JACC Vol. 19, No. 2
February 1992:295–6

Editorial Comment

Intracranial Hemorrhage After Thrombolytic Therapy: A Therapeutic Conflict*

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> For extreme illnesses, extreme treatments are most fitting.
> Hippocrates, *Aphorisms*. I.6
>
> As to diseases, make a habit of two things—to help, or at least do no harm.
> Hippocrates, *Epidemics*. Bk. I, Sect. XI

These two Hippocratic statements are well known to most physicians. The first is often cited when the physician prepares for an aggressive intervention against a lethal disease and the second when drugs or procedures are associated with iatrogenic complications. These two pieces of Hippocratic advice conflict when discussing thrombolytic therapy for acute myocardial infarction. On the one hand, aggressive interventional therapy, including intravenous thrombolytic agents, has been repeatedly associated with decreased in-hospital and long-term mortality after acute infarction. On the other hand, controlled trials and clinical experience have clearly documented hemorrhagic deaths secondary to thrombolytic therapy itself. Many of these iatrogenic deaths are the result of intracranial hemorrhage.

The present study. In most of the carefully controlled, randomized trials of thrombolytic therapy, the incidence of intracranial hemorrhage has been low (0.3% to 0.6%), although a frequency of up to 1.6% has been reported (1–5). In this issue of the Journal, De Jaegere and coworkers (6) report a high rate of intracranial hemorrhage (1%) in a registry of 2,469 patients with acute myocardial infarction admitted to 61 hospitals in the Netherlands. The clear implication of this study is that registry patients are at higher risk for intracranial hemorrhage compared with the highly selected population of the randomized controlled trials. Since the Dutch registry patients probably resemble nonstudy patients in the United States, one anticipates that rates of intracranial hemorrhage will also be higher in patients with "routine" infarction treated with thrombolytic agents in the United States.

As in all such studies, a number of questions can be raised concerning the study of De Jaegere et al. (6). What clinical criteria were used to make the diagnosis of intracranial hemorrhage? Most *but not all* patients with this diagnosis had a computed tomographic (CT) scan of the brain. How was the presence of intracranial hemorrhage determined in patients who did not undergo CT scanning? How were registry data validated and standardized among the 61 institutions? What were the dose and route of administration when heparin was given? These and many other questions will need to be answered in future communications from this registry and others monitoring thrombolytic therapy. Eventually, some of these issues will need to be addressed in more formal clinical trials. The importance of these questions is clear, because higher rates of intracranial hemorrhage with attendant increased mortality may alter assessments of risk/benefit ratio in managing patients with acute myocardial infarction.

Predicting increased risk of intracranial hemorrhage. Given the very high mortality rate associated with intracranial hemorrhage, cardiologists are anxiously seeking strategies to prevent or at least decrease the risk of its occurrence. Several clinical factors have been associated with intracranial hemorrhage (Table 1) (5–7). This does not mean that these factors necessarily cause intracranial hemorrhage; they are merely associated with an increased risk of its occurrence.

Many clinicians avoid using thrombolytic agents in the presence of these risk factors. In so doing, they may be rendering a disservice to their patients because the increased risk of dying from acute myocardial infarction treated conventionally may far outweigh the risk of intracranial hemorrhage. Clearly, more data from registries and controlled trials are required to construct a complete picture of thrombolytic therapy risk/benefit ratio in the presence of risk factors for intracranial hemorrhage.

An American patient with an acute myocardial infarction is approximately one-third to one-half as likely as his or her

Table 1. Factors Associated With Increased Risk of Intracranial Hemorrhage

Factors associated with increased risk in one study
Use of anticoagulant drugs on admission*
Diabetes mellitus
Female gender*
rt-PA dose 150 mg vs. 100 mg*
Calcium channel blocker therapy on admission
Factors associated with increased risk in more than one study
Older age (>65 years)*
Low body weight (<70 kg)*
Hypertension on admission*
Cerebrovascular disease by history

*Multivariate analysis confirmed these factors to be independent predictors of intracranial hemorrhage.

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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0735-1097/92/$5.00

JACC Vol. 19, No. 2
February 1992:295–6

European counterpart to receive thrombolytic therapy (Goldberg RJ. Unpublished observations from the Worcester Heart Attack Study, 1986–1990). Thus, our European cardiology colleagues do not assess risk/benefit ratio associated with thrombolytic therapy in the same manner that we do. This disparity needs to be examined closely: are we treating too few patients or are they treating too many? My own prejudice lies with the former assertion.

Conclusions. We know that thrombolytic therapy decreases mortality associated with acute myocardial infarction but at an increased risk for intracranial hemorrhage. A variety of clinical factors are associated with this increased risk, although the benefits of thrombolytic therapy may outweigh this risk. These associations and the affiliated risk/benefit ratio require intense scrutiny in the future. Like so many important clinical questions in the past:

> All our knowledge brings us nearer to our ignorance,
> All our ignorance brings us nearer to death.
>
> T.S. Eliot, "The Rock"

References

1. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarctions: ISIS-2. Lancet 1988;2:349–60.
2. Wilcox RG, Von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). Lancet 1988;2:525–30.
3. AIMS Trial Study Group. Long-term effects of intravenous anistreplase in acute myocardial infarction: final report of the AIMS study. Lancet 1990;335:427–31.
4. Van de Werf F, Arnold AER. Intravenous tissue plasminogen activator and size of infarct, left ventricular function, and survival in acute myocardial infarction. Br Med J 1988;297:1374–9.
5. Gore JM, Sloan M, Price TR, et al. Intracerebral hemorrhage, cerebral infarction, and subdural hematoma after acute myocardial infarction and thrombolytic therapy in the TIMI study. Circulation 1991;83:448–59.
6. De Jaegere PP, Arnold AA, Balk AH, Simoons ML. Intracranial hemorrhage in association with thrombolytic therapy: incidence and clinical predictive factors. J Am Coll Cardiol 1992;19:289–94.
7. Anderson JL, Karagounis L, Allen A, Bradford MJ, Menlove RL, Pryor TA. Older age and elevated blood pressure are risk factors for intracerebral hemorrhage after thrombolysis. Am J Cardiol 1991;68:166–70.