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Acute Stroke: Evaluation and Treatment

Summary

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Introduction

Stroke defines an acute vascular event in the brain and is a leading cause of death and disability. Ischemic stroke results from decreased blood flow to a portion of the brain with consequent cell death. Hemorrhagic stroke, on the other hand, is a result of bleeding into the brain. Ischemic stroke is far more common and is potentially treatable with thrombolytic therapy. While effective, the wide application of this therapy has been hampered by restrictive selection criteria based on time since onset of symptoms. Successful treatment requires a system capable of rapidly identifying and evaluating prospective candidates. In this context, use of community education, specific ED protocols and designated treatment centers may demonstrate some advantages. Evidence is emerging that patient selection by time since stroke onset, imaging characteristics, and intra-arterial treatment may increase the probability of recanalisation of occluded vessels. Normalization of serum glucose, acute blood pressure management and surgical extraction of intracerebral clot may be of benefit in some circumstances.

The purpose of this report is to systematically review the available literature in the field of acute stroke evaluation and treatment. The task of the University of Ottawa Evidence-based Practice Center (UO-EPC) involved the following three areas: (1) What interventions in acute stroke (<24 hours from onset) are effective in reducing morbidity and mortality? (2) How do safety and effectiveness of these interventions vary by timing in relation to onset of symptoms? (3) What is the evidence that specific systems of care improve outcomes of acute stroke?

Methods

The databases searched were MEDLINE® (1966 to April Week 4 2004), EMBASE (last 6 months) and CINAHL® (1982 to April Week 5 2004) using the OVID interface. Also searched were the Stroke Trials Directory, the Cochrane Stroke Group Registry, conference proceedings from the 28th International Stroke Conference 2003 (*Stroke,* February 2004) and the American Academy of Neurology Annual Meeting (published in *Neurology*). The Effective Practices and Organization of Care (EPOC) registry was searched by the Cochrane review group.

All results of searches for evidence were provided to two reviewers for assessment. All studies were screened by both reviewers by reviewing the bibliographic records, and when meeting inclusion criteria, the subsequent full-text of the record. If the reviewers did not agree in finding at least one unequivocal reason for excluding the study, it was entered into the next phase of the review. The reasons for exclusion were noted using a modified QUOROM format.

Two reviewers independently abstracted the contents of each included study using an electronic Data Abstraction form developed

especially for this review. Data abstracted included the study and population characteristics, intervention characteristics and relevant outcomes of included studies.

Attempts were made to minimize and, where not possible, explain statistical and clinical heterogeneity. Pooled estimates were only calculated if clinically and statistically appropriate. In situations where it was felt that quantitative synthesis could not be performed, a qualitative narrative synthesis was conducted.

Results

Intervention A

Does surgery impact the outcome in patients with acute intracerebral hematoma? Twenty-three studies were identified by our search. Meta-analysis was conducted on four studies. The four trials had a total of 246 subjects. The pooled estimate favored treatment; however, the confidence interval crossed the null (OR=0.24 [0.02, 3.03]). A meta-analysis for the outcome of death produced similar results (OR=0.62 [0.34, 1.13]). The meta-analysis was repeated including the study published after the period included in the search strategy. This study had significantly greater numbers than the other included studies; however, the conclusion of the meta-analysis was not altered. Once again, the odds ratio for death had a point estimate favoring treatment; however, the confidence interval clearly crossed the null (OR=0.81 [0.54, 1.22]). Moderate heterogeneity was noted.

Intervention B

Does antihypertensive treatment reduce stroke-related mortality and disability in patients with acute intracerebral hemorrhage (ICH)? Six studies were identified that investigated antihypertensive therapy for ICH. Four of these were non comparative case series and thus were excluded from our review. Two unique studies met eligibility criteria and were pre- and post-designs. Neither study commented on outcomes of death or disability. One suggested that cerebral perfusion pressure was not altered with antihypertensive therapy.

Intervention C

Does intra-arterial (IA) thrombolysis reduce stroke-related mortality and disability in adults with acute ischemic stroke? Of the 37 studies identified by the search strategy, five unique publications met criteria for inclusion. Two studies could be combined with the pooled estimates for death

and disability and death favoring treatment with a confidence interval which crossed the null in both cases: death and disability (OR=0.55 [0.29, 1.16]), and death (OR=0.78 [0.42, 1.47]). Thus, while the pooled estimates for these outcomes are not statistically significant the possibility of substantial benefit from intra-arterial therapy cannot be excluded. A pooled estimate of the impact on disability alone could not be obtained from the available data. A single study[1] suggests an absolute improvement in the proportion of subjects with a mRS score < or = 2 of 15 percent. The odds ratio for this outcome was 2.13 (1.02, 4.42).

Intervention D

Does treatment to normalize blood glucose levels reduce stroke-related mortality and disability in adults with acute stroke? No studies were identified which specifically addressed this question. Two unique publications demonstrated the feasibility of reduction in serum glucose levels but were not designed to measure clinical outcome.

Intervention E

Does mechanical clot disruption reduce stroke-related mortality and disability in adults with acute ischemic stroke? Ten studies were identified by the search criteria and one, which fell outside the search dates, was provided by an expert. Of these, two unique RCTs met the criteria for inclusion. Both evaluated the effect of ultrasound enhanced thrombolysis in middle cerebral artery (MCA) occlusion. Primary end points differed but the treatment effect in both studies favored intervention.

Intervention F

Is the effectiveness and safety of thrombolytic therapy for adults with acute ischemic stroke affected by time from onset to treatment? No single study has attempted to investigate the impact of timing on thrombolysis treatment outcome. However, five unique publications examining treatment outcomes across relevant time windows were included.[2]

Studies examining enrollment of patients 3 to 5 hours after stroke onset and 0 to 6 hours after onset did not show treatment benefit.[2,3] Reanalysis of the NINDS trial data[4] suggested improved functional outcome for the 0-90 minute stratum as compared with the 91-180 minute interval. A patient level meta-analysis of six trials of tPA treatment for ischemic stroke with treatment windows between 0 and 6

hours was identified which examined the relationship between onset to treatment time and outcome.[5] A clear association was found between onset to treatment time and outcome. The odds ratio for favorable outcome with tPA treatment in the 0 to 90 minute interval was 2.81 (95% CI 1.75-4.50). This decreased to 1.15 (0.90-1.47) in the 271 to 360 minute interval. No increase in mortality was noted until the 271-360 minute interval.

Intervention G

Do pretreatment CT scoring systems affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke? Two unique studies were included in this analysis.[6] Prospective evaluation of CT scoring systems was not available, and both included studies are evaluations of CTs conducted during the course of prospective trials of thrombolysis in stroke. Analysis of CT scans from patients in the NINDS trial demonstrates that while early infarct changes are common, they correlate poorly with outcome.[6] A weak association between early CT changes and outcome was noted in the PROACT 2 trial.[7]

Intervention H

Do pretreatment MRI scoring systems affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke? Six studies were identified that addressed the effectiveness of an MRI scoring system for ischemic stroke. One multiple prospective cohort study[8] and one single prospective cohort study,[9] published in 2002 and 2003, were included in our review. Three non comparative case series reports[10-12] and one case study were excluded for level of evidence.[13] Neither of the included studies used MRI measures prospectively to make decisions on thrombolysis. Both, however, provided correlations with surrogate measures which may be useful in clinical decision making. Recanalisation and initial diffusion-weighted imaging (DWI) lesions were found to correlate with clinical outcome and infarct volume at 60 days. In addition, in patients treated with intravenous tPA, time to peak was correlated with recanalisation at day 1. Thirteen of 15 patients (93 percent) whose baseline time-to-peak was less than or equal to 36.9 milliseconds recanalized within the first day versus 5 of 15 patients (35.7 percent) whose time-to-peak was greater than 36.9 milliseconds.[9] Suarez and colleagues[8] reported a single-center cohort in which the presence of cortical infarct on MRI was used to select patients for IA treatment following IV treatment. MR imaging added 17 minutes to the treatment

protocol and thus was felt to be feasible but due to the absence of a comparison group no comment can be made about marginal effectiveness over current treatment protocols.

Intervention I

Do CT perfusion/angiography affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke? Three studies (four publications) examining CT perfusion/angiography for ischemic stroke were identified.[14-17] One potentially relevant trial[14,15] was published in abstract form and the authors were contacted to determine if subsequent articles were published. These were excluded following full text screening. Study design could not be determined in two publications and were excluded for level of evidence.[18,19] One single retrospective cohort study[16] and one case-control study,[17] published in 2001 and 2004, respectively, were included in our review.

The hyperdense MCA sign was evaluated in a small cohort of patients treated with either IV or IA Thrombolysis.[17] The hyperdense MCA sign was associated with a greater probability of recovery with IA than intravenous treatment (37 percent versus 13 percent). This observational data[17] suggests that this sign may be used as a tool to triage patients between intravenous and IA treatment. There is a higher probability that proximal large vessel occlusion as reflected by this sign may be associated with worse outcomes intravenously. This observation will require testing in a prospective study.

Kilpatrick and colleagues[16] reported on a retrospective cohort of 51 patients from a single center between 1997 and 2000. A CT angiogram showing patent vessels was associated with a rate of infarct of 7 percent (1/14 patients) while CT angiogram showing occlusion had an infarct rate of 60 percent (6/10) (p=0.008).

Intervention J

Are community education programs effective in reducing stroke-related disability and mortality? One controlled clinical trial,[20] six before-after studies,[21-26] and one study for which the study design could not be determined,[27] investigated the use of community education programs for acute stroke. Subsequently, seven studies were excluded for level of evidence.[21-27] Only one study[20] was included for our review. This study was a controlled clinical trial and was published in 2003.

Morgenstern et al.[20] reported on the third phase of the TLL Temple Foundation Stroke Project. Target behaviors of lay community (the "at-risk group"), EMS, ED physicians, neurologists, and community primary care providers were identified, and educational and infrastructure changes were initiated. A portion of the multilevel intervention public service announcements were created using local role models, volunteers were trained to take the message to community groups, and educational pamphlets were distributed.

Intervention K

Are designated centers effective in reducing stroke-related disability and mortality? It has been hypothesized that to increase utilization of thrombolytics, a dedicated stroke center strategy should be developed.[28] No studies meeting eligibility criteria for investigating the use of designated centers as defined by the Brain Attack Coalition were identified by our searches.[28] The studies we included were felt to most closely resemble the model of a designated stroke center as defined by the Brain Attack Coalition and detailed by Alberts et al.[28] in their recommendations for the establishment of primary stroke centers. Both studies were single prospective cohort designs and were published between 2000 and 2003.

Hill et al.[29] reported on building a "brain attack" team to administer thrombolytic therapy to patients with acute stroke and on their initial experience with IV-administered thrombolytics. A complex system of interventions involving all levels of the system involved in acute stroke care was reorganized. Over the course of the study period improvements in certain parameters were noted. Overall, symptom onset to treatment time was significantly decreased from a mean of 167.8 minutes to 147.4 minutes.[29]

Lattimore and colleagues reported on a similar process of designation and implementation of processes to enhance thrombolysis. An increase in the proportion of ischemic stroke treated with tPA from 1.5 percent to 10.5 percent was noted.[30]

Intervention L

Are ED protocols for the management of acute stroke effective in reducing disability and mortality? Our search identified one case-control study,[31] two single prospective cohort studies,[32,33] two single retrospective cohort studies,[34,35] two non-comparative case series studies,[36,37] and two studies whose design could not be determined.[38,39] The case-control and non-comparative studies were excluded for level of evidence. Four studies, published between 1999 and 2003, examining the effect of ED protocols for management of acute stroke met our eligibility criteria and were included in our final analyses.[32-35]

Smith et al.[34] reported on the establishment of ED procedures and training established for the purposes of thrombolytic treatment. The program relied on ED physicians, with neurology consultation, as primarily responsible for treatment. Treatment times in this model compared favorably with those in models involving comprehensive stroke team response. A similar effort is reported by Akins.[35] Similar treatment times were achieved when ED physicians treated as compared to consulting neurologists. The rate of protocol violations was initially higher in the ED group (30 percent versus 5 percent) than the neurologist group but was reduced by staff education. Jahnke et al.[33] described a comprehensive stroke pathway implemented in the ED. Following this intervention the stroke pathway was initiated in 97 percent of patients as opposed to 40 percent prior. The door to needle time decreased from a mean of 111 minutes to 77 minutes.

Discussion

Currently, available data do not support a role for surgery in the treatment of acute intracerebral hemorrhage. Results, however, do not preclude benefit from surgery which involves modalities other than those studied in the acute trials (e.g., minimally invasive technologies) or treatment of hemispheric hematoma at very early timeframes. Further, the available literature did not comment on cerebellar hematoma and thus this analysis does not apply to infratentorial hemorrhage.

In spite of potential importance, availability of therapy and ease of administration of antihypertensive agents, very little data exists to suggest that their use is of benefit (or results in harm) in the setting of acute ICH. A similar situation exists regarding glucose management for acute ischemic stroke. Further studies are required in both these areas.

IV thrombolysis with tPA is effective and efficacious for acute ischemic stroke within 3 hours of symptom onset. The effectiveness is strongly linked to time since onset of symptoms with shorter times demonstrating significantly better outcomes. Patient level meta-analysis suggests that treatment may be effective up to 270 minutes with treatment increasing the odds of death beyond 270 minutes. Further work is needed to define the risks and benefits of treatment outside the 3 hour window prior to advocating widespread use in these patients. Intra-arterial therapy remains an option for a subgroup of patients with large vessel occlusions principally in the middle cerebral

artery distribution. The evidence for this intervention, however, remains less robust than for IV therapy. Limited data is available regarding patient characteristics predicting outcome. The system changes required to ensure prompt delivery of appropriate therapy are complex and operate on multiple levels. In spite of their critical role, little data exists regarding the efficacy of these interventions and, in particular, the relative efficacy of various components with regard to patient outcomes.

Ultrasound for enhancement of thrombolysis in the setting of MCA occlusion has suggested efficacy in two studies and a definitive trial to demonstrate the benefit and risks is required.

CT and MR imaging for patient selection and prediction of outcome in thrombolysis has yet to be prospectively evaluated. The two included CT studies[6,7] differ in onset to evaluation time with only a weak correlation between CT changes and outcome seen in the trial enrolling patients from 0-6 hours. Neither study quantified CT changes. The Alberta Stroke Program Early CT Score (ASPECTS) score is an easily quantifiable scoring system for early infarct changes.[40] Retrospective evaluation of the ASPECTS score suggests that values below 7 correlate with poorer outcomes. As CT is widely available, this system deserves further exploration. Additional information relevant to treatment decisions may be provided by CT angiography. Occlusion of proximal vessels is associated with higher rates of infarction and thus may influence treatment modalities.

MRI DWI lesions correlate with the presence of infarcts in small cohorts of patients and time to peak measures on early scans may correlate with recanalization after IV tPA treatment. These findings require reproduction and further evaluation. The multiplanar abilities and potential for acquisition of multiple parameters are potentially attractive features of this modality and may assist in selecting patients with a greater ratio of benefit to harm in intravenous and intra-arterial treatment paradigms.

The narrow time window for thrombolysis in acute stroke as well as the relationship between time to treatment and outcome has led to the exploration of a number of strategies for optimization of outcomes. Community education programs regarding the symptoms of stroke have not been independently evaluated but rather studied in the context of more comprehensive system changes. Thus, it is unclear if these programs are effective in improving patient outcomes. Further exploration is also required regarding the content and targeting of such programs. Descriptions of designated treatment centers have shown the feasibility of this approach but an evaluation of published criteria for and marginal effectiveness of such designations remains to be performed.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Ottawa Evidence-based Practice Center, under Contract No. 290-02-0021. It is expected to be available in July 2005. At that time printed copies may be obtained free of charge from the AHRQ Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 127, *Acute Stroke: Evaluation and Treatment.* In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

Suggested Citation

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