CLINIC-IQ

Does Aggrenox® (Aspirin/Dipyridamole) Reduce the Risk of Recurrent Stroke to a Greater Degree than Aspirin Alone?

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Answer: Yes - modestly
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Level of evidence: A
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Summary of the issue

Stroke is the third most common cause of adult mortality in the United States, accounting for 6.25% of total deaths in 2004. One estimate suggests that the national incidence of stroke exceeds 700,000 cases per year of which 200,000 are recurrent attacks. Ischemic stroke constitutes 87% of all strokes with 13% contributed to hemorrhagic strokes and subarachnoid bleedings.[1] With nearly 4.5 million survivors, it is the most frequent source of long-term disability in the American society. Over a lifetime, the cost of ischemic stroke is estimated to be more than $140,080 per person, calculated in 1999 dollars.

Kleindorfer et al found that the overall ischemic stroke rate, after the initial transient ischemic attack (TIA), was 17% at 6 months, the majority (65%) occurring within 30 days after the initial TIA. They also report a 6% rate of stroke or TIA two days after the initial event. The short-term rate of stroke or recurrent TIA was 26% during the six months after TIA.[2] The 10-year stroke risk in patients with prior TIA is 18.8% with a combined 10-year stroke, MI or vascular death risk of 42.8%.[3]

Aspirin produces a modest reduction in the risk for a second stroke and is widely used for initial therapy. Dipyridamole inhibits platelet aggregation by different mechanisms than aspirin, and so the combination of aspirin and extended-release dipyridamole (Aggrenox ®) should work better than either agent alone. Dipyridamole reduces platelet aggregation through two main mechanisms. It inhibits adenosine uptake into platelets, endothelial cells and erythrocytes in a dose dependant manner, at therapeutic concentrations (0.5 – 1.9μg/ml). It also inhibits cyclic guanosine monophosphate (cGMP) phophodiesterase activity in platelets and vascular smooth muscle cells. The resultant elevation of intracellular concentrations of cyclic adenosine monophosphate (cAMP) and cGMP produces a relaxation of vascular smooth muscle and inhibition of platelets. Aspirin reduces platelet aggregation by irreversibly inhibiting platelet cyclo-oxygenase, preventing thromboxane synthesis.[4]

Earlier studies failed to demonstrate an added benefit when aspirin was combined with immediate-release dipyridamole (Persantine®). Various pharmacokinetic studies have demonstrated the benefit and efficacy of extended-release dipyridamole over the immediate-release formulation.[5,6,7]

Summary of evidence

Results of early clinical trials[8-10,15] to evaluate the efficacy of dipyridamole, both immediate and extended release formulations, and aspirin for prevention of secondary involved small numbers of patients. Pooled analysis of these studies showed a relative risk reduction of a major vascular event of 3% in the combination dipyridamole and aspirin group compared with aspirin alone. A Cochrane review confirmed these results and showed that in patients with other types of vascular disease, the dipyridamole and aspirin combination was no more effective than aspirin alone.[11] The European Stroke Prevention Study I (ESPS-1) was the first study with a sufficient patient population to demonstrate the potential benefit of the combination of dipyridamole and aspirin for the prevention of secondary stroke for patients with prior ischemic stroke or transient ischemic attacks.[12] However, unanswered questions remained regarding the contribution made by dipyridamole and aspirin individually, as well as the most appropriate doses of dipyridamole and aspirin required for efficacy while minimizing gastrointestinal and bleeding side effects. The aim of the ESPS-2 and ESPRIT trials were to resolve this uncertainty by comparing dipyridamole and aspirin with aspirin alone in patients with a transient ischemic attack or a minor ischemic stroke of presumed arterial origin.

In a randomized, double-blind, parallel-group, ex-vivo study conducted by the Miller, et al, whole blood samples were collected from 96 (48 male and 48 female) healthy volunteers (19-58 years of age) one-half hour before and two hours after a 3.5-day treatment period with aspirin 25 mg (n=23), extended-release dipyridamole 200 mg (n=22), a combination of aspirin 25 mg and extended-release dipyridamole 200 mg (n=24), or placebo (n=24)

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administered twice daily (morning and evening).[13] The samples were incubated over a thrombogenic matrix to stimulate blood flow over a vessel wall, and automated microscopy and morphometry were used to assess the size of individual platelet thrombi that attached to the matrix. Drug concentrations and cyclo-oxygenase inhibition were also assessed. Results demonstrated that the interaction between whole blood platelets and subendothelial matrix was reduced by 20% ($p<0.01$) in the dipyridamole treatment group, 54% ($p<0.01$) in the aspirin treatment group, and 71% ($p<0.01$) in ER-dipyridamole and aspirin treatment group versus placebo during the 3.5-day treatment period. This finding confirms that both dipyridamole and aspirin inhibit platelet aggregation and that their effects are additive. Differences in the mechanisms of action of dipyridamole and aspirin probably account for these additive effects. Dipyridamole alone significantly inhibited thrombus formation compared with aspirin alone or placebo ($p<0.01$) while the combination of aspirin and dipyridamole significantly inhibited the formation of large thrombi compared with aspirin alone or placebo ($p<0.05$). Results also confirmed that complete inhibition of platelet cyclo-oxygenase could be achieved with low dose (50 mg/day) aspirin.

The second European Stroke Prevention Study (ESPS-2)[14] trial was designed to confirm the efficacy of dipyridamole and aspirin alone and in combination in the prevention of secondary stroke in patients who had transient ischemia of the brain or ischemic stroke due to thrombosis.[14] With 6,602 patients, ESPS-2 was the largest clinical trial dedicated to the study of recurrent stroke. Its results were published in 1996. Patients who experienced a stroke or TIA within the three months before enrollment were studied in a multicenter, randomized, double-blind, placebo-controlled, prospective trial with 2-year follow-up at 3-month intervals. Stroke was the qualifying event in 76% of the patients while 24% had a transient ischemic attack. The study incorporated a 2 x 2 factorial design with random allocation of patients into one of four twice-a-day treatments: ASA 25 mg (1,649 patients), extended release dipyridamole 200 mg (1,654 patients), aspirin 25 mg plus ER-dipyridamole 200 mg (1,650 patients) or placebo (1,649 patients). The study protocol defined two primary endpoints: stroke (fatal and non-fatal) and death from all causes.

Pairwise treatment group comparisons of ESPS-2 data demonstrated that fatal and non-fatal stroke risk was reduced by 16.5% ($p=0.036$) with extended release dipyridamole 200 mg alone and 18.9% ($p=0.009$) with aspirin 25 mg alone compared to placebo. The combination of extended release dipyridamole 200 mg and aspirin 25 mg (Aggrenox®) reduced the risk of fatal and non-fatal stroke by 36.8% ($p<0.001$) compared with placebo, supporting the additive antiplatelet efficacy of the active ingredients. Aggrenox® therapy reduced the risk of fatal and non-fatal stroke by 22.1% ($p<0.008$) (95% CI 9-33) compared with aspirin and 24.4% ($p=0.002$) compared with extended dipyridamole 200mg alone. Clinically significant reductions in the risk of stroke and death were also demonstrated in patients treated with extended release dipyridamole (15.6%, $p=0.013$), aspirin alone (13.8%, $p=0.01$), and Aggrenox® (24.2%, $p<0.001$) versus placebo. None of the treatments reduced the risk of death alone. The absolute risk reduction with the combination compared with aspirin alone was 3% at two years (NNT = 33).

Headache, nausea and vomiting were reported in a similar number of patients treated with Aggrenox® and extended release dipyridamole 200 mg alone, while dyspepsia, hemorrhage, melena and anemia had a similar incidence in the Aggrenox® and aspirin 25 mg alone treatment groups.

The Esprit Study Group conducted a randomized controlled, open-label study in 79 centers in 15 countries and randomized a total of 2,739 patients with TIA or minor ischemic stroke (Rankin grade ≤3) presumed to be arterial in origin. Auditing of outcome events was blinded. Primary analysis was by intention to treat.[15] Patients were randomized to ASA (30 mg – 325 mg daily, mean 75 mg) or extended-release dipyridamole (200 mg twice daily) plus ASA (30 mg – 325 mg daily, mean 75 mg). Patients were seen every six months by their physician or a nurse. Patients were followed for a period of up to five years (mean 3.5 years). Patients on the combination treatment discontinued the trial medication more often than those on aspirin alone (n=470; 34% vs. n=184; 13%) mainly because of adverse events, most commonly headaches.

The primary outcome of the study was the composite endpoint of death from vascular causes, non-fatal stroke, nonfatal MI, or major bleeding complication, whichever occurred first. Secondary endpoints included death from all causes. Primary outcome events arose in 173 (13%) patients on aspirin and extended release dipyridamole and in 216 (16%) on aspirin alone (hazard ratio 0·80, 95% CI 0·66–0·98; absolute risk reduction 1·0% per year, 95% CI 0·1–1·8). The absolute risk reduction corresponds with a number of patients to treat with the combination of aspirin and extended release dipyridamole to prevent death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction or major bleeding complications of 104 (95% CI 55-1006) per year. The relative risk reduction with the combination of aspirin and extended dipyridamole was 20%.

The Esprit Study Group performed, as part of their report, a new meta-analysis that included the results from ESPRIT, ESPS-2 and a meta-analysis of four earlier studies[12] comparing aspirin alone vs. the combination of aspirin and dipyridamole. The meta-analysis included 3,888 patients on the combination therapy, 3,907 patients on aspirin alone, and total number of outcome events was 1,158. The overall risk ratio for the composite outcome of vascular death, stroke, or myocardial infarction was 0·82 (95% CI 0·74–0·91).

Comments

Stroke is the leading cause of adult disability and dependency in western society. Aggressively controlling stroke risk factors, such as hypertension, diabetes and smoking, should provide significant benefit in reducing stroke risk; however, it is difficult to realize the full potential of these approaches in clinical practice. A number of pharmacological agents are available to reduce the risk of stroke in conjunction with the mentioned risk factor reductions, one of these is the antiplatelet agents, specifically aspirin and dipyridamole.

ESPS-2 showed that dual therapy reduced the risk of stroke more than aspirin alone, but the results were much debated. ESPRIT showed and confirmed that the combination therapy of extended release dipyridamole and aspirin is more effective than aspirin alone for the primary endpoint of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major

bleeding complication. The results of these two large independent trials, with slightly different features is a major strength, as is the new meta-analysis (included in the ESPRIT report) showing a significant treatment effect. In addition, a comprehensive analysis comparing aspirin, clopidogrel, and the aspirin/dipyridamole combination (using ESPS-2 data) showed the aspirin/dipyridamole combination to be the most cost-effective alternative from both in a 2-year and lifetime treatment perspective.[16]

The American Heart Association, American Stroke Association Council on Stroke and the American Academy of Neurology recommend antiplatelet therapy for prevention of noncardioembolic ischemic stroke in patients who have experienced a transient ischemic attack (TIA) or artherothrombotic ischemic stroke. The recommendations include: 1) antiplatelet treatment for risk reduction of a recurrent stroke in patients with a noncardioembolic stroke. Aspirin alone, or in combination with extended-release dipyridamole and clopidogrel are acceptable agents for initial therapy and are considered safe; 2) The combination of aspirin and extended-release dipyridamole is suggested instead of aspirin alone. Clopidogrel may be considered instead of aspirin alone; 3) Clopidogrel is an acceptable choice in patients with documented aspirin sensitivity; 4) The combination of aspirin and clopidogrel is not routinely recommended due to the increased risk of hemorrhage; 5) No evidence is available that an increased dose of aspirin is of additional benefit in patients who suffer an ischemic stroke while taking aspirin.[17]

Search terms

Stroke, aspirin, Aggrenox,® dipyridamole, transient ischemia

Inclusions and exclusions

We limited our review to randomized controlled trials and meta-analyses.

Reviewed articles

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