emic stroke. These trials may not have been blinded, but they were randomized and used death as a common outcome event, which cannot, of course, be affected by ascertainment bias. The nonrandomized studies of thrombolysis (which make up the majority of available reports in the literature) were included simply to highlight how unusable they are to obtain a true assessment of the effect of thrombolysis and also to show the totality of the evidence and how important it is to stop doing nonrandomized comparisons.

With respect to large-scale trials of acute stroke treatment, it is important to remember that it has taken nearly 40 years for the myocardial infarction (MI) trials to reach their current level of sophistication and size. Thrombolysis for MI was nearly rejected in error until in the early 1980s a proper overview analysis demonstrated that there could be as much as 25% reduction in death; this finding was subsequently borne out by the large randomized controlled trials. Myocardial infarction care had the advantage of being organized into coronary care units with rapid admission policies. The approach to acute stroke care probably requires considerable rationalization for any acute stroke treatment to work for the generality of patients, but if promising treatments are not properly tested, no treatment for acute stroke will ever be found. Because of these practical difficulties, it will probably take many years to establish whether any acute stroke treatments currently under trial are effective. Moreover, although there are more patients with MI than with stroke, there will still be about 5 million new cases of ischemic stroke in the United States in the next 10 years! The latter are hardly rare or less deserving in our attempts to find a treatment. In any event, we cannot be sure how long it is after ischemic stroke onset that treatment—any treatment—is ineffective. In the MI field, theory suggested that thrombolysis could not work after 6 hours; fortunately, MI trialists insisted on a longer time window and showed that treatment even 12–24 hours after chest pain onset gave worthwhile benefit.

With regard to hemorrhagic transformation, we clearly stated that the trend toward increased cerebral hematoma formation with tissue plasminogen activator (tPA) in acute ischemic stroke was similar to that seen when streptokinase and tPA were compared in ISIS-3 and GISSI-2 in acute MI. Obviously, ascertainment of the true cerebral hemorrhage rate with each thrombolytic drug will be possible only by direct comparison in large randomized studies, as stated in our article.

The conclusion of our review was that evidence of benefit for thrombolysis in acute ischemic stroke was very tentative but was sufficient to encourage larger randomized trials to establish the true practicality and risk/benefit ratio.

References


2. ISIS-2 Collaborative Group: Randomised trial of intravenous streptokinase oral aspirin, both or neither among 17,187 cases of acute myocardial infarction. Lancet 1988;2:349–360

3. ISIS-3 Collaborative Group: Randomised trial of intravenous streptokinase, tissue plasminogen activator or aspirin/placebo among 46,000 cases of acute myocardial infarction. Lancet 1992;339:753–770


Increased Thromboxane Biosynthesis in Patients With Acute Cerebral Ischemia

Included in the article by Koudstaal et al. are results indicating that urinary excretion of a thromboxane metabolite was increased in a significant proportion of ischemic stroke patients but not in those with transient ischemic attacks or in nonvascular neurological inpatients. These findings are virtually identical to those reported in a paper published previously in Stroke. An interesting apparent difference in the results, however, is that the earlier work described increased thromboxane excretion in male but not female stroke patients. Koudstaal et al refer only briefly to the issue of gender; this subject would appear to warrant more attention.

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References


Response

Fisher and Zipser1 measured the urinary excretion of thromboxane (TX) B2, the nonenzymatic hydrolysis product of TXA2. This is thought to reflect primarily the intrarenal synthesis of TXA2 (see Reference 2 for a review). In contrast, we reported measurements of the urinary excretion of 11-dehydro-TXB2, which derives from enzymatic degradation of TXB2 through the 11-dehydro-dehydrogenase pathway and is considered to reflect primarily the extrarenal (largely platelet) synthesis of TXA2.

With regard to the importance of gender, we found no statistically significant difference in thromboxane biosynthesis between men and women, the excretion rate being 356±963 (n = 47) and 531±857 (n = 32), respectively (p = 0.41), in the total study population and 485±1149 (n = 32) and 790±1042 pmol/mmol creatinine (n = 19), respectively (p = 0.35), in patients with cerebral ischemia. Thus, the apparent discrepancy between Dr. Fisher’s earlier findings and our own is probably related to the different cellular sources of TXA2 being investigated in the two studies.

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References


Corrections

Clarification

I would like to clarify my editorial comment concerning the manuscript by Ueda et al entitled, “Changes in Extracellular Glutamate Concentration Produced in the Rat Striatum by Re-
Increased thromboxane biosynthesis in patients with acute cerebral ischemia.
M Fisher

*Stroke*. 1993;24:912
doi: 10.1161/01.STR.24.6.912

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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