Emboli Rate During and Early after Carotid Endarterectomy after a Single Preoperative Dose of 120 mg Acetylsalicylic Acid—A Prospective Double-Blind Placebo Controlled Randomised Trial


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Purpose. To investigate whether a single pre-operative dose of 120 mg acetylsalicylic acid (ASA) decreased either (1) emboli rate, as detected by transcranial Doppler (TCD), during and early after carotid endarterectomy (CEA) and (2) clinical intra- and post-operative signs suggestive of embolism or increased bleeding tendency.

Design. Prospective, double-blind placebo controlled trial.

Patients and methods. One-hundred consecutive patients were randomised to receive either 120 mg ASA (n=48) or placebo (n=49) by suppository on the night before CEA; three patients were excluded. Emboli were counted and expressed as emboli rate (ER). The incidence of bleeding complications was assessed. Surgeons were asked to indicate which patients had received ASA or placebo.

Results. There were no significant differences between the ASA and placebo groups in ER in the intraoperative and postoperative periods. ER higher than 0.9 min⁻¹ was associated with a significantly increased risk of complications (26 vs. 0%, P<0.01). No extra bleeding complications were observed in the ASA group. Surgeon assessment of whether or not ASA had been administered had a sensitivity of 42% and a specificity of 70%.

Conclusion. A single pre-operative dose of ASA (120 mg) did not reduce significantly the emboli rate during and after CEA and surgeons could not correctly identify whether or not ASA had been administered.

Keywords: Emboli; Carotid endarterectomy; Acetylsalicylic acid; Transcranial Doppler sonography; Randomised controlled trial.

Introduction

Platelet aggregation inhibitors are widely used for secondary stroke prevention and to reduce the risk of re-infarction after a previous myocardial infarct.¹ In carotid surgery, a single dose of acetylsalicylic acid (ASA) administered the evening before surgery has been reported to reduce neurological events.² The risk of mortality and stroke after carotid endarterectomy (CEA) is 6.3–8.1%,³ and thromboembolism is reported to be the most important pathogenic factor in stroke associated with CEA.⁴⁻⁷ Because ASA may reduce the risk of thromboembolic events, we investigated whether a single pre-operative dose of 120 mg ASA could reduce the number of embolic signals detected by transcranial Doppler (TCD) after carotid surgery and thus reduce the incidence of cerebrovascular complications. Because bleeding may be a complication of ASA, we also monitored the effect of ASA on bleeding events and asked surgeons whether they could identify, during surgery, which patients had been treated with ASA.

Patients and Methods

During a 4-year period, 100 consecutive patients who were scheduled for carotid surgery were randomised. Ninety-four patients had a ≥80% stenosis and 6 had a 60–80% stenosis of the ipsilateral carotid artery, as assessed by duplex scanning. A contralateral occlusion

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was present in 9 patients. Three randomised patients were excluded (one a TCD monitoring failure because of absence of acoustic window, two with allergy to ASA). Forty-eight patients were assigned to the ASA group and 49 to the placebo group. Ipsilateral symptomatic carotid artery disease was present in 82 patients (amostrus fugax, n=11, transient ischeamic attack, n=29, minor stroke Rankin, n=32, major stroke (Rankin 3–4), n=10). Fifteen patients underwent surgery for an asymptomatic carotid stenosis, 4 of whom had had symptoms in the territory of the contralateral carotid artery.

All patients were treated with acenocoumarol, and the use of aspirin was discontinued, at least 9 days before surgery (median ASA group, 21 days, range 9–66; median placebo group, 30, range 10–92, P=0.09, Mann–Whitney). Randomisation was provided by the hospital pharmacist. The pharmacist had manufactured sequentially numbered suppositories (Witepsol H15, Bufa bv, Uitgeest, The Netherlands), which contained either 120 mg ASA or placebo according to a pre-constructed random treatment allocation list. Once a patient had consented to the trial, they received a (consecutive) number, this number was conveyed to the pharmacist. The matching suppository was sent to the ward and was administered to the patient the night before operation. Both the patient and the medical personnel were blinded as to which treatment the patient had received. The randomisation key was disclosed after completion of the trial.

All procedures were performed under general anaesthesia. All patients received systemic heparin (5000 IU), without reversal by protamine sulphate. Standard carotid endarterectomy was performed. A venous patch was always used for closure of the arteriotomy.

TCD (EME 2-64 B, Eden Medizinische Technik, Ueberlingen, Germany) monitoring of the ipsilateral middle cerebral artery was performed with a 2 MHz pulsed wave transducer attached to the ipsilateral temple during the operation and was kept in situ in the recovery room. A shunt was used during the operation if after cross-clamping the ipsilateral middle cerebral artery (MCA) mean blood flow velocity decreased to 30% or less of the preclamping mean blood flow velocity in the MCA.

We investigated the occurrence of emboli in three periods: the dissection period, from skin incision until carotid clamping; the wound closure period, from 3 min after restoration of the internal carotid artery flow until the end of the operation; and the post-operative period. Patients were monitored for 20 min in the recovery room. All TCD signals were stored on tape for off-line analysis. Embolic signals were identified according to the criteria of the Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. The number of emboli counted in each period is expressed as the emboli rate (ER) in emboli/minute (e/min). All patients underwent a neurological evaluation, including classification according to the modified Rankin scale, by a board-certified neurologist (DML) before the operation and in the postoperative period, as soon as the patient regained consciousness. This was repeated if the patient had not fully recovered from general anaesthesia. The last two neurological evaluations were 2 days and 3 months after surgery. Study endpoints were TIA (defined as symptoms lasting less than 24 h), minor stroke (defined as symptoms lasting longer than 24 h and Rankin score ≤ 2), major stroke (defined as severe permanent impairment affecting daily functioning and Rankin ≥ 3), and death.

Statistical analysis used Mann–Whitney, Pearson Chi-square and Fischer exact tests, with SPSS® for Windows (release 11.0, SPSS Inc., Chicago, IL) (2003), and Instat 2.05 (Graphpad Software Inc., San Diego, CA). Differences were considered significant at P < 0.05.

All patients gave their informed consent before surgery. The ethics committee of our institution approved this study.

**Results**

The flow of patients through the trial is shown in Fig. 1. There were no significant differences in the distribution of the stroke classification between the ASA and placebo groups (Table 1). The groups were well matched for age, sex, smoking habit, incidence of hypertension, ischaemic heart disease, diabetes, hypercholesterolaemia, and dysbasia (Table 2). There was a non-significant trend for the placebo group to have a higher International Normalized Ratio (INR) (1.5 ASA group vs. 1.9 placebo group, P=0.069, Mann–Whitney; Table 2).

Emboli were detected in 56% of the patients in the dissection period (48% in the ASA group; 62% in the placebo group). These emboli were detected during the wound closure period in 47% patients (53% in the ASA group; 40% in the placebo group), and during the post-operative period in 76% of the patients in the postoperative period (78% in the ASA group; 75% in the placebo group). The emboli rates in all three periods were not significantly different between the ASA and the placebo groups (Fig. 2, Table 3). In each group, the emboli rate (ER) in the three periods differed significantly (postoperative > dissection >
wound closure period) (Friedman test for matched groups, \(P < 0.0001\)). Only in the placebo group during the postoperative period was there a significant difference (Mann–Whitney, \(P = 0.023\)) between the ER of men and women. The difference in ER during the postoperative period between ASA and placebo in women was not statistically significant (\(P = 0.163, \text{ Table 3}\)).

There was an increase in ER during three periods (dissection, wound closure and postoperative) for shunt versus no shunt in the placebo group, most significant in the postoperative period (\(P = 0.001\)). There were no significant differences between the ER of the subgroups in the dissection period of the placebo group or in the three periods of the ASA group.

Cerebrovascular complications occurred in 6 patients (6.2%), three in the ASA group (one TIA, one minor stroke, one major stroke) and three in the placebo group (one TIA, two minor strokes) (\text{Table 4}). All these complications were recognized in the recovery room. Two complications became apparent immediately after the patients regained consciousness: both were men and had their highest ER during the dissection period. The other four patients developed complications within 2 h after surgery, and had their highest ER during the postoperative monitoring period. Median interval between restoration of the internal carotid artery circulation and the start of monitoring in the postoperative period was 51 min (range 31–240 min, third quartile 62 min) and was not significantly different between the two groups (Mann–Whitney test, \(P = 0.97\)).

\textbf{Fig. 1.} CONSORT diagram showing flow of patients through the trial.

\textbf{Table 1.} Distributions of the pre-operative stroke classification and contralateral carotid artery occlusion between the ASA and placebo groups

<table>
<thead>
<tr>
<th></th>
<th>ASA ((n = 48))</th>
<th>Placebo ((n = 49))</th>
<th>(P^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>10</td>
<td>5</td>
<td>0.175</td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>6</td>
<td>5</td>
<td>0.759</td>
</tr>
<tr>
<td>TIA</td>
<td>16</td>
<td>13</td>
<td>0.512</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>12</td>
<td>20</td>
<td>0.131</td>
</tr>
<tr>
<td>(Rankin 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major stroke</td>
<td>4</td>
<td>6</td>
<td>0.740</td>
</tr>
<tr>
<td>(Rankin 3–4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>4</td>
<td>5</td>
<td>0.743</td>
</tr>
<tr>
<td>carotid artery occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Fisher exact test.

\textbf{Table 2.} Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>ASA</th>
<th>Placebo</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.1 (49–83)</td>
<td>68.0 (45–80)</td>
<td>0.91(^a)</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>33/15</td>
<td>31/18</td>
<td>0.52(^b)</td>
</tr>
<tr>
<td>Smoking</td>
<td>52%</td>
<td>57%</td>
<td>0.61(^b)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60%</td>
<td>69%</td>
<td>0.72(^b)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>54%</td>
<td>36%</td>
<td>0.09(^b)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15%</td>
<td>18%</td>
<td>0.66(^b)</td>
</tr>
<tr>
<td>Dysbasia</td>
<td>15%</td>
<td>20%</td>
<td>0.45(^b)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>27%</td>
<td>35%</td>
<td>0.42(^b)</td>
</tr>
<tr>
<td>Shunt</td>
<td>7 (15%)</td>
<td>10 (20%)</td>
<td>0.59(^c)</td>
</tr>
<tr>
<td>INR (median; mean; SD; range)</td>
<td>1.5; 1.7; 0.51; 1.9; 1.9; 0.64; 1.1–3.5</td>
<td>1.1–3.5</td>
<td>0.069(^a)</td>
</tr>
</tbody>
</table>

\(a\) Mann–Whitney test.
\(b\) Pearson Chi-square test.
\(c\) Fisher exact test.

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There was no significant difference in the number of complications, including the number of venous bleeds after surgery, between the two groups (Table 4). The length of the wound closure period was not different between the two groups (Mann-Whitney test, $P = 0.877$) and even when only the upper 10th percentile ($O_{30}$ min) was considered there was no difference between the groups (Fisher exact test, $P = 0.435$, odds ratio 2.68, 95% CI, 0.493–14.564). Venous bleeding at the site of surgery occurred in four patients (two each in the ASA and placebo groups). The INRs of these patients were 1.3, 2.9, 3.5, and 3.8, respectively.

Data from both groups were combined to evaluate the risk of cerebrovascular complications in relation to the ER. Patients were then stratified into two groups according to the number of ER: group I ($I < 0.9$ e/min ($n = 74$; ASA: $n = 38$, placebo: $n = 36$), and group II, $I \geq 0.9$ e/min ($n = 23$; ASA: $n = 10$, placebo: $n = 13$). There was no significant association between either the ASA or placebo groups and stratification into group I or II (Fisher exact test, $P = 0.634$). More cerebrovascular complications occurred in group II: 26 vs. 0% ($P < 0.0001$, odds ratio 55.3, 95% CI 3–1030, Fisher exact test).

Surgeons were not able to identify those patients treated with ASA (specificity for ASA use 70%; sensitivity 42%, positive predictive value of 58%; negative predictive value of 55%).

**Discussion**

A single pre-operative dose of 120 mg ASA did not significantly reduce the ER or the number of patients with emboli during and after carotid endarterectomy. The patient characteristics of the two groups were comparable. As shown in an earlier study, a high number of embolic signals correlated with a higher incidence of cerebrovascular complications.6,10 The number of cerebrovascular complications (6.2%) may seem rather high. One possible explanation for this was that a neurologist made both the pre- and postoperative neurological assessments. This is known to result in a higher complication rate than assessment by surgical staff.11 In the present study, there were three minor strokes, (Rankin $\leq 2$), two transient ischemic attacks (TIA) and one major stroke (Rankin $> 2$). One TIA (in the placebo group) would not have been noticed if the neurological assessment had been postponed until the end of the day of surgery, in which case the complication rate would have reduced to 5.1% (major stroke 1%).

In two patients the neurological deficit was present at awakening. Both had their highest ER in the dissection period. In the other four patients the complications developed within 2 h after surgery,
and they had their highest ER in the postoperative monitoring period. This supports the correlation of high ER and cerebrovascular complications. In both groups, the ER was higher and more patients had emboli during the postoperative period than during the other periods.

The significant difference \( (P = 0.023) \) in ER between women and men in the placebo group during the postoperative period was not observed in the ASA group. Therefore, although the difference in ER during the postoperative period between women in the two groups was not significant, one could infer that ASA had a more pronounced anti-embolic effect in women than in men. A significantly higher ER was found only in the subgroup with a shunt in the placebo group compared with the no shunt placebo group. However, the numbers are small; therefore the clinical significance is unclear.

Human and animal studies have shown that platelet deposition is increased at the site of CEA, reaching a maximum 20 min to 1 h after exposure to Indium-111 labelled platelets.\(^{12,13}\) Embolism from the operative site during CEA is considered the principal cause of cerebrovascular complications.\(^5\) Levi et al. found emboli to be most prevalent in the early (within 1 h) postoperative period, with a strong association between a high emboli count in this period and the development of ischaemic stroke.\(^{10}\) In our study, the median interval (51 min) between the restoration of internal carotid artery flow and the start of postoperative monitoring fell into this range, suggesting that the timing of the start of monitoring was appropriate for detection of emboli.

ASA inhibits platelet aggregation and many surgeons believe that its use causes noticeable intraoperative oozing and increases operative bleeding complications. Indeed, this commonly held opinion has led many clinics to withdraw ASA before surgery. However, ASA prevents vascular events in patients who have had a TIA or minor stroke. Because low and medium doses are equally effective,\(^{14}\) but side-effects are dose related,\(^{15}\) we used a moderate dose of 120 mg ASA, aiming at an antithrombotic effect without promoting gastrointestinal complications.\(^{14,16}\) This dose may have been too low to establish a clear result. In the study by Lindblad et al. (1993), 75 mg aspirin was given the evening before carotid surgery.\(^2\) This reduced the incidence of postoperative stroke without complete recovery within a week.\(^2\) Although in the present study a higher dose of ASA was given, a clear effect on the ER and clinical complications was not seen. However, the patients in the study of Lindblad had also received dextran 40 during, and 3 days after the operation, which is known to reduce emboli in the postoperative period.\(^{17}\)

We did not investigate the effects of the single dose of ASA on platelet function using aggregation tests. Previous studies have shown the effect of ASA on platelet aggregation to be dose dependent, with non-response occurring in about 10% of cases.\(^{18-20}\) Differences between men and women in this respect have not been reported. There was a large variation in the number of postoperative embolic signals registered, ranging from 0 to 3.8 in the ASA group to 0–7.5 in the placebo group. The number of patients may have been too small to detect a significant decrease in embolic signals. Moreover, the data were not normally distributed, which meant that reliable power calculations were not possible.

A recently published study in which 100 CEA patients on routine aspirin therapy (150 mg) were randomised to 75 mg clopidogrel or placebo the night before surgery, reported a significant reduction of postoperative emboli in the clopidogrel group.\(^{21}\) Because clopidogrel has a different way of platelet aggregation inhibition than ASA,\(^{22}\) this study reported on a combined effect on emboli versus the effect of ASA alone. It remains to be seen whether clopidogrel alone will have the same anti-embolic effect as in combination with ASA.

We had anticipated an increased bleeding tendency as a side effect of ASA. This was not seen in our study. The length of the wound closure period, which can be considered an indirect marker for hemostasis,\(^{21}\) was not different between the two groups, even if we considered only the upper 10th percentile. In the study of Payne et al.\(^{21}\) Clopidogrel did prolong the wound closure period. This may reflect the intrinsic differences between ASA and clopidogrel, as reported by Hayes et al.\(^{23}\) Furthermore, 3 of the 4 patients with (venous) bleeding had a high INR. Acenocoumarol is an anticoagulant with relatively short half life (11 h), so fluctuations in the INR are more prone to happen than with anticoagulants with long half life, such as phenprocoumon.

The surgeons, who were unaware of which drug had been administered, could not identify which patients had been given ASA. No differences in bleeding complications were seen between the two groups. This is in accordance with the findings of West et al.\(^{24}\) Therefore we conclude that ASA can be safely administered preoperatively, without the risk of additional bleeding complications, as reported earlier.\(^2\) Moreover, our findings confirm that a postoperative ER higher than 0.9 min\(^{-1}\) should be considered a warning signal for cerebrovascular complications.\(^6\)
Conclusion
A single preoperative dose of 120 mg ASA did not provide a significant decrease in the ER or the number of patients with emboli during and after carotid endarterectomy. ASA did not affect the number of cerebrovascular or bleeding complications. Surgeons could not correctly identify patients who had received ASA. Further prospective studies, preferably with higher doses of ASA and with more patients are needed to elucidate the role of ASA in reducing the occurrence of emboli during and shortly after carotid endarterectomy.

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S.H.A.J.T. and D.M.L. have equally contributed to the design, analysis, data interpretation of this study, and writing the article. We thank M.A.J. van Duijn, PhD, for her statistical expertise and G.H. Wieneke, PhD, for his critical remarks. There is no conflict of interest.

References