Medical Treatment of Transient Ischemic Attacks: Does It Influence Mortality?

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All randomized studies published on the medical treatment of transient ischemic attacks in which controls received no treatment or placebo and in which mortality was reported were reviewed. Using the odds ratio method, we analyzed the results to determine if treatment had an effect on expected mortality. Studies were analyzed separately according to the treatment modality used. Chronic anticoagulation was used in four studies and platelet inhibitors in 12 (14 trials). This meta-analysis showed that neither treatment modality significantly reduces mortality. Chronic anticoagulation may have an adverse effect, and even though platelet inhibitors appeared to reduce mortality, no significance can be demonstrated, and the 95% confidence intervals did not allow us to rule out the possibility, albeit small, of an adverse effect or no effect at all. (Stroke 1988;19:397–400)
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V = E(1 - n/N)(N - d)/(N - l). If the results of a single value of $^3.84$ was considered significant at $p = 0.05$. O — E would be negative, $\chi^2$ statistics for all individual studies indicated that drug treatment was beneficial, determining from 0 and have a variance (V) calculated as $V = E(1 - n/N)(N - d)/(N - l)$. If the results of a single study indicated that drug treatment was beneficial, O — E would be negative. $\chi^2$ statistics for all individual studies had one degree of freedom, and, therefore, a value of $\geq 3.84$ was considered significant at $p \leq 0.05$.

In our analysis, direct comparison of patients in one study with patients in another was avoided by considering the results (O — E) of each trial as an independent, randomly fluctuating estimate of the true effect of drug therapy on the relative risk of mortality. The grand total (GT) of O — E from several similar studies was examined; any overall beneficial effect from drug therapy yielded a negative GT. Similarly, if therapy were without effect, GT would differ only randomly from 0 with $V$ equal to the sum of the individual variances (SIV). An estimate of the pooled odds ratio of death among treated patients relative to placebo and no-treatment controls was calculated as $e^{\sigma^2/SIV}$. A pooled odds ratio of $<1.0$ represented a beneficial effect of drug treatment. Pooled odds ratios were calculated separately for classes of studies employing chronic anticoagulation, aspirin, and nonaspirin platelet inhibitors. The pooled odds ratio for all randomized, placebo-controlled studies employing any antiplatelet agent, including aspirin and aspirin plus sulfipyrazine, was also calculated. In studies in which a single placebo group was used for comparison with multiple drug treatment groups, the placebo group data were used only once in the pooled analyses. The 95% confidence intervals of the pooled odds ratios were calculated as $e^{\sigma^2/SIV \pm 1.96SIV}^{12}$. A beneficial effect of drug therapy was considered significant if the pooled odds ratio was $<1.0$ and the 95% confidence intervals did not encompass 1.0.

**Results**

No individual study employing anticoagulants, aspirin, or other antiplatelet agents significantly reduced mortality when compared with placebo or no-treatment controls. The most common cause of death observed was cardiac.
Table 1 depicts the data of the chronic anticoagulation studies, which provide no good evidence for any effect of anticoagulant therapy on mortality. Only 190 patients have been evaluated, 95 treated with chronic anticoagulation versus 95 no-treatment controls in four studies. The pooled odds ratio of 1.3 indicates that an adverse effect from chronic anticoagulation on mortality is likely. However, the 95% confidence intervals were wide and included values from 0.54 to 3.12. Thus, we could not rule out a substantial beneficial or adverse effect.

Also in Table 1, the data of the aspirin studies are presented. A total of 779 patients have been evaluated in aspirin versus placebo studies. From these results, our best estimate of the effect of aspirin on mortality is a 32% reduction (pooled odds ratio of 0.68). This estimate, however, is not significant since the 95% confidence interval ranges from 0.36 to 1.31 so we cannot rule out no effect or adverse effect of treatment.

Also in Table 1, data on 1,316 patients evaluated in studies employing a single platelet inhibitor other than aspirin are presented. The pooled odds ratio was 0.81, with a 95% confidence interval of 0.56 to 1.16. The results of these studies indicate that the best estimate of the overall effect of nonaspirin platelet inhibitors is a reduction in the relative risk of mortality of 19% when compared with placebo controls. This estimate, again, was not significant and we could not rule out, although less likely, an absence of effect or an adverse effect on mortality.

Discussion

By using the odds ratio method, or meta-analysis, we avoided direct comparisons between studies and concentrated only on their results. We specifically avoided comparing results from the chronic anticoagulation studies with those of the different platelet inhibitors. Their methodologies were, in general, quite different; the older chronic anticoagulation studies had multiple flaws in their designs;24,25 other than the small number of patients studied. Baker et al.,18 for instance, eliminated from their study as misdiagnosed those patients in the control group who suffered intracerebral hemorrhage. However, they kept as complications of therapy those cases suffering intracerebral hemorrhage who were in the treatment group. This, no doubt, is reflected in their mortality results. In the latest of the chronic anticoagulation studies, published in 1975, Bradshaw and Brennan21 did not prospectively randomize all patients, and even though they did not have deaths due to intracerebral hemorrhage, their treatment group experienced a higher incidence of myocardial infarction, which accounted for their higher mortality.

The studies in which platelet inhibitors were used to treat TIA patients had, in general, better methodologies, and, except for those of Acheson et al26 and Acheson and Hutchinson27 all were published within the last decade. These studies included more patients, and their designs were more in keeping with sounder statistical methods; nevertheless, flaws can be found in all of them.28

Because of the similar trend in the results of the aspirin and nonaspirin platelet inhibitors classes, we combined them to express the mortality risk reduction for all platelet inhibitor studies. Although these studies employed different drugs, their methodologies are comparable, and the effect of the treatment is similar; therefore, we thought it justified to pool their results. Additionally, we found similarities between the pooled odds ratios and confidence intervals for the aspirin (0.68, 0.36–1.31) and the nonaspirin platelet inhibitor classes (0.81, 0.56–1.16). The observed GT O–E is −8.56, indicating that there were eight fewer deaths in the treatment groups than would have been expected if platelet inhibitor therapy had no effect on mortality and, therefore, eight more deaths in the placebo control groups. These data indicate that a total of 16 deaths might have been prevented during the studies if all enrolled patients had received antiplatelet therapy. The pooled odds ratio was 0.79, a value that would suggest a 21% reduction in the risk of death associated with antiplatelet therapy, three fewer deaths for every 100 patients treated. This difference, however, did not reach significance. The 95% confidence interval included 0.57 to 1.09. Although our best estimate is that antplatelet therapy reduced the risk of mortality by 21%, we cannot rule out, although less likely, no effect or a mildly detrimental effect. None of the studies by themselves demonstrated a significant reduction in mortality. However, as a class, the platelet inhibitor studies show that it may be more likely than not that mortality was reduced.

In only two studies were results for men and women reported separately,24,27 and in neither was there a difference in mortality between the sexes.

Failure of chronic anticoagulation, aspirin, and other platelet inhibitors to protect against mortality in the reviewed studies may reflect their failure to prevent cardiac complications in these patients, and it may be independent of their effectiveness in reducing the incidence of ischemic stroke in patients with TIA.

References

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