

Role of Abciximab in the Management of Acute Ischemic Stroke

EBEM Commentator Contact

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Ciccone A, Abraha I, Santilli I. Glycoprotein IIb-IIIa inhibitors for acute ischaemic stroke. *Cochrane Review* 2006; Issue 4. Chichester, UK: John Wiley and Sons.

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The *Annals'* EBEM editors helped prepare the abstract of this Cochrane systematic review, as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To assess the efficacy and safety of glycoprotein IIb-IIIa inhibitors in the management of acute ischemic stroke and evaluate whether early administration improves the outcome. The results of single therapy or treatment in conjunction with thrombolytic agents were also examined.

DATA SOURCES

The Cochrane Stroke Group trials register was searched up to May 2005, as well as the following electronic databases: Cochrane Central Register of Controlled Trails (The Cochrane Library Issue 2, 2005), MEDLINE (1966 to 2005) and EMBASE (1980 to 2005). Relevant reference lists were searched. Trial authors and pharmaceutical companies were also contacted to identify further published, unpublished, and ongoing trials. Pharmaceutical companies contacted included Centocor Inc. Malvern, Eli Lilly and Company, GlaxoSmithKline, Merck Sharp & Dhome, and Roche.

STUDY SELECTION

Unconfounded randomized controlled trials examining glycoprotein IIb-IIIa inhibitors in the management of acute

ischemic stroke were considered for this review. Patients of any age with definite acute ischemic stroke were selected and only studies in which treatment using glycoprotein IIb-IIIa inhibitors was initiated within 6 hours of symptom onset were included. Any glycoprotein IIb-IIIa inhibitor, irrespective of agent, duration of treatment, dosage, or route of administration, was considered.

Outcome variables analyzed were efficacy and safety. Efficacy was measured by death or severe disability (modified Rankin scale 3 to 6) at follow-up performed at 3 months or longer after stroke. Safety was estimated by death and evidence of symptomatic intracranial hemorrhage and major extracranial hemorrhage.

DATA EXTRACTION AND ANALYSIS

Titles identified by the search were reviewed independently by 3 reviewers, and relevance to the meta-analysis was recorded. The method of randomization, blinding of outcome evaluators, balance of baseline prognostic factors (age, stroke severity, and time from stroke onset), and whether all the randomized patients were accounted for in the analysis were independently extracted.

Concealment of allocation, blinding in outcome evaluation, intention-to-treat analysis, and balance of baseline prognostic factors were evaluated and graded as present, absent, or unclear. The 4 criteria to assess quality were used to derive an overall assessment of validity for each study.

MAIN RESULTS

Two trials (Abciximab Emergent Stroke Treatment Trial [ESTT]^{1,2}; Adams et al³) involving a total of 474 patients were included. Nine studies were excluded. Five relevant ongoing trials were identified (AbESTT-II⁴; Cheung⁵; Combined Approach to Lyss Utilizing Eptifibatide and rt-PA in Acute Ischemic stroke [CLEAR] trial⁶; Safety of Tirofiban in Acute Ischemic Stroke [SaTIS]⁷; Study of Efficacy of Tirofiban in Acute Ischemic Stroke [SETIS]⁸ for future update of the review.

Both the included trials compared the effects of intravenous abciximab to a placebo. The AbESTT study used a dose of 0.25 mg/kg bolus followed by a 0.125 mg/kg per minute infusion for

Table. Combined meta-analysis (n=474).

Outcome Measures	Effect Measure (95% CI)	Comments
Efficacy		
Death or dependency	OR=0.79 (0.54–1.17)	Inconclusive
Safety		
Death from all causes at the end of follow-up	OR=0.67 (0.36–1.25)	Inconclusive
Symptomatic intracranial hemorrhage	OR=4.13 (0.86–19.67)	Inconclusive; however, the trend to increased intracranial bleeding is concerning.
Major extracranial hemorrhage	OR=1.51 (0.25–9.12)	Inconclusive
Thrombocytopenia	Proportions: 6.3% (1.7–14.3) ¹ 1.5% (0.1–3.0) ²	Inconclusive; data only available for treatment groups.

CI, Confidence interval; OR, odds ratio.

12 hours, and the Adams et al³ study was a dose escalation study; 4 dose tiers of abciximab were evaluated against placebo.

The median National Institutes of Neurological Disorders and Stroke Scale score in the patients was 9 for the AbESTT trial and 15 for the Adams et al³ study.

The Table provides a summary of the 2 trials and their outcomes.

CONCLUSIONS

Meta-analysis of the pooled data does not support the routine use of glycoprotein IIb-IIIa inhibitors for patients with acute ischemic stroke. The benefits and adverse effects may be clarified after the publication of the 5 ongoing trials.

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COMMENTARY: CLINICAL IMPLICATION

Despite decades of study, patient delay in seeking treatment for acute ischemic stroke symptoms remains the major impediment to receiving early, definitive treatment, as reported by the American Stroke Association in 2006.⁹ Today the accepted pharmacologic treatments for acute ischemic stroke include aspirin administration once hemorrhagic stroke has been ruled out¹⁰ and thrombolysis with recombinant tissue plasminogen activator in nonhemorrhagic stroke less than 3 hours old.¹⁰ After Food and Drug Administration approval,¹¹ there has been suboptimal use of recombinant tissue plasminogen activator because of delayed patient presentation. There have also been concerns about safety because treatment is associated with a 6.4% risk of intracerebral hemorrhage.¹²

Agents that inhibit the glycoprotein IIb-IIIa receptor have been shown to be effective inhibitors of platelet aggregation and thrombus formation and have the potential to be effective in acute strokes. Randomized clinical trials have shown that glycoprotein IIb-IIIa inhibitors effectively reduced life-

threatening complications in patients undergoing percutaneous coronary intervention or presenting with an acute coronary syndrome.¹³ Glycoprotein IIb-IIIa inhibitors are now under investigation for acute ischemic stroke and are being evaluated either alone or with other treatments, within or beyond the 3-hour “therapeutic window” of recombinant tissue plasminogen activator.

Using comprehensive searches and an unbiased selection process, this Cochrane review summarizes the efficacy and safety of glycoprotein IIb-IIIa inhibitors in patients with acute ischemic stroke either alone or combined with thrombolytic agents. Using evidence from 2 trials involving a total of 474 patients, the authors concluded that the available evidence does not support the routine use of glycoprotein IIb-IIIa inhibitors.

Of the studies included in this review, both were classified as high quality (ie, low risk of bias). Therefore, quality does not help to explain the nonsignificant results reported in this review. The efficacy results need to be interpreted with caution because the number of patients included in all trials remains relatively small. The AbESTT-II, a relevant ongoing trial identified by the reviewers, stopped recruitment of patients because of excess intracranial hemorrhages in the treatment group and an unfavorable risk:benefit ratio.

TAKE-HOME MESSAGE

Because of an aging population and ongoing community education to promote early presentation, emergency physicians can expect to encounter more patients with symptoms compatible with stroke in the future. According to this review, there is insufficient evidence to recommend glycoprotein IIb-IIIa inhibitors as safe and efficacious treatments for acute ischemic stroke. It is expected that the publication of ongoing multicenter trials will provide more precision about the role of glycoprotein IIb-IIIa inhibitors in the management of acute ischemic stroke.

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EBEM TEACHING POINT

Importance of unconfounded randomized controlled trials.

A randomized controlled trial is an experiment in which 1 or more interventions are compared to a control, placebo, or no intervention treatment and assignment to intervention is performed randomly. One of the strengths of a randomized controlled trial is that it assigns treatment without knowledge of patient factors. Therefore, the design attempts to balance the known and unknown confounders among the treatment groups. A confounder is a factor that is associated with both the intervention (or treatment) and the outcome of interest. For example, if the ages of patients vary between the intervention arms, it may be difficult to decide whether a lower risk of death in one group is due to the intervention or the difference in ages. Age is then referred to as a confounder, or a confounding variable. For a comparison to be unconfounded, the 2 treatment groups must be treated identically except for the intervention itself and the intervention groups must be balanced in the measured confounders.

Confounding is a major concern in all experiments; however, this concern is even higher in nonrandomized studies. For instance, to estimate the effect of heparin in acute stroke, a randomized controlled trial of acetylsalicylic acid+heparin versus acetylsalicylic acid+placebo-heparin would provide an unconfounded comparison, as long as the groups were balanced. However, a cohort study in which heparin and acetylsalicylic acid-treated patients were compared with those with acetylsalicylic acid alone would likely provide a confounded comparison of the effect of heparin.

The importance of an unconfounded randomized controlled trial is in its ability to provide a valid estimate of treatment effect. Despite efforts to balance the known and unknown confounders in a randomized controlled trial, the design is not without fault and imbalance may occur. This is particularly true in small randomized controlled trials (especially in those in which block randomization is not used), or it may be due to chance. In cases in which an imbalance is identified among

groups on suspected confounding factors, an adjusted analysis is recommended to confirm the univariate results.

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