treatment. In addition, nine abstracted studies were primarily laboratory studies without clinical outcomes.[57,58,60-63,65,68,70]

The ability to address the key question was further hampered by the major methodologic deficiencies that characterized many of the abstracted articles. Common problems included:

1. Poorly defined burn etiology and degree;
2. Unclear method of treatment allocation;
3. Absence of a control group with no topical anti-inflammatory;
4. Unclear duration of treatment, especially the point at which heparin is first administrated;
5. Outcome variables that are vague and unlikely to be reproducible; and
6. Use of descriptive statistics (no comparative statistics).

Conclusion. Further studies with well-defined populations, treatment regimens, and outcomes are needed to address all three of the above sub-questions. Outcomes must be valid, quantitative, and reproducible. The adverse effects of heparin treatment in burns must also be examined because there is a void on this topic in the literature.

Question 2. What are the Contraindications of Heparin Use in Burns?

Findings from the abstracted articles. Four of the abstracted articles specifically addressed the issue of contraindications to the use of heparin in burn patients.[72-75] This was limited to listing contraindications for subcutaneous or intravenous applications of heparin such as bleeding diathesis, bleeding history, active bleeding or associated trauma with potential bleeding, active intestinal ulcer, thrombocytopenia, liver disease, renal disorders, or allergy to heparin. The authors of two articles[72,73] wrote that these contraindications were exclusion criteria, while the

authors of the other two articles[74,75] wrote that none of the patients in their studies had any of these contraindications.

Application of existing evidence to the domain of burn treatment. When using heparin in burn patients, it would be prudent to apply the same precautions as would be applied to the use of heparin in patients with thromboembolic disease.

The most common contraindication for heparin in patients with thromboembolic disease is bleeding. The risk of bleeding increases with higher heparin doses and is associated with patients' anticoagulant responses, the method of heparin administration, the co-administration of anti-platelet or fibrinolytic agents, and recent trauma or surgery. Bleeding is as frequent with low molecular weight heparins (LMWHs) as with unfractionated heparin (UFH). In one study, bleeding was observed in 5.2 percent of patients who were given continuous intravenous heparin and in 4.1 percent of patients who were given subcutaneous heparin.[2] Both groups received approximately the same mean dose over 24 hours.

Heparin can cause thrombocytopenia and is therefore contraindicated in patients who have had recent surgery (primarily for venous problems) or pre-existing cardiovascular disease (primarily arterial).[76] The incidence of thrombocytopenia was reported to be 0.3 percent in patients treated with heparin prophylaxis and 2.4 percent in patients treated with heparin therapeutically.[2] Heparin-induced thrombocytopenia is an antibody-mediated process that can lead to arterial or venous thrombosis.

The estimated incidence of vertebral fractures in people receiving long-term UFH therapy is three out of 100. Approximately 30 out of 100 people who receive therapeutic doses of heparin for longer than one month will experience reduced bone density that can lead to osteopoenia or osteoporosis.[77] The risk of osteoporosis was observed in groups of patients who had received long-term heparin therapy (> 6 months) at doses greater than 15,000 anti-Xa units. Much of the research on heparin and osteoporosis has been confined to pregnant women, so prolonged heparin use is contraindicated in this group.[76] Osteoporosis is less common with LMWHs than with UFH.

Much of the available evidence regarding contraindications to heparin concerns subcutaneous or intravenous applications of the substance. In some of the abstracted articles, heparin was applied topically and there is no information regarding the contraindications of heparin when administered by this route.

Reported adverse effects of heparin in treating burns. Fifteen of the abstracted articles did not contain reports of adverse effects in the use of heparin to treat burns. The methods sections of these articles did not indicate that monitoring for adverse effects was an objective of any of this research. Srivastava et al. reported a clear monitoring protocol for adverse effects (in their case, bleeding) and they did not find any increases in bleeding secondary to heparin use.[73] Two other articles contained reports of bleeding in heparin-treated patients[74];[75] and one article[70] had mention of the fact that no heparin-related adverse effects were observed in the sample.

The incidence of bleeding was low when reported. One heparin-treated patient in a pediatric study (n = 19) bled on the burn surface, but the role of heparin as a contributing factor was unclear because the patient also had sepsis, which was a major cause of this person's death.[74] In another study (n = 9), three patients who received topical heparin beginning on the fifth day of hospital admission developed bleeding on day 8 of the study.[75] However, the authors attribute

the bleeding to a treatment error: the dose of heparin was not reduced following burn revascularization. The bleeding may have been avoided if heparin was titrated properly.

Quality Assessment of Abstracted Articles

Overview

Ten of the nineteen abstracted articles (Group A) pertained directly to the use of heparin to treat burns or the complications of burns.[59,64,66,67,69,71-75] The other nine articles (Group B) contained information that could be used to make indirect inferences about heparin and burns.[57,58,60-63,65,68,70]

Given that nine of the abstracted articles were published in 1988 or before, and five were RCTs, certain sections of the EPH Tool applied to only a fraction of the entire set of 19 articles. For example, the questions in the EPH Tool about sample size and power calculations applied to only the more recently published articles because reporting guidelines for published manuscripts are a relatively new phenomenon. Consequently, articles published two decades ago do not reflect the same reporting standards as today. Another example of the EPH Tool's restricted applicability is the section on intervention integrity, which is designed for RCTs because the investigator assigns the exposure.

To standardize the EPH Tool across all 19 articles, the questions that were universally applicable to all of the articles were considered in the quality assessment. These questions were: (1) selection bias – participants representative of study population, percentage of selected participants who agreed to participate, completion rate; (2) study design – allocation to treatment groups, use of valid data collection instruments; (3) control of confounding – reported differences between exposure groups with respect to important confounders, attempts to control confounding; (4) statistical methods – use of appropriate statistical methods, finding of statistical significance. The removal of certain questions meant that the EPH Tool's qualitative scoring algorithms could not be used to assign scores of weak, moderate, or strong to the various sections of the scale. Instead, written commentary is provided below on what the answers to the EPH Tool suggest for study quality. This information is summarized in Table 7.

Selection Bias

At least half of the articles were vulnerable to selection bias. The authors of five Group A articles[64,67,69,71,73] and five Group B articles[60,62,65,68,70] simply reported the numbers of patients that participated in the research. The authors did not mention the recruitment time period, nor whether consecutive sets of patients were assessed for study eligibility. The omissions in reporting, coupled with a conservative approach to quality assessment, meant that one could not rule out the possibility that highly selected groups of patients were used in these articles. Indeed, the authors of one article wrote that they used "a selected series" of patients.[69] These ten articles were rated as not likely to contain participants who were representative of the study population. Conversely, two Group A articles[66,72] were rated as very likely to contain representative participants, two[74,75] were rated somewhat likely, and one[59] was rated not to somewhat likely. Of the Group B articles, one[63] was rated as somewhat to very likely, two were rated somewhat likely,[57,58] and one[61] was rated not to somewhat likely.

The omissions in reporting extended to the participation rate (e.g., the percentage of recruited patients who actually participated in the research). The authors of six Group A articles[59,66,67,69,71,73] did not report any data on this subject, nor did the authors of four Group B articles.[60,61,65,68] In articles that did contain information, the participation rate was 80 percent or better in four articles.[57,62,70,75] In four Group A articles[59,64,69,71] and six Group B articles,[57,58,60-62,65] the authors reported little or no data (e.g., age, sex) on the characteristics of people who did participate.

Reporting was better for completion rates. Excluding a chart review,[64] the other nine Group A articles had completion rates of 80 percent or more. One Group B article[58] had a completion rate of 75 percent and six[57,60-62,68,70] (excluding a database review[63]) had completion rates of 80 percent or more. Completion rates were not reported in one Group B article.[65]

Study Design

Eight[59,64,66,69,71,73-75] Group A articles reported on non-randomized, comparative (e.g., cohort) studies and two reported on RCTs.[67,72] The major problem with the cohort studies was a lack of information on how the treatments (exposures) were allocated between exposure groups. Without this information, it is impossible to ascertain whether the characteristics of the different exposure groups could have influenced treatment allocation or treatment outcome. For example, in the chart review, all of the patients who did not receive heparin died.[64] If these patients would not have been eligible to receive heparin, perhaps because they were too sick, then the comparison with heparin-treated patients is invalid. In the two RCTs, the method of randomization was not reported, thus raising questions about whether confounding variables had been evenly distributed among the treatment groups. Indeed, in one of the RCTs, more severely burned patients were randomized to the control group.[72]

In Group B, three articles[61,62,70] were RCTs, three[58,63,65] were non-randomized, comparison (cohort) studies, two[60,68] were non-randomized, comparative laboratory studies, and one[57] was a before/after study. Treatment allocation was also an issue in this group. The authors of the RCTs did not report the method of randomization, and one of the non-RCTs had an explanation for the allocation of heparin treatment.[68] Of course, it should be noted that none of the studies in Group B were designed to evaluate the direct effect of heparin treatment in burn injury. Consequently, these authors cannot be expected to comment on the allocation of heparin.

None of the studies in either group contained mention of whether people who assessed study outcomes were blinded to treatment allocation. This raises the specter of bias due to differential misclassification. However, the presence and impact of said bias cannot be assessed given the dearth of information in the published study reports.

Valid data collection instruments were used in one article from Group A.[66] In another article from Group A, a non-validated, and not fully explained, four-point scale was used to measure pain.[69] For Group B, eight studies had valid data collection instruments. These instruments were primarily laboratory tests to measure biological factors such as platelet aggregation[60] or D-dimer levels.[57] One Group B article did not contain mention of the data collection instruments that were used in the research.[65]

Control of Confounding

There was no attempt to control for possible confounding in any of the 19 articles. In three Group A articles[64,69,71] and three Group B articles,[60,63,65] there was no mention of basic potential confounders such as age, sex, or comorbidity. Differences between exposure groups with respect to important confounders were reported in five Group A articles[64,66,72,74,75] and four Group B articles.[58,60,63,70] Six non-RCTs[57,59,65,68,69,73] in Groups A and B did not contain specific mention of any differences. Three of the RCT publications did not include comparisons of study participants across treatment groups.[61,62,67] The authors of one RCT did report such comparisons for age, sex, and TBSA.[70]

Statistical Methods

Statistical methods were basic between-group comparisons of data such as the mean number of doses of pain medication. This was the case for five Group A articles[59,67,72,74,75] and five Group B articles.[57,58,63,68,70] In Group A, which involved articles that directly examined heparin in burns, three[64,66,69] of the articles did not appear to contain any comparative statistical methods and the authors of two articles[71,73] made no attempt to do any statistical comparisons whatsoever. In three Group B articles,[60-62] standard errors were reported and comparisons were done, but the types of statistical tests used in the analyses were not reported, nor were p-values provided.

Four articles in Group A[59,72,74,75] and four articles in Group B[61,62,68,70] contained information on whether statistically significant differences were found at the 5 percent level for outcomes involving heparin. This information was not contained in the remaining articles from either group.

Conclusion

The overall quality of the 19 abstracted articles on heparin use in burn care is poor. Selection bias cannot be ruled out for many of the articles because the authors did not report on patient recruitment or participation rate. Similarly, non-reporting was a problem in the area of study design because only one published manuscript contained a report of how treatments (exposures) were allocated amongst study participants.[68] As well, none of the authors provided information on whether outcome assessors were blinded as to treatment allocation. For confounding, potential differences between treatment groups on important confounders were reported in half of the articles, and no attempts were made in any of the articles to address possible confounding. Statistical methods – when reported – were simple between-group comparisons. Many authors did not report the type of statistical test nor provide a p-value. In some instances, no statistical comparisons were performed at all.

Table 5. General characteristics of the abstracted studies

Study	Study Design	Length of Follow-up	Description of Sample	Sample Size	Number/ % Male	Mean Age/ Range	Etiology of Burn	Degree of Burn	TBSA Involvement
Acharya, 1973, United Kingdom[69]	Cohort	NR	Accident department admissions	Hirudoid cream: n = 36* Anacal ointment: n = 16* Antibiotics: n = 33 *Includes heparin	NR/NR	NR/NR	NR	1st	N/A
Curreri et al., 1975, U.S.[61]	RCT	14 days	Hospital admissions	3 groups: heparin, aspirin, control (numbers in each group not reported)	NR/NR	NR/NR	NR	NR	> 30%
Desai et al., 1988, U.S.[59]	Cohort	7 days	Pediatric hospital admissions	Heparin: n = 47 (admitted 1990-1994) Control: n = 43 (admitted 1985-1989)	NR/NR	Control group: 8.2 years/NR Heparin group: 7.7 years/NR	Inhalation injury	3rd	50-55 %
Iashvili et al., 1986, Soviet Union (Georgia)[66]	Cohort	80 days (mean follow-up over four groups)	Burn center admissions	Heparin + nicotinic acid: n = 36 Heparin + Contrical: n = 36 Heparin + nicotinic acid + thrental + phytin + alpha-tocopheral: n = 36 Control: n = 36	87/60%	NR/16 - 60 years	Group receiving 5 drugs and controls: inhalation injury Other two groups: NR	NR	NR
Khadzhiiski et al., 2001, Bulgaria[67]	RCT	3 years	Hospital admissions	Heparin: n = 32 Control: n = 27	NR/NR	NR/1 year and up (upper bound NR)	NR	2nd	0-3% reported for one group
Kuz'muk et al., 1971, Russia[65]	Cohort	20 days	Hospital admissions	Heparin: n = 50 (divided into two groups based on degree of burn and TBSA) Control: n = 30	NR/NR	NR/NR	NR	1st-3rd	>10%

Table 5. General characteristics of the abstracted studies (continued)

Study	Study Design	Length of Follow-up	Description of Sample	Sample Size	Number/ % Male	Mean Age/ Range	Etiology of Burn	Degree of Burn	TBSA Involvement
Mariano et al., 2004, Italy[68]	NRC	Group 1: ~ 1 month Group 2: ~2 months	Intensive care unit admissions with burns, septic shock, polytrauma, and acute renal failure	Group 1: n = 6 (treated with citrate + Coupled Plasma Filtration Adsorption) Group 2: n = 7 (treated with heparin + Coupled Plasma Filtration Adsorption)	10/77%	Group 1: 57 years/26 - 77 years Group 2: 44 years/21 - 60 years	NR	NR	Group 1: 18-35%; Group 2: 40-60%
Mims et al., 1977, U.S.[60]	NRC	10 minutes per experiment (laboratory study)	Burn unit admissions	34 blood samples from seven burn patients; unknown number of blood samples from 10 controls (normal volunteers)	NR/NR	NR/NR	Thermal	NR	8.5-90%
Ono et al., 1984, Japan[71]	Cohort	N/A	Burn patients	Heparin: n = 4 Control: n = 8	N/A/N/A	N/A/N/A	NR	NR	TBSA > 30%
Peng et al., 2005, China[70]	RCT	4 months	Burn unit admissions	Heparin + veno-venous continuous renal replacement therapy: n = 10 Controls: n = 10	19/95%	Heparin + veno-venous: 34.3 years/NR; Controls: 32.0 years/NR	NR	NR	65.8 ± 13.7%
Reyes et al., 2001, Mexico[75]	Cohort	NR	Admission to emergency room or intensive care unit following industrial explosion	Heparin on admission: n = 4 Heparin starting day 5: n = 5 (2 patients received heparin before day 5)	8/89%	30 years/ 17 - 40 years	Flame	2nd, 3rd	51% (30-90%)
Srivastava et al., 1988, India[73]	Cohort	NR	Admissions to burns and plastic surgery unit	Heparin (topical and systemic): n = 25 Control: n = 25	Heparin: 11/44% Control: 14/56%	8 - 55 years	NR	3rd	> 40%
Venkatacha-lapathy et al., Unpublished, India[72]	RCT	7 days	Burn unit admissions	Heparin: n = 50 Control: n = 50	49/49%	NR/15 - 35 years	Flame, scald	2nd	5-50%

Table 5. General characteristics of the abstracted studies (continued)

Study	Study Design	Length of Follow-up	Description of Sample	Sample Size	Number/ % Male	Mean Age/ Range	Etiology of Burn	Degree of Burn	TBSA Involvement
Wahl et al., 2002, U.S. (a)[57] + (b)[58†]	Cohort	NR	Hospital admissions	DVT: n = 7 No DVT: n = 23	22/73%	DVT: 49 ± 23 years/NR; No DVT: 44 ± 17 years/NR	Flame or flash: n = 25 (9 with inhalation injury)	NR	17 ± 23%
Wahl and Brandt, 2001, U.S.[63]	Cohort (data-base review)	3.5 years	Burn center admissions	DVT: n = 8 (3 given low molecular weight heparin) No DVT: n = 319	DVT: 7/88%; No DVT: NR/NR	DVT: 44 ± 17 years; No DVT: 43 ± 19 years	NR	2nd, 3rd	DVT: 34 ± 19%; No DVT: 17 ± 19%
Waymack et al., 1988, U.S.[64]	Cohort (chart review)	N/A	Pediatric burn unit admissions with renal vein thrombosis	Heparin: n = 3 Control: n = 3	NR/NR	NR/1.5 - 9 years	NR	NR	33-90%
Zayas et al., Unpublished, El Salvador[74]	Cohort	1 year	Pediatric hospital admissions	Heparin: n = 10 (admitted 1999) Control: n = 9 (admitted 1998)	11/58%	3.5 years/ 0.25 - 8 years	Flame, scald	2nd, 3rd	≥ 20%

TBSA = total body surface area involvement; NR = not reported; RCT = randomized controlled trial; NRC = non-randomized comparison; DVT = deep vein thrombosis; N/A = not applicable.

†Wahl et al. studies labeled (a)[57] and (b)[58] were conducted using the same group of patients.

Table 6. Heparin treatment regimens and results – abstracted studies

Author	Type of Heparin	Method of Heparin Administration	Heparin Treatment Regimen	Outcomes	Results	Adverse Effects – Heparin
Acharya[69]	Hirudoid anti-coagulant (100 g equivalent to 25,000 units of heparin)	Topical	NR	1) Pain relief (relief within 5 minutes to 3 hours) 2) Healed (reduction of the burned or inflamed surface by ≥ 50% within 3 days)	1) Hirudoid cream group: 27/36 pain relief and 19/36 healed 2) Anacal ointment group: 16/16 pain relief and 4/16 healed 3) Antibiotic group: 24/33 pain relief and 16/33 healed	NR
Curreri et al.[61]	NR	Subcutaneous	5,000 units	Fibrin split-product concentration	No quantitative data reported in the published article	NR
Desai et al.[59]	NR	Aerosolized	5,000 units of aerosolized heparin alternating with 3 ml of a 20% solution of acetylcystine, every 2 hours for the first 7 days after injury	1) Reintubation 2) Atelactasis 3) Mortality	1) Reintubation: heparin group 3/47, control group 12/43. 2) Atelactasis: heparin group 20/47, control group 30/43 3) Mortality: heparin group 2/47, control group 8/43†	NR
Iashvili et al.[66]	NR	Subcutaneous	6,000 units in the 3 groups treated with heparin	1) Changes in the gastrointestinal mucosa (e.g., ulcers, erosions, and hemorrhages) 2) Separation of the burn eschar 3) Time between burning and development of the wound surface ready for auto grafting 4) The period of treatment between burning and complete healing	1) Changes in the gastrointestinal mucosa: control group12/20, group 4 (complete therapeutic regimen) 7/20 2) Separation of the burn eschar: 7-9 days faster in group 4 3) Time between burning and development of the wound surface ready for auto grafting: 44% shorter in group IV 4) The period of treatment between burning and complete healing: Reduced 30 days in group 4	NR
Khadzhi-iski et al.[67]	Heparin (cream and dressing)	Topical	5,000 IU	Cicatrisation	Significant reduction in primary cicatrisation in 37 treated children and adults compared to 27 controls†	NR

Table 6. Heparin treatment regimens and results – abstracted studies (continued)

Author	Type of Heparin	Method of Heparin Administration	Heparin Treatment Regimen	Outcomes	Results	Adverse Effects – Heparin
Kuz'muk et al.[65]	NR	NR	NR	1) Prothrombin activity 2) Thrombotest value 3) Plasma recalcification time 4) Plasma tolerance to heparin 5) Fibrinogen concentration	No quantitative data reported in the published article	NR
Loebl et al.[62]	NR	Subcutaneous	20,000 units in four divided doses	Autologous half-life of erythrocytes	No quantitative data reported in the published article	NR
Mariano et al.[68]	NR	Continuous infusion	Heparin + CPFA as renal replacement therapy	1) Blood flow 2) Used cartridges/session 3) Blood iCa^{2+} 4) Blood pH and bicarbonates	No quantitative data reported in the published article	NR
Mims et al.[60]	Beef lung and intestinal mucosal	NR	Heparin not used for treatment (heparin was used as a re-agent)	Platelet aggregation	In contrast to controls, 15% of blood samples from burn patients demonstrated spontaneous aggregation, and 69% showed either first or second phase aggregation after exposure to heparin	NR
Ono et al.[71]	NR	Infusion	10,000 - 20,000 IU daily	1) Platelet counts 2) Fibrinogen levels 3) Plasminogen levels 4) Fibrin degradation product levels	No quantitative data reported in the published article	NR
Peng et al.[70]	Heparin and low molecular weight heparin	Intravenous	100 - 1,500 units	1) Median stay in ICU 2) Total days in hospital 3) Mortality	No quantitative data reported in the published article	No heparin-related adverse effects observed

Table 6. Heparin treatment regimens and results – abstracted studies (continued)

Author	Type of Heparin	Method of Heparin Administration	Heparin Treatment Regimen	Outcomes	Results	Adverse Effects – Heparin
Reyes et al. 2001[75]	NR	Infusion, subcutaneous, sprayed or dripped via needle, aerosolized	1st application was 5,000 IU/ml dripped or sprayed on open burn surfaces or injected into burn blisters - retreatment at 5 - 10 minute intervals for 20 - 30 minutes	1) Mean doses of pain medication 2) Swelling 3) Fasciectomy 4) Burn revascularization	1) Mean doses of pain medication: heparin group (received heparin day 1) = 4 doses, control group (received heparin day 5 and later) = 24 doses† 2) Patients given heparin on day 1 had less burn swelling and body swelling, and no fasciectomies, compared to patients given heparin on day 5 3) Burn revascularization was faster in patients given heparin on day 1	Bleeding
Srivastava et al.[73]	NR	Topical and systemic	1) Systemic route: 10,000 units/10% burn area, repeated every 4-6 hours; increased to maximum 300-400 units/15% burn/kilogram body weight 2) Topical application: 25,000 units/10% burn	1) Mortality 2) Mean healing time 3) Full thickness Eschar separation 4) Raw area fit for grafting 5) Graft take	1) Mortality: heparin group 3/25, control group 11/25 2) Mean healing time: heparin group 6 days (superficial) and 15 days (deep dermal), control group 10 days (superficial) and 28 days (deep dermal) 3) Eschar separation: heparin group 12 days, control group 21 days 4) Fit for grafting: heparin group 20 days, control group 36 days 5) Graft take: heparin group 95%, control group 65%	No observed bleeding
Venakatachalapathy et al.[72]	Heparin sodium solution (bovine intestinal mucosa)	Dripped onto burn surfaces or injected into burn blisters	200 IU/ml	1) Mortality 2) Days in hospital 3) Number of skin grafts	1) Mortality: heparin group 0/50, control group 5/50 2) Days in hospital: heparin group had 29 patients discharged in ≤ 10 days, control group had 3 patients discharged in ≤ 10 days† 3) Number of skin grafts: heparin group 4/50, control group 10/50	NR
Wahl et al. (a)[57] + (b)[58‡]	Low-molecular-weight heparin (enoxaparin)	Subcutaneous	40 units 4x/day	Development of upper or lower extremity DVT or pulmonary embolism	7 patients had DVT (1 patient had upper extremiy DVT and 2 patients had both upper and lower extremity DVT). 6 patients had Superficial Vein Thrombosis (SVT) in the upper extremities.	NR

Table 6. Heparin treatment regimens and results – abstracted studies (continued)

Author	Type of Heparin	Method of Heparin Administration	Heparin Treatment Regimen	Outcomes	Results	Adverse Effects – Heparin
Wahl and Brandt[63]	Low-molecular-weight heparin	NR	NR	DVT	NR (for heparin)	NR
Way-mack et al.[64]	NR	NR	NR	1) Mortality 2) Normal pyelogram (heparin group)	1) Mortality: heparin group 0/3, control group 3/3 2) Normal pyelogram: heparin group 3/3, control group not given test	NR
Zayas et al.[74]	Sodium aqueous heparin (swine intestine)	Intravenous and topical liquid	1) Scald burns: intravenous one-day dose was 400 IU/kg body weight/15% burn size 2) Explosion-fire-smoke burns: total one-day dose was 1,000 - 1,200 IU/kg body weight/15% burn size 3) Topical use (2 - 3X daily): 5,000 IU/ml sprayed via needle onto burn wound surfaces or injected into burn blisters	1) Survival 2) Days in hospital 3) Sepsis 4) Bleeding	1) Survival: heparin group 6/10, control group 1/ 9† 2) Days in hospital: heparin group average 36.6 days, control group average 11.4 days (n = 7) 3) Sepsis: heparin group 4/10, control group 9/9† 4) Bleeding: heparin group 1/10, control group 0/9	Bleeding

NR = not reported; DVT = deep vein thrombosis; SVT = superficial vein thrombosis; CFPA = Coupled Plasma Filtration Adsorption.
†$p < 0.05$ (in studies without this indication, the results were not statistically significant at the 5% level or the authors did not report whether the results were significant)
‡Wahl et al. studies labeled (a)[57] and (b)[58] were conducted using the same group of patients.

Table 7. Quality assessment of abstracted articles – Group A

	Selection Bias			Study Design			Control of Confounding		Statistical Methods	
Authors	**Participants Representative of Study Population**	**PR**	**CR**	**Explained Treatment Assignment of Subjects**	**Blinding**	**Use of Valid Data Collection Tools**	**Groups Differ on Confoun-ders**	**Control of Confoun-ding**	**Statistical Methods Used**	**SS of Results Reported**
Acharya[69]	Not likely	NR	≥ 80%	No	NR	No	NR	No	NR	No
Desai et al.[59]	Not to somewhat likely	NR	≥ 80%	No	NR	No	NR	No	Between-group compari-sons	Yes
Iashvili et al.[66]	Very likely	NR	≥ 80%	No	NR	Yes	Yes	No	NR	No
Khadzhiiski et al.[67]	Not likely	NR	≥ 80%	No	NR	No	NR	No	Between-group compari-sons	No
Ono et al.[71]	Not likely	NR	≥ 80%	No	NR	No		No	NR	No
Reyes et al.[75]	Somewhat likely	≥ 80%	≥ 80%	Yes	NR	No	Yes	No	Between-group compari-sons	Yes
Srivastava et al.[73]	Not likely	NR	≥ 80%	No	NR	No	NR	No	NR	No
Venakatac-halapathy et al.[72]	Very likely	≥ 80%	≥ 80%	No	NR	No	Yes	No	Between-group compari-sons	Yes
Waymack et al.[64]	Not likely	N/A	N/A	No	NR	No	Yes	No	NR	No
Zayas et al.[74]	Somewhat likely	≥ 80%	≥ 80%	Yes	NR	No	Yes	No	Between-group compari-sons	Yes

Table 7. Quality assessment of abstracted articles – Group B

	Selection Bias			Study Design			Control of Confounding		Statistical Methods	
Authors	**Participants Representative of Study Population**	**PR**	**CR**	**Explained Treatment Assignment of Subjects**	**Blinding**	**Use of Valid Data Collection Tools**	**Groups Differ on Confoun-ders**	**Control of Confoun-ding**	**Statistical Methods Used**	**SS of Results Reported**
Curreri et al.[61]	Not to somewhat likely	NR	≥ 80%	No	NR	Yes	NR	No	Between-group compari-sons	Yes
Kuz'muk et al.[65]	Not likely	NR	NR	No	NR	NR	NR	No	NR	No
Loebl et al.[62]	Not likely	≥ 80%	≥ 80%	No	NR	Yes	NR	No	Between-group compari-sons	Yes
Mariano et al.[68]	Not likely	NR	≥ 80%	Yes	NR	Yes	NR	No	Between-group compari-sons	Yes
Mims et al.[60]	Not likely	NR	≥ 80%	No	NR	Yes	Yes	No	Between-group compari-sons	No
Peng et al.[70]	Not likely	≥ 80%	≥ 80%	No	NR	Yes		No	Between-group compari-sons	Yes
Wahl et al.[57]	Somewhat likely	≥ 80%	≥ 80%	No	NR	Yes	NR	No	Between-group compari-sons	No
Wahl et al.[58]	Somewhat likely	≥ 80%	75%	No	NR	Yes	Yes	No	Between-group compari-sons	No
Wahl et al.[63]	Somewhat to very likely	N/A	N/A	No	NR	Yes	Yes	No	Between-group compari-sons	No

PR = participation rate; CR = completion rate; SS = statistical significance; NRC = non-randomized comparison; NR = not reported; RCT = randomized controlled trial; N/A = not applicable.

Chapter 4. Discussion and Future Research

Overall Summary of Evidence from the Abstracted Studies

There is no strong evidence in the 19 abstracted articles to indicate that the non-anticoagulant properties of heparin improve clinical outcomes in the treatment of burn injury. The lack of evidence is largely a function of the poor quality of the articles. Many of the articles did not contain clinical outcomes and in those that did, these outcomes were not always well defined. Additionally, the quality of several of the studies was low, with high potential for selection bias, inadequate control of confounding, and no mention of the use of blinding during exposure and outcome assessment.

Pain and cosmesis—outcomes of high clinical interest in burn injury—were often improperly measured in the studies in which they were considered. Instead of using a valid and reliable tool such as the McGill Pain Scale[78] to measure pain, the authors of two studies[72,75] measured pain by looking at the degree of use of pain medication. The problem with this approach is that physician judgment may be substituted for patient judgment when it comes to the use (and degree of use) of pain medication. Since the studies were not blinded, there may also have been an a priori belief that heparin-treated patients would not need pain medication, and this might have influenced whether they actually got the medication. Thus, one cannot be sure that use of pain medication adequately measures patient pain. In another study, the authors asserted that heparin provided more pain relief than conventional treatment because of the anecdotal observation that "The noisy din and distressing emotional ambience of the Emergency Room or the Burn Ward was soon replaced by a quiet calm [once patients received heparin]."[74] Anecdotal observations such as this do not constitute evidence of a treatment effect.

For cosmesis, two studies relied on patient photographs to show a benefit for heparin-treated patients.[72,75] However, in one of these studies, the authors did not show photographs of all of the patients.[72] In both studies, the number of days after injury on which the published photographs were taken varied, as did the parts of the patients' bodies that were photographed. To be acceptable for demonstrating treatment efficacy in a research study, photographic evidence must be standardized, e.g., all patients should be photographed, each patient's photographs should be taken at the same points in time during follow-up, and the same parts of each patient's body should be photographed (from the same angles). As well, a protocol must be developed to ensure that photographic evidence is interpreted in a standardized manner, much like is done in studies where imaging tests are used to assess treatment efficacy.

Contextual Issues Regarding the Evidence from Abstracted Studies

The time and location of many of the abstracted studies deserve particular note. The studies spanned more than three decades, beginning in 1971. During this period, burn care underwent a major transformation, the hallmark of which was markedly improved survival.[45,46] At one American burn center, burn survivability—measured by the LA_{50}— improved from 43 percent (young adults) and 23 percent (older adults) in 1940 to 60.8 percent (young) and 39.2 percent (older) in the late 1970s and early 1980s. Even more dramatic was the improvement in pediatric

burn survival at this center, which was 51 percent in 1940 and 93 percent in 1986.[45] Further transformation occurred with the development of networks of specialized burn treatment centers in some countries. These centers are capable of handling local injuries and the treatment of people with serious burn injuries who are transferred from distant locales. Burn care was aided by advancements in multiple areas of medicine, including critical care medicine, wound infection control, antimicrobial therapy, surgical therapy, specialized burn care research, and coordinated methods of burn patient transfer. Early excision therapy became possible within the context of these advances and it has become a standard component of surgical care for full thickness burn injuries in some countries.[46]

In the articles abstracted for this evidence report, the treatment protocols employed by some of the researchers did not match these aforementioned approaches to burn care. Thus, even if the evidence for using heparin in the treatment of burn injury was stronger, it would be difficult to apply this evidence to all clinical contexts. For example, Venkatachalapathy et al.,[72] who conducted their work in Pondicherry, India, reported a lag of 1 to 8 hours between the time of burn injury and the initiation of treatment. The lags were caused by either medico-legal matters at referral hospitals or referral distances of up to 150 kilometers. In contrast, the regionalization of specialized burn care in the United States has enabled the development of burn patient transfer protocols, including use of air ambulances and accompanying medical support services, that minimize transfer delays due to bureaucracy or distance.[45] In the studies by Zayas et al.,[74] Reyes et al.,[75] and Srivastava et al.,[73] burn injuries included full thickness burns, but none of the authors reported whether early excision or grafting was used in the treatment of these injuries. Early excision and grafting of full thickness burn injuries is currently common practice in some countries.[47]

Some of the differences between study protocols and standards of burn care were temporal in nature. For example, Waymack et al.'s chart review was published in 1988 and included charts from 20 years earlier.[64] Therefore, this study was not likely to contain treatment protocols that reflect the current state of the art. Additionally, given the publication dates of the articles, the types of heparin that were studied are probably not used today. Low molecular weight heparins (LMWHs) have largely replaced unfractionated heparin (UFH) for some clinical indications because LMWHs possess superior pharmacodynamic and pharmacokinetic properties, as well as fewer side effects.[3] Recently, a synthetic LWMH was developed and is now available for clinical use.[4]

The other reason for the difference between study protocols and standards of burn care related to the originating country or region of the study. Of the 10 abstracted articles that pertained directly to the use of heparin in the treatment of burns (Table 7 – Group A), two were from India and two were from Latin America. In both locations, the research focus was on heparin's wound healing effects in relation to cosmesis, function, and mortality. In the United States, the research focus was on heparin's anticoagulant effects in relation to venous thrombosis (deep vein thrombosis,[57,58,63] renal vein thrombosis[64], as well as on heparin's anti-inflammatory effects in relation to inhalation injury.[59]

Heparin and Sepsis

In the abstracted studies, claims regarding heparin use in burn care included beneficial effects with respect to the treatment of sepsis in pediatric[73,74] and adult burn patients.[73] Sepsis is

associated with a heightened inflammatory response and adverse activation of the coagulation cascade.[79] Eradication of sources of infection is one goal of sepsis treatment.

Early excision and grafting therapy has been utilized to ameliorate factors that can contribute to the development of sepsis. This therapy has led to improved survivability for pediatric burn patients.[80] Wound sepsis and contamination both decreased in one study comparing early excision and grafting to conventional wound debridement therapy.[81] Yet early excision and grafting may not be the current standard of burn care in some countries. New therapeutic efforts for treatment of sepsis have been targeted at the dysregulation of the coagulation system during sepsis. Heparin's place within this new area of research is both complicated and controversial. In phase III trials regarding sepsis and anticoagulant agents such as activated protein C (APC), tissue factor pathway inhibitor, and antithrombin III, heparin may have been a confounder. Hypothesized explanations for this effect included heparin's reversal of the pro-coagulant effects of sepsis or the negation of the anticoagulant effects of the aforementioned agents.[79] Heparin may therefore have singular beneficial effects on the survival of patients with critical illness (including sepsis).[79] The studies of Zayas et al.[74] and Srivastava et al.,[73] albeit methodologically weak, suggest that heparin's hypothetical role in the care of sepsis and burn injury specifically warrants further investigation. Furthermore, the investigation of heparin's role in the treatment of sepsis may be of particular importance due to issues of cost. Both Reyes et al.[75] and Zayas et al.[74] commented on the low cost of heparin. The implication is that this substance might entail a more affordable and sustainable medical intervention for patients with burn injury and sepsis in some countries. Davidson et al.[82] reported comparable survival benefits with heparin relative to APC in the treatment of sepsis and Kent et al.[83] noted that heparin was less expensive than APC (e.g., $8.00 for a 96-hour heparin infusion versus $6,700 for a 96-hour APC infusion).

Heparin and smoke inhalation

Heparin may entail benefits for the treatment of smoke inhalation. One of the abstracted studies contained reports of beneficial outcomes in this area.[59] Further investigation is warranted because inhalation injury remains a significant factor related to mortality in burn injury.[84]

Heparin and Psychiatric and Psychosocial Outcomes

The pain associated with a burn injury or wound debridement can adversely affect the psychiatric or psychosocial health of people with burn injury. Wound healing, accompanied by hypertrophic scarring, contractures, functional disability, or cosmetic disfigurement, may also detract from adequate post-burn psychiatric and psychosocial adjustment. The abstracted studies were reviewed to see if there was any evidence to suggest that the use of heparin to treat burns would lead to improved psychiatric and psychosocial outcomes for burn victims.

The authors of the abstracted studies did not systematically examine the psychiatric or psychosocial adjustment of patients with burn injury. Zayas et al. anecdotally addressed the problem in their study of severe pediatric burn injury.[74] They reported that heparin use eliminated burn pain and the concomitant 'distress' associated with wound care. The authors described children who received heparin as "cooperative" during wound care. Similar results were reported for adult patients who had significant burn injuries.[72] However, the adult reports were also anecdotal and not based on any reliable and valid measures of psychiatric or psychosocial adjustment.

There has been considerable academic and clinical attention focused on the psychopharmacological and non-pharmacological means of ameliorating burn pain and the distress associated with acute wound care.[85-88] Hospitalized, burn-injured children and adolescents in the acute injury phase have been identified to be at risk for developing acute stress disorder (ASD) or post-traumatic stress disorder (PTSD).[89-91] In pediatric and adult patients with burn injury, the pain associated with the injury and subsequent care is thought to be an etiologically significant component of patients' early psychiatric and psychological adjustment.[51,92] Zayas et al.,[74] Venakatachalapthy et al.,[72] and Srivastava et al.[73] employed a mixture of anecdotal and objective measures of wound healing, scarring, and contractures, but they reported only immediate clinical outcomes at the time of discharge. They did not consider the psychiatric or psychosocial impact of the burn injuries. Heparin's place as an effective intervention for the prevention or amelioration of psychiatric and psychosocial outcomes associated with burn injuries awaits further systematic research.

Conclusion

In conclusion, this report summarizes the evidence for the use of heparin to treat burns. After a thorough and systematic literature search and article screening process, 19 articles from 18 unique studies were abstracted and included in this report. From the perspective of heparin's non-anticoagulant properties, there was some evidence that heparin use might result in improved outcomes for burn patients in areas such as mortality, wound healing, pain, and cosmesis. However, this evidence was not strong, and therefore not supportive of, the use of heparin in the treatment of burns. The lack of strong evidence largely resulted from the fact that many of the abstracted studies suffered from serious methodological weaknesses and were altogether of poor quality. Although the evidence is beset by these problems, there still remains a great deal of clinical interest in, and active use of, heparin in burn care. This report contains recommendations for future research into heparin's use in the treatment of burn injury.

Future Research into Heparin as a Treatment for Burns

Future research into the use of heparin to treat burns should have the following minimum design requirements: well-defined study populations, clearly defined and relevant clinical outcomes (measured using accepted and objective criteria), and valid comparison groups. Future studies should also utilize strong designs that minimize confounding (e.g., randomized controlled trials [RCTs]) and avoid the pitfalls of the 19 articles that were abstracted for this evidence report. These pitfalls included unclear methods of allocation and treatment,[67,69,93] no power calculations or use of validated, well-defined outcomes,[67,69,72] and little discussion of potential biases or study limitations (a problem with all of the abstracted studies). For RCTs, manuscripts should be written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines, which promote consistent and transparent reporting of RCT results so that readers can assess study quality.[94]

Design of Studies of Heparin in the Treatment of Burns

Issues to Consider

The following issues are important to consider when designing studies of heparin in the treatment of burns.

Population. There is great heterogeneity within the burn patient population. These patients can be categorized by burn etiology, burn depth, and burn surface area. Each of these domains has important effects on clinical outcomes such as pain, scarring, length of stay, and mortality. Few of the abstracted studies appropriately defined the populations of interest with respect to these domains. Future studies should be sufficiently powered to perform subgroup analyses by these domains, or they should be designed to focus on a specific type of burn patient (e.g., patients with bilateral upper or lower extremity burns).

To maximize the applicability of study results, researchers should seek to enroll consecutive patients during a pre-specified time period rather than to rely on convenience samples that may be more atypical of the general patient population. For RCTs, which generally have poor generalizability, researchers should attempt to focus on less selective study populations.[95]

Intervention. Some of the abstracted studies contained poor definitions of the type of heparin that was used to treat patients. The following issues must be clarified in future studies:

- Heparin type, concentration, and carrier;
- Time of application, including how soon after injury, frequency of application, and duration of application; and
- Method of application, including concomitant treatments such as dressings.

Control group. Controls must be recruited during the same time frame and from the same locations as people who will be receiving active heparin. For RCTs, the determination of whether a study participant goes into the control or heparin group should be made randomly using a computer-generated algorithm.

The use of historical controls is inappropriate because temporal differences in patient characteristics or treatment protocols might lessen the comparative similarity of the study groups.

Modes of treatment between groups must be as similar as possible, save for the use of heparin in the active treatment group. For example, if heparin is applied using an oil-based carrier, then the control group must have the same carrier applied without heparin. A failure to do so might exaggerate the potential treatment benefits of heparin because it is plausible that the application of the carrier itself could create a protective barrier for the burns. Similar arguments can be made for other carriers.

Outcomes. Many of the abstracted studies focused on non-clinical, or poorly defined clinical, outcomes. To influence medical practice, well-defined, valid, and clinically relevant outcomes must be used in future studies. Validated outcome measures have been developed for use in burns, but they have not yet been applied to assess heparin. For example, one extremely

germane outcome in burn injury is scar appearance, which can be measured using the Vancouver Scar Scale.[96]

Focus of Future Studies of Heparin in the Treatment of Burn Injury

Two sets of studies are proposed to investigate the efficacy of heparin in the treatment of burn injury.

First set of studies. In some countries, the wound healing effects of heparin have been the focus of much research. However, the abstracted evidence is not strong enough to support heparin use as the standard of care for wound healing. Since the lack of strong evidence is due to the poor quality of the abstracted articles, further research into heparin's wound healing properties is justifiable and recommended. As discussed in Chapter 1, there is basic science evidence for heparin's use as a wound healing agent in burn injury, and there is clinical evidence that a temporary dermal replacement consisting of cross-linked collagen and chondroitin-6-sulfate (a molecule similar in structure to heparin) with a silicone coating can promote wound healing in the burned hand.[97] Indeed, improved wound healing and the possibility of correspondingly improved cosmesis and function are desired objectives for burn care.[47]

Given that research into heparin's ability to heal burn wounds is in its early stages, a preliminary trial is recommended to study whether heparin can accelerate the healing of donor areas for skin grafts. The study population would consist of adults and adolescents who would be randomized to receive heparin plus standard treatment or standard treatment alone as wound care for the donor area of a skin graft (a wound equivalent to a partial thickness burn). In the heparin group, standard, UFH would be applied topically to the donor area approximately 24 hours after stoppage of bleeding. Outcomes would include healing time of the donor area, pain, itching, and scarring. If bleeding persists, heparinoids (e.g., non-anticoagulant heparin) instead of UFH can be used in the heparin group. Research of this type may have an impact on the psychiatric morbidity associated with burn injuries and care, especially morbidity from skin grafting and the pain and discomfort of donor areas. Therefore, psychiatric outcomes such as ASD and PTSD should be evaluated in the proposed study.

If outcomes in the preliminary trial are better in the heparin versus control group, then a second trial could be conducted in adults, adolescents, and children. This trial would involve people with bilateral upper or lower extremity burns (i.e., both hands, arms, or legs). Topical heparin would be applied to one extremity and standard care would be applied to both extremities. Each participant would act as his or her own control, and the extent to which the burn on each extremity heals would be compared using the same outcomes as in the preliminary trial discussed above. Extremity-specific outcomes may also be used in the comparison. For example, if burned hands are the extremity in question, then outcomes could include a thumb opposition score, fingertip-to-palm distance measure, and prehensile score.[97] Psychiatric outcomes would also be the same as in the preliminary trial, plus there would be an assessment of quality of life.

The trials would be multi-center so that an adequate number of people could be recruited to obtain a power of at least 80 percent. In the case of burn injuries that require early excision and grafting, the route of heparin administration might be of particular relevance. Intravenous and subcutaneous routes may be preferable in this research arena because there would not be direct

contamination of graft sites, whereas topical heparin in combination with early excision and grafting might negatively affect graft take and present an unethical risk for patients.

Second study. The second proposed study would involve a single RCT to examine the use of aerosolized heparin to treat critically injured burn patients who are suffering from inhalation injury. Pediatric and adult populations would be randomized to receive standard treatment plus aerosolized heparin or standard treatment alone. Based on the anti-inflammatory properties of heparin (which are summarized in the introduction), it is thought that heparin could contribute to improved outcomes in people with inhalation injury. One of the abstracted studies found positive benefits from using aerosolized heparin and acetylcystine in the treatment of inhalation injury in children, but selection bias could not be ruled out because the control and heparin groups were recruited at different points in time, the authors were not clear as to whether consecutive patients were approached for recruitment into the study, and the authors did not report a participation rate.[59]

Possible outcomes for the RCT on inhalation injury would include mortality, reintubation rate, length of stay in the intensive care unit (ICU), and incidence of pulmonary complications (e.g., acute respiratory distress syndrome, atelectasis, and pneumonia). As with the first set of studies, there should be an investigation of the psychiatric morbidity associated with burn injury and care. In addition to evaluating ASD, PTSD and quality of life, two additional psychiatric outcomes should be examined on account of the ICU context of the RCT, namely ICU psychosis and delirium. The RCT would be carried out in burn centers with advanced levels of technological support to meet patients' intensive care needs and facilitate the use of aerosolized heparin. In addition, burn care centers with advanced technological support would likely enable the identification and description of an optimal patient population. This is particularly important because inhalation injury is strongly associated with mortality, which may act as a confounder in this type of research if not well documented. Multi-site research will be necessary to ensure adequate patient recruitment and meet sample size requirements.

Additional basic science research. The trial of heparin's wound healing properties on donor areas for skin grafts could involve a basic science component. Blood samples or tissue biopsies could be taken from trial participants and examined to gain information on the mechanisms of heparin's action (e.g., heparin's effect on wound-healing cytokines).

Study outcomes. A variety of clinical outcomes should be considered for the next generation of studies on heparin and burns. The outcomes would vary slightly depending on whether adult or pediatric populations are studied. Some of these outcomes are:

1. Mortality;
2. Incidence of medical procedures following initial treatment with heparin or standard therapy (e.g., reintubation, excision, grafting);
3. Pain (measured using the McGill Pain Scale[78]);
4. Scarring (measured using the Vancouver Scar Scale[96]);
5. Itching (measured via the amount of anti-pruritic medications used [e.g., Benadryl®])
6. Quality of Life (measured using the Health Outcomes Burn Questionnaire[98,99] for children and the Burn-Specific Health Scale[100] for adults); and
7. Post-traumatic Stress Disorder (measured using the Child Stress Disorders Checklist[101] for children and a selected range of measurement methodologies[102] for adults).

Studies that are designed with the above precepts in mind will overcome the pitfalls of the abstracted articles and provide the clinical community with a clearer picture of the efficacy of the various uses of heparin in the treatment of burns.

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Acronyms and Abbreviations

ACCP	American College of Chest Physicians
AHRQ	Agency for Healthcare Research and Quality
APC	Activated Protein C
ASD	Acute Stress Disorder
bFGF	basic Fibroblast Growth Factor
CFPA	Coupled Plasma Filtration Absorption
CHF	Chronic Heart Failure
CONSORT	Consolidated Standards of Reporting Trials
CPB	Cardio Pulmonary Bypass Surgery
Da	Daltons
DVT	Deep Vein Thrombosis
EPH Tool	Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies
GAGs	Glycosaminoglycans
ICU	Intensive Care Unit
LA_{50}	Lethal Level of Accumulation at 50 Percent Effect Level
LMWH	Low Molecular Weight Heparin
LV	Left Ventricular
MU-EPC	McMaster University Evidence-based Practice Center
PE	Pulmonary Embolism
PTSD	Post-Traumatic Stress Disorder
RCT	Randomized Controlled Trial
RVT	Renal Vein Thrombosis

SRS	Systematic Review Software
SVT	Superficial Vein Thrombosis
TBSA	Total Body Surface Area
TEP	Technical Expert Panel
TFPI	Tissue Factor Pathway Inhibitor
TOO	Task Order Officer
U.S.	United States
UFH	Unfractionated Heparin
VEGF	Vascular Endothelial Growth Factor
VTE	Venous Thromboembolism

Appendix A – Technical Expert Panel

Bishara Atiyeh, MD, FACS, PhD
Secretary General, WHO: Mediterranean Council for Burns & Fire Disasters
Clinical Professor, Division of Plastic and Reconstructive Surgery
American University of Beirut Medical Center
Beirut, Lebanon

David Herndon, MD
President, International Society for Burn Injuries
Chief of Staff, Galveston Shriners Hospital
Galveston, Texas

Leo Klein, MD, PhD
Brigadier General, Surgeon General of the Czech Armed Forces (retired)
Head, Dept. of Burns Medicine, Prague Burn Center
Associate Professor, 3rd Medical Faculty, Charles University
Prague, Czech Republic

Ján Koller, MD, CSc, PhD
President, European Association of Tissue Banks
Head, Teaching Department for Burns and Reconstructive Surgery
Central Tissue Bank
University Hospital Bratislava Ruzinov
Bratislava, Slovak Republic

Gurvaneet Randhawa, MD, MPH
Task Order Officer, Agency for Healthcare Research and Quality
Rockville, Maryland

Michael J. Saliba Jr., MD
Nominator of the heparin and burns topic to AHRQ
Chairman, The Saliba Burns Institute
La Jolla, California

Glenn Warden, MD, MBA
President and CEO, Warden BioScience Associates
Salt Lake City, Utah

Steven E. Wolf, MD
Professor, Department of Surgery
University of Texas Health Science Center at San Antonio
Director, US Army Institute of Surgical Research Burn Center
Brooke Army Medical Center
Fort Sam Houston, Texas

Appendix B – Search Strings

Ovid MEDLINE(R) December 2005

1 exp BURNS/ (34176)
2 (burn or burns or scald$).ti,ab. (27779)
3 (burn or burns or scald$).kw,kf. (39)
4 thermal injur$.mp. (3113)
5 or/1-4 (41466)
6 Glycosaminoglycans/ (18154)
7 exp Heparin/ (43913)
8 heparin, therapeutic/ (0)
9 anticoagulant$.mp. (45650)
10 fibrinolytic agent$.mp. (15759)
11 glucosaminoglycan$.mp. (227)
12 heparin.mp. (62357)
13 (heparinic acid or alpha-heparin or alpha heparin or liquaemin or sodium heparin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (304)
14 or/6-13 (120774)
15 or/7-8,12-13 (63236)
16 5 and 15 (178)
17 5 and 14 (293)
18 animals/ not (humans/ and animals/) (3013652)
19 17 not 18 (204)
20 16 not 18 (120)
21 limit 20 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comment or congresses or consensus development conference or consensus development conference, nih or controlled clinical trial or "corrected and republished article" or dictionary or directory or duplicate publication or editorial or evaluation studies or festschrift or government publications or guideline or historical article or interview or journal article or lectures or legal cases or legislation or letter or meta analysis or multicenter study or news or newspaper article or overall or patient education handout or periodical index or practice guideline or randomized controlled trial) (120)
22 limit 21 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or evaluation studies or randomized controlled trial) (5)
23 limit 20 to (addresses or bibliography or biography or case reports or comment or congresses or dictionary or directory or editorial or interview or lectures or letter) (20)
24 16 not 23 (158)
25 from 24 keep 1-158 (158)

EMBASE December 2005

1 Glycosaminoglycans/ (8239)
2 exp Heparin/ (56642)
3 heparin, therapeutic/ (0)
4 anticoagulant$.mp. (44490)
5 fibrinolytic agent$.mp. (10502)
6 glucosaminoglycan$.mp. (131)
7 heparin.mp. (74395)
8 (heparinic acid or alpha-heparin or alpha heparin or liquaemin or sodium heparin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (281)
9 or/1-8 (115664)
10 or/2-3,7-8 (74395)
11 (Alpha Heparin or Ammonium Heparinate or Benzalkonium or Heparin or Clarin or Contusol or Disebrin or Eleparon or Elheparin or Elheparon or Endogenous Heparin or Epiheparin or Gag 98 or Hepalean or Heparinate Sodium or Heparine or Heparine Novo or Heparinic Acid or Heparin Lock Flush or Heparin Monosulfate or Heparin Ointment or Heparin Potassium or Heparin Sodium or Heparin Sulfate or Heparin Sulfuric Acid or Heparitin Monosulfate or Hepcon or Hep Lock or Hepsal or Lipo Hepin or Lipohepin or Liquaemin or Liquaemin or Sodium Liquemin or Menaven or Monoparin or Mucoitin Polysulfate or Mucoitin Polysulfate Ester or Mucoitin Sodium Polysulfate or Multiparin or Noparin or Panheparin or Panhepin or Panheprin or Praecivenin or Pularin or Sodium Heparin or Thrombareduct or Thromboliquin or Thromboliquine or Thrombophlogat or Thrombophob or Thrombophob Gel or Thrombosamine or Thrombosamine Heparin or Thrombosamine Heparine or Thrombo Vetren or Unfractionated Heparin or Vetren or Vister).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (77001)
12 2 or 3 or 7 or 8 or 11 (77001)
13 exp burn/ or exp chemical injury/ (21157)
14 (burn or burns or scald$ or thermal injur$).mp. (27192)
15 13 or 14 (29169)
16 12 and 15 (245)
17 animal/ or (animal/ and human/) (15813)
18 animals/ not (humans/ and animals/) (12812)
19 16 not 18 (245)
20 limit 19 to (editorial or erratum or letter or note or "review") (59)
21 19 not 20 (186)
22 from 21 keep 1-186 (186)

CINAHL December 2005

1 Glycosaminoglycans/ (41)
2 exp Heparin/ (1872)
3 heparin, therapeutic/ (0)
4 anticoagulant$.mp. (1997)
5 fibrinolytic agent$.mp. (823)

6 glucosaminoglycan$.mp. (2)
7 heparin.mp. (2304)
8 (heparinic acid or alpha-heparin or alpha heparin or liquaemin or sodium heparin).mp. [mp=title, subject heading word, abstract, instrumentation] (16)
9 or/1-8 (4465)
10 or/2-3,7-8 (2306)
11 (Alpha Heparin or Ammonium Heparinate or Benzalkonium or Heparin or Clarin or Contusol or Disebrin or Eleparon or Elheparin or Elheparon or Endogenous Heparin or Epiheparin or Gag 98 or Hepalean or Heparinate Sodium or Heparine or Heparine Novo or Heparinic Acid or Heparin Lock Flush or Heparin Monosulfate or Heparin Ointment or Heparin Potassium or Heparin Sodium or Heparin Sulfate or Heparin Sulfuric Acid or Heparitin Monosulfate or Hepcon or Hep Lock or Hepsal or Lipo Hepin or Lipohepin or Liquaemin or Liquaemin or Sodium Liquemin or Menaven or Monoparin or Mucoitin Polysulfate or Mucoitin Polysulfate Ester or Mucoitin Sodium Polysulfate or Multiparin or Noparin or Panheparin or Panhepin or Panheprin or Praecivenin or Pularin or Sodium Heparin or Thrombareduct or Thromboliquin or Thromboliquine or Thrombophlogat or Thrombophob or Thrombophob Gel or Thrombosamine or Thrombosamine Heparin or Thrombosamine Heparine or Thrombo Vetren or Unfractionated Heparin or Vetren or Vister).mp. [mp=title, subject heading word, abstract, instrumentation] (2329)
12 2 or 3 or 7 or 8 or 11 (2331)
13 exp burn/ or exp chemical injury/ (5156)
14 (burn or burns or scald$ or thermal injur$).mp. (5878)
15 13 or 14 (6313)
16 12 and 15 (12)
17 animal/ or (animal/ and human/) (630)
18 animals/ not (humans/ and animals/) (630)
19 16 not 18 (12)
20 limit 19 to (editorial or erratum or letter or note or "review") [Limit not valid in: CINAHL; records were retained] (3)
21 19 not 20 (9)
22 from 21 keep 1-9 (9)

EBM Reviews - Cochrane Central Register of Controlled Trials December 2005

1 Glycosaminoglycans/ (171)
2 exp Heparin/ (2686)
3 heparin, therapeutic/ (0)
4 anticoagulant$.mp. (2762)
5 fibrinolytic agent$.mp. (1185)
6 glucosaminoglycan$.mp. (8)
7 heparin.mp. (5293)
8 (heparinic acid or alpha-heparin or alpha heparin or liquaemin or sodium heparin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (71)
9 or/1-8 (7651)
10 or/2-3,7-8 (5388)

11 (Alpha Heparin or Ammonium Heparinate or Benzalkonium or Heparin or Clarin or Contusol or Disebrin or Eleparon or Elheparin or Elheparon or Endogenous Heparin or Epiheparin or Gag 98 or Hepalean or Heparinate Sodium or Heparine or Heparine Novo or Heparinic Acid or Heparin Lock Flush or Heparin Monosulfate or Heparin Ointment or Heparin Potassium or Heparin Sodium or Heparin Sulfate or Heparin Sulfuric Acid or Heparitin Monosulfate or Hepcon or Hep Lock or Hepsal or Lipo Hepin or Lipohepin or Liquaemin or Liquaemin or Sodium Liquemin or Menaven or Monoparin or Mucoitin Polysulfate or Mucoitin Polysulfate Ester or Mucoitin Sodium Polysulfate or Multiparin or Noparin or Panheparin or Panhepin or Panheprin or Praecivenin or Pularin or Sodium Heparin or Thrombareduct or Thromboliquin or Thromboliquine or Thrombophlogat or Thrombophob or Thrombophob Gel or Thrombosamine or Thrombosamine Heparin or Thrombosamine Heparine or Thrombo Vetren or Unfractionated Heparin or Vetren or Vister).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (5440)
12 2 or 3 or 7 or 8 or 11 (5535)
13 exp burns/ (664)
14 (burn or burns or scald$ or thermal injur$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1175)
15 13 or 14 (1257)
16 12 and 15 (5)
17 from 16 keep 1-5 (5)
18 from 17 keep 1-5 (5)

WOS (Web of Science) December 2005

TS=((heparin* OR Benzalkonium or Clarin or Contusol or Disebrin or Eleparon or Elheparin or Elheparon or Epiheparin or Gag 98 or Hepalean or Heparitin Monosulfate or Hepcon or Hep Lock or Hepsal or Lipo Hepin or Lipohepin or Liquaemin or Liquaemin or Sodium Liquemin or Menaven or Monoparin or Mucoitin Polysulfate or Mucoitin Polysulfate Ester or Mucoitin Sodium Polysulfate or Multiparin or Noparin or Panheparin or Panhepin or Panheprin or Praecivenin or Pularin or Thrombareduct or Thromboliquin or Thromboliquine or Thrombophlogat or Thrombophob or Thrombophob Gel or Thrombosamine or Thrombo Vetren or Vetren or Vister) AND (burn or burns or scald* or thermal injur*))

BIOSIS December 2005

TS=((heparin* OR Benzalkonium or Clarin or Contusol or Disebrin or Eleparon or Elheparin or Elheparon or Epiheparin or Gag 98 or Hepalean or Heparitin Monosulfate or Hepcon or Hep Lock or Hepsal or Lipo Hepin or Lipohepin or Liquaemin or Liquaemin or Sodium Liquemin or Menaven or Monoparin or Mucoitin Polysulfate or Mucoitin Polysulfate Ester or Mucoitin Sodium Polysulfate or Multiparin or Noparin or Panheparin or Panhepin or Panheprin or Praecivenin or Pularin or Thrombareduct or Thromboliquin or Thromboliquine or Thrombophlogat or Thrombophob or Thrombophob Gel or Thrombosamine or Thrombo Vetren or Vetren or Vister) AND (burn or burns or scald* or thermal injur*))

Appendix C – List of Excluded Studies

Agnelli G, Sonaglia F. Prevention of venous thromboembolism. Thromb Res 2000; 97(1):V49-V62
Status: Excluded because no comparison group

Akhtar M, Gang RK. Treatment of Burns with Topical Heparin - Study of Its Analgesic Effect. Chirurgia Plastica 1979; 5(1):51-3
Status: Excluded because no comparison group

Aronson SB, Elliott JH, Moore TE Jr., et al. Pathogenetic approach to therapy of peripheral corneal inflammatory disease. Am J Ophthalmol 1970 Jul; 70(1):65-90
Status: Excluded because no use of heparin in burns

Askoseljavaara S, Alho A, Sundell B, et al. Heparin Improves and Alpha-Blocker Treatment Possibly Impairs Host-Resistance in Burns. Burns 1977; 4(2):140-2
Status: Excluded because no use of heparin in burns

Author(s) Unknown. Ophthalmic levocabastine for allergic conjunctivitis. Med Lett Drugs Ther 1994; 36(920):35-6
Status: Excluded because no use of heparin in burns

Bahm J. The fatal fight for upper limb preservation in severe electrical burns. Microsurgery 1997; 17(5):286-9
Status: Excluded because no comparison group

Ballinger WF, Wise L. Gastric mucus: quantitative and qualitative studies in humans and dogs. Br J Surg 1969 Sep; 56(9):701-2
Status: Excluded because no use of heparin in burns

Barret JP, Desai MH, Herndon DN. Effects of tracheostomies on infection and airway complications in pediatric burn patients Burns 2000; 26(2):190-3.
Status: Excluded because no use of heparin in burns

Berkessy S. Letter: High-dosage heparin treatment of large burns. JAMA 1973 Dec 17; 226(12):1464
Status: Excluded because no comparison group

Boyce ST, Greenhalgh DG, Kagan RJ, et al. Skin anatomy and antigen expression after burn wound closure with composite grafts of cultured skin cells and biopolymers. Plast Reconstr Surg 1993 Apr; 91(4):632-41
Status: Excluded because no use of heparin in burns

Boyce ST, Goretsky MJ, Greenhalgh DG, et al. Comparative assessment of cultured skin substitutes and native skin autograft for treatment of full-thickness burns. Ann Surg 1995 Dec; 222(6):743-52
Status: Excluded because no use of heparin in burns

Braunstein KM, Dodds KA, Stewart G, et al. Heparin Cofactor Activity Following Thermal Injury. Am J Clin Pathol 1978; 70(4):632-6
Status: Excluded because no use of heparin in burns

Brean L, Bormioli M, Angela GC, et al. Coagulation disorders due to burns. Disseminated intravascular coagulation (DIC) and its possible prevention. Minerva Med 1975 Aug 29; 66(55):2729-42
Status: Excluded because no comparison group

Burkhardt H, Zellner PR, Moller I. Factor XIII deficiency in burns. Chirurg 1977 Aug; 48(8):520-3
Status: Excluded because not retrievable

Buyukcelik A, Akbulut H. Thromboembolism in patients with cancer. Turkish Journal of Haematology 2004; 21(1):7-11
Status: Excluded because no comparison group

Cancio LC, Mozingo DW, Pruitt BA Jr. Strategies for diagnosing and treating asphyxiation and inhalation injuries: How to recognize warning signs and minimize morbidity/mortality risk. J Crit Illn 1997; 12(4):217-29
Status: Excluded because no comparison group

Cancio LC. Current concepts in the pathophysiology and treatment of inhalation injury. Trauma 2005; 7(1):19-35
Status: Excluded because no use of heparin in burns

Chen X-L, Sun Y-X, Hu D-L. An unusual case of volatile organic compounds explosion burns. Burns 2005; 31(2):240-2
Status: Excluded because no comparison group

Clagett GP, Anderson FA Jr., Geerts W, et al. Prevention of venous thromboembolism. Chest 1998; 114(5 Suppl):531S-60S
Status: Excluded because no comparison group

Cox CS. Heparin for smoke inhalation injury. Crit Care Med 2003; 31(4):1291
Status: Excluded because no comparison group

Criado PR, Ramos RDO, Criado RFJ, et al. Severe cutaneous adverse reactions to drugs - Relevant aspects to diagnosis and treatment - Part I: Anaphylaxis and anaphylactoid reactions, erythroderma and the clinical spectrum of Stevens-Johnson syndrome & toxic epidermal necrolysis (Lyell's disease). An Bras Dermatol 2004; 79(4):471-88
Status: Excluded because no use of heparin in burns

Danielsson P, Nilsson L, Nettelblad H, et al. Is there a need for antithrombin III substitution early after burn injury? Burns 1997 Jun; 23(4):300-5
Status: Excluded because no comparison group

Davanzo F, Ruggeroni ML, Trojsi C, et al. A new therapy for hydrofluoric acid burns. Med Lav 1987; 78(4):333-6
Status: Excluded because no comparison group

DeAngelis V, Matrisciano F. Use of acetyl-cysteine in corneal burns: Our experiences. Rass Int Clin Ter 1991; 71(22):1035-7
Status: Excluded because no comparison group

Dellinger RP. Respiratory and critical care medicine: Preface. Sem Respir Crit Care Med 2001; 22(1):1-2
Status: Excluded because no use of heparin in burns

Demling R, Wolberg WH. Effect of heparin and cold immersion on burn edema. Surg Forum 1977; 28:29-30
Status: Excluded because animal study

Demling RH, Mazess R, Hanson J, et al. Effect of Heparin on Edema After 2nd-Degree and 3rd-Degree Burns. J Surg Res 1979; 26(1):27-32
Status: Excluded because animal study

Demling RH. The burn edema process: Current concepts. J Burn Care Rehabil 2005; 26(3):207-27
Status: Excluded because no comparison group

Di Stefano F, Giglio A, Vinci M, et al. Low molecular weight heparins for long-term therapy of peripheral vascular disease. Results of a controlled study. Curr Ther Res Clin Exp 1988; 44(1):1-10
Status: Excluded because no use of heparin in burns

Dougherty W, Waxman K. The complexities of managing severe burns with associated trauma. Surg Clin North Am 1996; 76(4):923-58
Status: Excluded because no comparison group

Dunlavey ES. Topical antibiotics in dermatology for uses other than acne. Curr Probl Dermatol 2000; 12(5):216-21
Status: Excluded because no use of heparin in burns

Durango Gutierrez LF, Vargas GF. Management of the burnt patient. Iatreia 2004; 17(1):54-61
Status: Excluded because no comparison group

Ellis RJ, Cunningham MT, Cook JD. Laboratory heparin resistance in burn injury complicated by venous thrombosis. Burns 1999; 25(8):749-52
Status: Excluded because no comparison group

Eriksson E, Plymforshell K, Robson MC. Distant Micro-Circulatory Changes After A Major Burn - Effects of Methyl Prednisolone, Dextran-40, Heparin and Normal Saline. Burns 1981; 7(3):158-61
Status: Excluded because animal study

Fecher AM, O'Mara MS, Goldfarb IW, et al. Analysis of deep vein thrombosis in burn patients. Burns 2004; 30(6):591-3
Status: Excluded because no comparison group

Finta B, Haines DE. Catheter ablation therapy for atrial fibrillation. Cardiol Clin 2004; 22(1):127-45
Status: Excluded because no use of heparin in burns

Fitts CT, Cathcart RS, III, Artz CP, et al. Acute gastrointestinal tract ulceration: Cushing's ulcer, steroid ulcer, Curling's ulcer and stress ulcer. Am Surg 1971 Apr; 37(4):218-23
Status: Excluded because no comparison group

Fortun J, Navas E. A critical approach to the pathogenesis, diagnosis, treatment and prevention of catheter-related bloodstream infections and nosocomial endocarditis. Clin Microbiol Infect 1999; 5(2 Suppl.):2S40-50
Status: Excluded because no use of heparin in burns

Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. Chest 2001; 119(1 Suppl.):132S-75S
Status: Excluded because no use of heparin in burns

Gehrke CF, Penner JA, Niederhuber J, et al. Coagulation defects in burned patients. Surg Gynecol Obstet 1971 Oct; 133(4):613-6
Status: Excluded because no use of heparin in burns

Geiger JP, Gielchinsky I. Acute pulmonary insufficiency. Treatment in Vietnam casualties. Arch Surg 1971 Apr; 102(4):400-5
Status: Excluded because no use of heparin in burns

Georgieva SA, Kobzeva TV. Blood Heparin Activity in Patients with Burns. Khirurgiya 1982(4):21-3
Status: Excluded because no comparison group

Ghislain P-D, Roujeau J-C. Treatment of severe drug reactions: Stevens-Johnson syndrome, toxicepidermal necrolysis and hypersensitivity syndrome. Dermatol Online J 2002; 8(1):147-58
Status: Excluded because no use of heparin in burns

Goodwin MN Jr. Selected anatomic burn pathology review for clinicians and pathologists. Aviat Space Environ Med 1989 Oct; 60(10 Pt 2):B39-B43
Status: Excluded because no use of heparin in burns

Gorman R, Gordan L, Zumberg M, et al. Successful use of argatroban as an anticoagulant in burn-related severe acquired antithrombin III deficiency after heparin failure. Thromb Haemost 2001; 86(6):1596-7
Status: Excluded because no comparison group

Grabosch A, Rokos H. Neopterin as parameter of cell-mediated immunity response in thermally injured patients. Burns 1992; 18(2):113-6
Status: Excluded because no comparison group

Guimbretiere J, Lebeaupin R, Pannier M. Burns and Heparin-Therapy. Anesthesie Analgesie Reanimation 1977; 34(6):1339-44
Status: Excluded because no comparison group

Guimbretiere J. Unbalanced coagulation among burned patients. Convergences Medicales 1982; 1(4):289-97
Status: Excluded because no comparison group

Hainaut J, Guilbaud J, Dhennin C, et al. Quantitation of at Iii on Chromogenic Substrate - Prognosis of Thermal-Injury with Heparin Treatment. Haemostasis 1982; 12(1-2):74
Status: Excluded because no comparison group

Hansbrough JF, Boyce ST, Cooper ML, et al. Burn wound closure with cultured autologous keratinocytes and fibroblasts attached to a collagen-glycosaminoglycan substrate. JAMA 1989 Oct; 262(15):2125-30
Status: Excluded because no comparison group

Harriger MD, Warden GD, Greenhalgh DG, et al. Pigmentation and microanatomy of skin regenerated from composite grafts of cultured cells and biopolymers applied to full-thickness burn wounds. Transplantation 1995 Mar 15; 59(5):702-7
Status: Excluded because no use of heparin in burns

Harrington DT, Mozingo DW, Cancio L, et al. Thermally injured patients are at significant risk for thromboembolic complications. Journal of Trauma-Injury Infection and Critical Care 2001; 50(3):495-9
Status: Excluded because no use of heparin in burns

Hatzifotis M, Williams A, Muller M, et al. Hydrofluoric acid burns. Burns 2004; 30(2):156-9
Status: Excluded because no use of heparin in burns

Hauben DJ, Mahler D, Neumann L. A burn formula in clinical practice. Ann R Coll Surg Engl 1981 Jul; 63(4):293-4
Status: Excluded because no use of heparin in burns

Hawkins DB, Demeter MJ, Barnett TE. Caustic ingestion: Controversies in management. A review of 214 cases. Laryngoscope 1980; 90(1):98-109
Status: Excluded because no use of heparin in burns

Hirsh J. Prevention of deep venous thrombosis. Br J Hosp Med 1981; 26(2):143-7
Status: Excluded because no comparison group

Hubsher J, Olshan AR, Schwartz AB, et al. Continuous arteriovenous hemofiltration for the treatment of anasarca and acute renal failure in severely burned patients. ASAIO Trans 1986 Jul; 32(1):401-4
Status: Excluded because no comparison group

Hurnikova M, Dostalova D. Continuous elimination methods in burn patients from the point of view of a nurse. Acta Chir Plast 2005; 47(2):55-7
Status: Excluded because no comparison group

Johansson SA. Platelets, coagulation factors and 5-hydroxytryptamine in sensitization, anaphylaxis and burn injuries. Effect of heparin and possible relation to intravascular coagulation. Acta Med Scand Suppl 1967; 471:1-30
Status: Excluded because no comparison group

Kereiakes DJ. The fire that burns within: C-reactive protein. Circulation 2003; 107(3):373-4
Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no comparison group

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Status: Excluded because no comparison group

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Status: Excluded because no comparison group

McAuliffe PF, Mozingo DW. Inhalation injury and ventilator management. Problems in General Surgery 2003; 20(1):97-105
Status: Excluded because no comparison group

McCall JE, Cahill TJ. Respiratory care of the burn patient. Journal of Burn Care & Rehabilitation 2005; 26(3):200-6
Status: Excluded because no comparison group

Mcmanus WF, Eurenius K, Pruitt BA Jr. Disseminated intravascular coagulation in burned patients. J Trauma 1973 May; 13(5):416-22
Status: Excluded because no comparison group

Miller SF. Blood platelets in severely injured burn patients. Burns 1999; 25(2):187
Status: Excluded because no comparison group

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no comparison group

Moore FD Jr. Therapeutic regulation of the complement system in acute injury states. Adv Immunol 1994; 56:267-99
Status: Excluded because no use of heparin in burns

Munster AM. The early management of thermal burns. Surgery 1980 Jan; 87(1):29-40
Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no comparison group

Parks DA, Skinner KA, Skinner HB, et al. Multiple organ dysfunction syndrome: Role of xanthine oxidase and nitric oxide. Pathophysiology 1998; 5(1):49-66
Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no comparison group

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Status: Excluded because no use of heparin in burns

Renard G, Hirsch M, Pouliquen Y. Sem and Tem Study of Heparin Injection in Anterior-Chamber After Experimental Alkali Burn of Cornea. Exp Eye Res 1977; 25(5):533-4
Status: Excluded because animal study

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no comparison group

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Status: Excluded because there is no comparison group

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Status: Excluded because there is no comparison group

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Status: Excluded because there is no comparison group

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no comparison group

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Status: Excluded because no use of heparin in burns

Summerly R, Jefferson BM. Sulphated acid mucopolysaccharides in actinic elastosis. Br J Dermatol 1969 Jan; 81(1):51-9
Status: Excluded because no use of heparin in burns

Thomas S, Humphries J, Fear-Price M. The role of moist wound healing in the management of meningococcal skin lesions: A case study. World Wide Wounds 1999 (June)
Status: Excluded because no use of heparin in burns

Traber DL, Traber LD. Airway blood flow changes and airway obstruction following lung injury. Arch Physiol Biochem 2003; 111(4):297-300
Status: Excluded because animal study

Tremblay R, Ethier J, Querin S, et al. Venovenous continuous renal replacement therapy for burned patients with acute renal failure. Burns 2000; 26(7):638-43
Status: Excluded because no use of heparin in burns

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Status: Excluded because no comparison group

Troshev K, Dimitrov R. Application of heparin in the local treatment of burns. Acta Chir Plast 2001; 43(4):143-4
Status: Excluded because no comparison group

Truong AT, Kowal-Vern A, Latenser BA. Aerosolized heparin does not improve pulmonary function in ventilated burn patients with < 50%TBSA. Crit Care Med 2001; 29(12):A49
Status: Excluded because no comparison group

Vaglini M, Ammatuna M, Nava M. Regional perfusion at high temperature in treatment of stage IIIA-IIIAB melanoma patients. Tumori 1983; 69(6):585-8
Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

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Status: Excluded because no use of heparin in burns

Yannas IV. What criteria should be used for designing artificial skin replacements and how well do the current grafting materials meet these criteria? J Trauma 1984 Sep; 24(9 Suppl):S29-S39
Status: Excluded because no use of heparin in burns

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Status: Excluded because no comparison group

Zamecnikova I, Tymonova J, Stetinsky J, et al. Critical and severe burn injury in children. Acta Chir Plast 2005; 47(1):16-8
Status: Excluded because no comparison group

Appendix D – Forms

Title and Abstract Level 1

1. Is there an abstract?

☐ Yes

☐ No

2. In the title, keywords or abstract, are any of the following terms mentioned with respect to burns?

Burns
Thermal Injuries
Scalds
Smoke Inhalation
Other burn related terms
None of the above
Can't tell

3. In the title, keywords or abstract, are any of the following terms mentioned with respect to heparin?

Heparin/Heparine/Alpha Heparin/Anticoagulant
Ammonium Heparinate/Benzalkonium
Clarin/Contusol/Disebrin/Eleparon
Elheparin/Elheparon/Gag 98/Noparin
Hepcon/Hep Lock/Hepsal/Epiheparin
Heparinate Sodium/Heparinic Acid/Fibrinolytic agent
Lipo Hepin/Lipohepin/Hepalean/Panheparin
Liquaemin/Sodium Liquemin/Multiparin
Panhepin/Panheprin/Praecivenin/Pularin
Menaven/Monoparin/Mucoitin Polysulfate
Thromboliquin/Thromboliquine/Thrombareduct
Thrombophlogat/Thrombophob/Thrombosamine
Vetren/Vister/Thrombo Vetren/Glucosaminoglycan
None of the above ➔ exclusion
Can't tell

4. What language is the study published in?

☐ English

- [ ] Other
- [ ] Can't tell

5. In this study, are the subjects

- [ ] humans
- [ ] animals ===> exclusion
- [ ] not applicable (i.e. lab studies, blood samples) ===> exclusion
- [ ] Can't tell

Title and Abstract Level 2

1. Is there a comparison group?

- [ ] Yes
- [ ] No
- [ ] Can't tell

2. In this study, Heparin has been used to:

- [ ] treat burn injury
- [ ] prophylaxis of thrombosis in burn injury
- [ ] treat complications of burn injury
- [ ] none of the above (exclude)
- [ ] can't tell

3. If excluded above,

Should this paper be kept for background information?

- [ ] Yes
- [ ] No

Full Text

1. What is the targeted use of Heparin?

- [ ] Treatment of burns
- [ ] Complications
- [ ] Prophylaxis of thrombosis
- [ ] None of the above (EXCLUDE)

2. What population does the study focus on

- [ ] adults
- [ ] children
- [ ] adults and children
- [ ] animals only (EXCLUDE)
- [ ] animals and humans
- [ ] can't tell

3. What is the study design?

- [ ] Randomized trial
- [ ] Non-randomized trial
- [ ] Cohort study
- [ ] Case-control study
- [ ] Cross-sectional Study
- [ ] Case Report/Case Series (EXCLUDE)
- [ ] Non-comparative study (EXCLUDE)
- [ ] Animal study (EXCLUDE)
- [ ] Review (EXCLUDE)

☐ Abstract only (EXCLUDE)

4. What variables are presented?

☐ Length of Hospital Stay

☐ Mortality

☐ TBSA

☐ Length of follow-up

☐ Type of heparin used

☐ Dose of heparin

☐ Complications of heparin

☐ Other: (Specify)

5. Language of paper

☐ English

☐ Not English (specify if known)

Data Abstraction

Please write NR if any of the requested information is not reported.

1. Number of groups in this study.

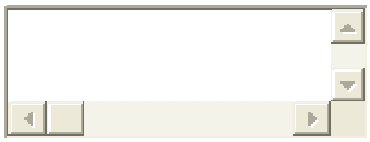
☐ 2

☐ 3

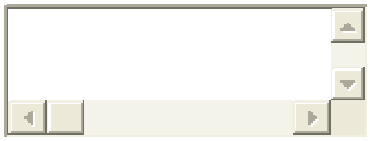
☐ 4

☐ 5

2. Year of Publication



3. Duration of Study



4. Location of study

- ☐ USA
- ☐ Canada
- ☐ Germany
- ☐ Italy
- ☐ France
- ☐ Britain
- ☐ Netherlands
- ☐ China
- ☐ Africa
- ☐ Australia
- ☐ Latin America
- ☐ Russia
- ☐ Japan
- ☐ Poland
- ☐ Spain
- ☐ Bulgaria
- ☐ India
- ☐ Other
- ☐ Not Reported

5. Funding Source

- ☐ Industry
- ☐ Government

Burns

Please write NR if any of the requested information is not reported.

1. Etiology of burn

- ☐ Flames
- ☐ Scald
- ☐ Chemical
- ☐ Contact
- ☐ Inhalation injury
- ☐ Electrical
- ☐ Combination
- ☐ Not reported

2. Degree of burn

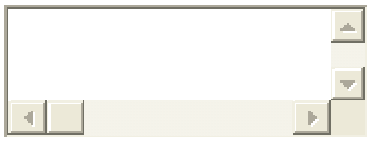
- ☐ First
- ☐ Second
- ☐ Third
- ☐ Not reported

3. Total Body Surface Area of burn (Percentage)

☐ Yes (Report page #) ☐

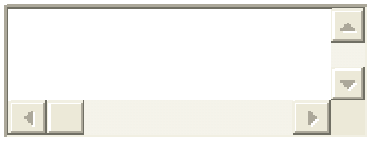
☐ No

4. Other descriptions of burns (extent, depth)



5. List co-morbid conditions reported in the sample.

6. Other Comments.



Heparin

Please write NR if any of the requested information is not reported.

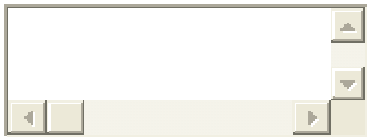
1. Heparin

☐ Type

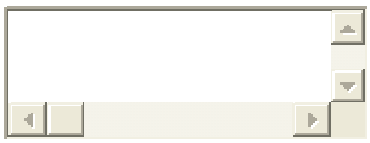
☐ Dose (International Units)

☐ Not Reported

2. Number of subjects receiving Heparin.



3. Number of subjects not receiving Heparin.

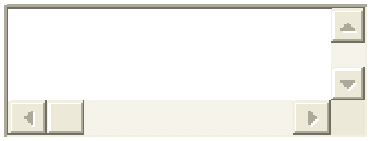


4. Describe the method of administration of Heparin.

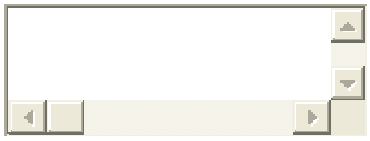
- [ ] Topical (Cream and dressing impregnated with Heparin) ☐
- [ ] Subcutaneous ☐
- [ ] Intravenous ☐
- [ ] Infusion ☐
- [ ] Aerosolized ☐
- [ ] Combination ☐
- [ ] Not Reported ☐

5. Describe the frequency at which Heparin was administered.

6. Describe the length of time Heparin was administered? (i.e. # of days)



7. Describe the time from injury that Heparin was first administered.



8. Did patients comply with the treatment? (Indicate number of patients)

☐ Yes

☐ No

☐ Not Applicable

☐ Not Reported

9. Was there an inpatient/outpatient treatment component?

☐ Yes (describe)

☐ No

10. Other Comments.

Results

Please write NR if any of the requested information is not reported.

1. Results

☐ There are no results presented in this study. (STOP)

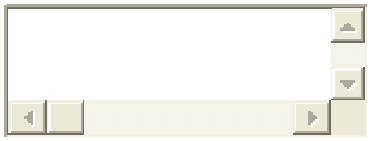
2. What type of outcome was described in this study?

☐ Clinical

☐ Non-clinical

☐ Not Reported

3. Did the authors identify one or more primary outcomes. If yes, then list.



4. How were the outcomes defined?

- [ ] Timing and need for surgical proceedure (i.e. grafting, debridement, fasciotomy)
- [ ] Quality of graft take (percentage)
- [ ] Pain (scale)
- [ ] Transfusion rate
- [ ] Mortality (prior to discharge from hospital)
- [ ] Length of stay: acute treatment (in hospital)
- [ ] Scarring (size, hypertrophic scarring)
- [ ] Decreased range of motion
- [ ] Respiratory measures ICU admission (length of intubation)
- [ ] Thromboses and emboli
- [ ] Complications (bleeding, infection...)
- [ ] Pruritis (Itching)
- [ ] Rehabilitation (follow-up of patient, re-grafting, reconstructive surgery)
- [ ] Quality of Life (scale)
- [ ] Psychiatric adjustment (post-traumatic stress disorder, anxiety and depression)
- [ ] Mortality (after discharge from hospital)
- [ ] Other

Appendix E - Quality Assessment - Effective Public Health Practice Project Quality Assessment Tool 2003

A Selection Bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?

- ☐ Very Likely
- ☐ Somewhat Likely
- ☐ Not Likely

2. What percentage of selected individuals agreed to participate?

- ☐ 80 - 100% Agreement
- ☐ 60 - 79% Agreement
- ☐ Less than 60% Agreement
- ☐ Not Reported
- ☐ Not Applicable

3. Rate this section (see dictionary)

- ☐ Strong
- ☐ Moderate
- ☐ Weak

B Allocation Bias

4. Indicate the study design

- ☐ RCT (go to question 5)
- ☐ Quasi-Experimental (skip to question 8)
- ☐ Case-Control (skip to question 8)
- ☐ Before/After study (skip to question 8)
- ☐ No Control Group (skip to question 8)
- ☐ Other (skip to question 8)

5. Is the method of random allocation stated?

- Yes
- No

6. If the method of random allocation is stated, is it appropriate?

- Yes
- No

7. Was the method of random allocation reported as concealed?

- Yes
- No

8. Rate this section (see dictionary)

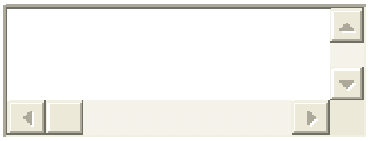
- Strong
- Moderate
- Weak

C Confounders

9. Prior to the intervention were there between group differences for important confounders reported in the paper?

- Yes
- No
- Can't tell

10. Relevant confounders reported in the study.



11. If there were differences between groups for important confounders, were they adequately managed in the analysis?

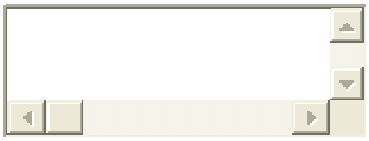
- Yes
- No

- [ ] Not Applicable

12. Were there important confounders not reported in the paper?

- [ ] Yes
- [ ] No

13. Relevant confounders NOT reported in the study.



14. Rate this section (see dictionary)

- [ ] Strong
- [ ] Moderate
- [ ] Weak

D Blinding

15. Was (were) the outcomes assessor(s) blinded to the intervention or exposure status of participants?

- [ ] Yes
- [ ] No
- [ ] Not Reported
- [ ] Not Applicable

16. Rate this section (see dictionary)

- [ ] Strong
- [ ] Moderate
- [ ] Weak
- [ ] Not Applicable

E Data Collection Methods

17. Were data collection tools shown or are they known to be valid?

- ☐ Yes
- ☐ No

18. Were data collection tools shown or are they known to be reliable?

- ☐ Yes
- ☐ No

19. Rate this section (see dictionary)

- ☐ Strong
- ☐ Moderate
- ☐ Weak

F Withdrawals and Drop-outs

20. Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest)

- ☐ 80 - 100%
- ☐ 60 - 79%
- ☐ Les than 60%
- ☐ Not Reported
- ☐ Not Applicable

21. Rate this section (see dictionary)

- ☐ Strong
- ☐ Moderate
- ☐ Weak
- ☐ Not Applicable

G Analysis

22. Is there a sample size calculation or power calculation?

- ☐ Yes

- ☐ Partially
- ☐ No

23. Is there a statistically significant difference between groups?

- ☐ Yes
- ☐ No
- ☐ Not Reported

24. Are the statistical methods appropriate?

- ☐ Yes
- ☐ No
- ☐ Not Reported

25. Indicate the unit of allocation.

- ☐ Community
- ☐ Organization/Institution
- ☐ Group
- ☐ Provider
- ☐ Individual

26. Indicate the unit of analysis.

- ☐ Community
- ☐ Organization/Institution
- ☐ Group
- ☐ Provider
- ☐ Individual

27. If the unit of allocation and the unit of analysis are different, was the cluster analysis done?

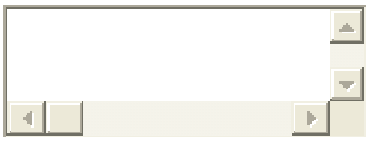
- ☐ Yes
- ☐ No

- [ ] Not Applicable

28. Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?

- [ ] Yes
- [ ] No
- [ ] Can't tell
- [ ] Not Applicable

29. Comments



H Intervention Integrity

30. What percentage of participants received the allocated intervention or exposure of interest?

- [ ] 80 - 100%
- [ ] 60 - 79%
- [ ] Less than 60%
- [ ] Not Reported
- [ ] Not Applicable

31. Was the consistency of the intervention measured?

- [ ] Yes
- [ ] No
- [ ] Not Reported
- [ ] Not Applicable

32. Comments