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Influence of Antiplatelet Therapy on Cerebral Micro-Emboli after Carotid Endarterectomy using Postoperative Transcranial Doppler Monitoring

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Aim. *To study the effect of different antiplatelet regimens (APT) on the rate of postoperative TCD registered micro-embolic signals (MES) following carotid endarterectomy (CEA).*
Design. *Prospective, randomised, double-blinded, pilot study.*
Methods. *The study group of 102 CEA patients (76 men, mean age 66.8 years) was randomised to routine Asasantin (Dipyridamole 200 mg/Aspirin 25 mg) twice daily (group I; n = 39), Asasantin plus 75 mg Clopidogrel once daily (group II; n = 33), or Asasantin plus Rheomacrodex (Dextran 40) 100 g/L iv; 500 ml (group III; n = 30). TCD monitoring of the ipsilateral middle cerebral artery for the occurrence of MES was performed intra-operatively and during the second post-operative hour following CEA. Primary endpoints were the rate of postoperative emboli and the occurrence of cerebrovascular complications. Secondary endpoint was any adverse bleeding.*
Results. *There were no deaths or major strokes. We observed 2 intraoperative TIA's (group II and III) and 1 postoperative minor stroke (group I). In comparison with placebo, Clopidogrel or Rheomacrodex in addition to Asasantin produced no significant reduction in the number of postoperative MES. There was no significant difference between the number of post-operative MES and different antiplatelet regimens. The incidence of bleeding complications was not significantly different between the 3 APT groups.*
Conclusion. *In the present study, we could not show a significant influence of different antiplatelet regimens on TCD detected postoperative embolization following CEA.*

Keywords: CEA; Cerebral (micro)embolism; TCD; Antiplatelet therapy.

Introduction

The in-hospital mortality of carotid endarterectomy (CEA) is 0–2% and the occurrence of ipsilateral minor or major stroke is reported 2–5%.[1,2] Intraoperative stroke, apparent on recovery from anaesthesia, has been virtually abolished by introducing a policy of intraoperative transcranial Doppler (TCD) monitoring.[3,4] However, this policy showed little effect on the prevention of early (<6 hours) postoperative stroke due to thrombosis of the endarterectomised zone, which continued to complicate 2.5% of CEA's.[4–6] It is well known that platelets begin to adhere to the endarterectomy zone within minutes of flow restoration[7] but it is still unknown why this becomes excessive in some patients, leading to new postoperative cerebral deficits.

Several centres have shown that patients destined to suffer an early postoperative stroke have a 1- to 2- hour period of increasing embolization before cerebral deficit becomes apparent.[4,8–12] The prevailing view is that, as the platelet thrombus accumulates, small particles are shed into the carotid circulation as micro-emboli. These micro-embolic signals (MES) can be detected by postoperative TCD monitoring of the ipsilateral middle cerebral artery (MCA). Overall, about 50% of patients with CEA will have one or more emboli detected in the postoperative period, but only about 5% will progress to high grade sustained embolization.[4,5,13] Of these, 30% to 60% will progress to

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thrombotic stroke.[8,10] Except for a meticulous surgical technique during endarterectomy the choice of antiplatelet therapy might be a powerful instrument to prevent these postoperative MES.[14–16] It is important to note that commonly used pretreatment regimens with antiplatelet agents, in most cases aspirin, do not abolish thrombo-embolization or embolic stroke in the early postoperative period.[17] Aspirin inhibits only 1 of the several pathways of platelet activation, and platelet activation through an aspirin insensitive pathway may be more important in the occurrence of thrombo-embolization.[18] Dual therapy with aspirin and Clopidogrel therefore may prove more effective in reducing thrombo-embolic complications.[15,19]

Postoperative monitoring for MES is believed to be a proper quantative diagnostic tool that helps in deciding which patients could benefit from additional treatment. Selective TCD guided administration of Dextran has already been shown successful in reducing embolization and progression to stroke.[13,20] However, this policy is expensive and labour intensive and is unlikely to be adopted into routine clinical practice. It would be preferable to target appropriate antiplatelet pharmacotherapy from the outset.

In the present study we compared three different perioperative antiplatelet regimens and their influence on clinical outcome and postoperative TCD detected embolization in patients undergoing CEA.

Methods

Study design

The present randomized and double blinded pilot study with 30 patients planned in each subgroup was performed between 2004 and 2006 in the St. Antonius Hospital, Nieuwegein, with Ethics Committee approval. All patients gave Informed Consent. Inclusion criteria were 1) internal carotid artery (ICA) stenosis of $\geq$70% on preoperative duplex ultrasound; 2) no preceding ipsilateral carotid intervention; 3) accessible transcranial window for TCD registration. Patients already on warfarin, dipyramidole, or Clopidogrel were excluded. Patients were defined asymptomatic in absence of cerebrovascular symptoms within 120 days prior to surgery.

Carotid endarterectomy

Patients underwent standard CEA under general anaesthesia. Surgery was executed by an experienced vascular surgeon or a vascular trainee under supervision. A shunt or patch was selectively used.

TCD monitoring

Continuous TCD monitoring of the ipsilateral MCA for the occurrence of MES was performed during operation and during the second hour postoperatively. Four successive stages of operation were: 1) dissection (skin preparation to carotid clamping; 2) shunt manipulation (shunt introduction to shunt removal); 3) clamp release; and 4) wound closure.[21] All TCD data were stored on CD Rom for offline analysis. Technical details of intraoperative[22] and postoperative[23] monitoring have been described previously. Postoperative embolization was quantified using standardized consensus criteria.[23,24] All TCD measurements were performed by a single highly experienced technician (MvdM). High grade postoperative embolization was defined as >20 MES per hour.

Trial medication

Three different antiplatelet regimens (APT) were compared in patients undergoing CEA.

Group I Asasantin 25/200 mg (dipyridamol 200 mg/aspirin 25 mg) 2dd orally. Started at least 3 days preoperative and continued for 3 months postoperative.

Group II As group I but with addition of Clopidogrel 1dd 75 mg; started at least 3 days preoperative and also continued for 3 months postoperative.

Group III As group I with addition of Rheomacrodex (Dextran 40) solution 100 g/L iv; 500 ml during the first 6 postoperative hours starting during skin closure.

In all patients, heparin (5.000 IU) was administered before cross-clamping; protamine reversal was not used. Platelet aggregation tests were not performed. Trial medication was blinded for both the surgeon and TCD technician. Analysis of CD-rom stored TCD data was performed on distance by T.H. and R.A. who were also blinded for trial medication. Heparin dose-response relationship was calculated with the activated clotting time (ACT).

Study outcome

Primary outcomes were the number of postoperative MES and the occurrence of adverse clinical

neurological symptoms. Secondary outcome was the occurrence of any bleeding complication. Before and after surgery, patients were evaluated by an independent neurologist. Any new neurological deficit lasting for >24 hours in the first 30 days was classified as a stroke. The severity of stroke was graded according to the modified Rankin scale.[23] Intraoperative stroke was defined as a persistent neurological deficit that became obvious at the conclusion of the operation, or at awakening from general anaesthesia. Postoperative stroke was defined as a persistent neurological deficit that developed within 48 hours after a symptom free interval.

Group size

Power calculations could not be performed. The present study was therefore a pilot with 30 patients planned in each subgroup.

Protocol intervention

Patients were operated on with intention to treat. Protocol intervention was defined as any reoperation or change in trial medication. Change of antiplatelet medication after the initial monitoring hour (second postoperative hour) was not considered to interfere with protocol. Any patient suffering high grade postoperative embolization was started on Rheomacrodex according to hospital protocol.[20] In these cases, TCD registration was prolonged for 1 extra hour to monitor the effect of drug intervention.

Statistical analysis

Data were analyzed using SPSS version 11.5 (SPSS Inc. Chicago, Illinois). Groups were compared with Students-T and chi-square test, or Mann-Whitney/Kruskal-Wallis (K-W) tests for non-normally distributed variables. Correlations were tested using Pearson correlation coefficient, or Spearman/Kendall (S/K) for non-normally distributed data. Probability values $p > 0.05$ were considered non-significant. To obtain a normal distribution, and for display purposes, a square root (sqrt) transformation of the number of emboli was employed.

Results

Demographics

We included 102 patients (76 male mean age 67.5; sd = 7.9, and 26 women mean age 64.7; sd = 10.1 ($p = 0.21$)). In 53 patients (52%) the operation was performed on the right side. Seventy-nine patients (77.5%) were symptomatic (amaurosis fugax (AF) 9 (8.8%), transient ischaemic attack (TIA) 34 (33.3%), minor stroke 32 (31.4%), and vertebro basilar insufficiency (VBI) 4 (3.9%). A shunt was used in 27 (36.3%) and a patch in 80 procedures (venous 47 (46%), Dacron 33 (32%)). All groups were well matched, with no significant difference in age, sex, weight, atherosclerotic risk factors, or presenting symptom.

Trial medication

Allocation of trial medication: Group I (Asasantin): 39 (38.2%), Group II (Asa/Plavix) 33 (32.4%), Group III (Asa/Rheo) 30 (29.4%). The allocation of men and women in medication groups was statistically not different (Chi^2) (Table 1). There was also no statistical significant difference in medication group allocation between the various clinical groups (Chi^2) (Table 2).

TCD registered micro-embolization

There was no correlation between the number of intraoperative MES during the 4 different operative phases (S/K correlation). The number of intraoperative emboli showed no difference between men and women (Mann-Whitney U test). There was no correlation between the intra- and postoperative MES (S/K coefficient: NS) (Fig. 1). Interestingly, only the number of emboli during woundclosure showed a correlation with postoperative MES (S/K r = 0.26/0.20, $p = 0.008/0.011$) (Fig. 2).

The total number of postoperative emboli in the second postoperative hour showed a wide range of variation (Table 3); and therefore a skewed distribution pattern (Fig. 3). Even after Sqrt (x) transformation the population mean was influenced by high individual outliers (Fig. 4). However, different approaches of analysis all showed a gradual decrease of MES in the second postoperative hour (Fig. 5). This effect was seen throughout the spectrum from low- to high-grade embolization. Women showed significantly more postoperative emboli than men. There was no significant correlation between the side of surgery

Table 1. Allocation of men and women in 3 medication groups

		Inclusion group		
		Asasantin	Asa/Plavix	Asa/Rheo
Sex	Male	27	24	25
	Female	12	9	5

Table 2. Allocation of preoperative symptoms to treatment groups

		Inclusion group			Total
		Asasantin	Asa/ Plavix	Asa/ Rheo	
Symptomatology	Asympt	11	7	5	23
	TIA	9	14	11	34
	Minor Stroke	14	6	12	32
	AF	5	3	1	9
	Other	0	3	1	4
Total		39	33	30	102

($p = 0.75$), the use of patch nor type of patch ($p = 0.89$) and/or shunt and the occurrence of postoperative embolization.

There was no significant difference between the number of postoperative emboli and different antiplatelet regimens (Kruskal-Wallis test) (Figs. 6, 7). Sub-analyses on sex, patients with ≥ 1 emboli, or only patients >20 emboli/hour also did not reach statistical significance.

Besides group III patients, another 8 patients (5M, 3F) required Rheomacrodex to control continued embolization (Group I (4) and Group II (4)). In all 8 patients Rheomacrodex successfully decreased the embolic rate, and no other adverse cerebral events occurred in these 8 patients. None of these patients was indicated for re-exploration.

Clinical outcome

No major strokes or deaths occurred. Adverse cerebral events occurred in 3 patients (3%). Two patients showed an intraoperative ipsilateral TIA (1 group II, 1 group III). In 1 patient an ipsilateral postoperative minor stroke was observed (group I). With this complication rate our study was underpowered to analyse a relationship between adverse cerebral events and APT. The patient with minor stroke had no preceding high-rate embolization. Five patients received re-exploration, all because of bleeding complication (NS) (Table 4).

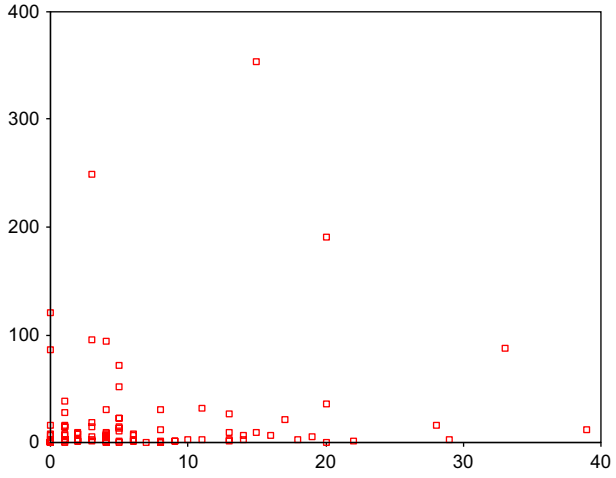

Fig. 1. Correlation of intra- and post-operative embolization. Non-parametric correlation: Spearman/Kendall correlation coefficients: non significant. (Total number of emboli during second postoperative hour versus Total number of emboli during carotid endarterectomy).

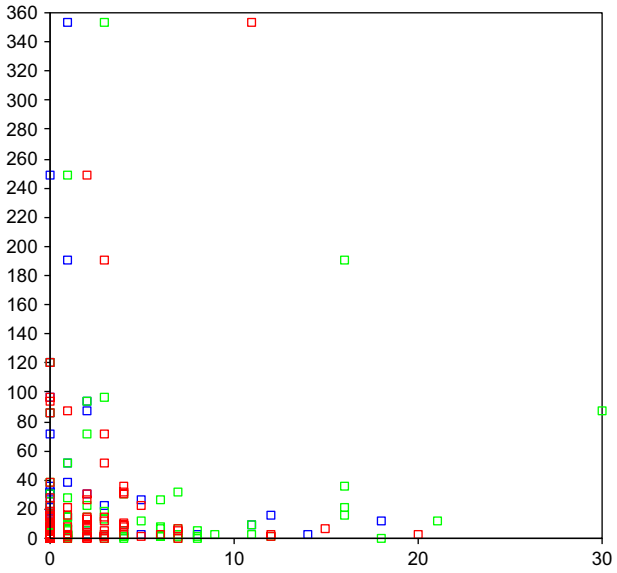

Fig. 2. Correlation of intraoperative parameters with postoperative embolization.(Blue = closure of the arteriotomy, green = restoration of circulation, red = dissection). (Postoperative number of emboli vs perioperative emboli). Only the number of emboli during woundclosure showed some correlation with the postoperative number of emboli (S/K r 0.26/0.20, $p = 0.008/0.011$).

Discussion

In the present pilot study, we could not show a significant influence of different antiplatelet regimens on

Table 3. Total number of TCD detected emboli in complete study group during the second postoperative hour (N = 102)

N	Valid	102
	Missing	0
Mean		20.29
Median		5.00
Std. Deviation		49.693
Range		354
Minimum		0
Maximum		354
Percentiles	25	1.00
	50	5.00
	75	15.00
	80	19.20
	90	47.40

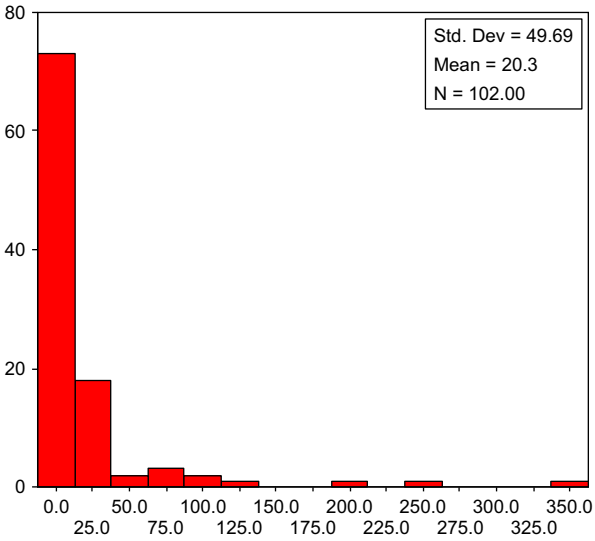

Fig. 3. Total number of TCD detected emboli during the second postoperative hour. (Frequency vs total number of emboli).

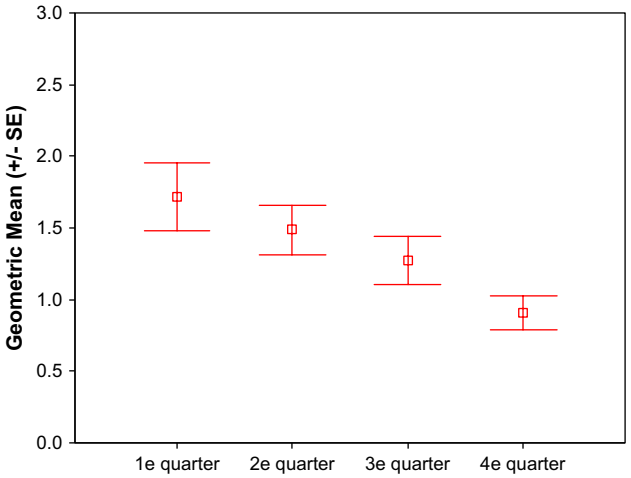

Fig. 5. Total number of TCD detected emboli durin the second postoperative hour. Data for complete study group after transformation, after splitting up for the separate quarters.

TCD detected postoperative embolization following CEA. In all 3 treatment sub-groups a gradual decrease of emboli in the second postoperative hour was shown. Women showed significantly more postoperative emboli than men, but there was no significant difference between sex and emboli in relation to APT. Two intraoperative TIA's and 1 postoperative minor stroke were noted. Eight patients required TCD directed Rheomacrodex to control continued embolization, which showed to be successful in lowering the embolic rate in all 8.

Postoperative stroke was previously assumed to follow technical error. However, in patients re-explored for postoperative cerebral deficit, a platelet-rich thrombus was invariably found adherent to an otherwise normal endarterectomy zone.[7,23,25] This suggested that it might be the patients' inherent platelet activity that determined those at risk of postoperative thrombotic stroke, and not technical error.[25] CEA involves the removal of atherosclerotic plaque with resulting exposure of a relatively large area of

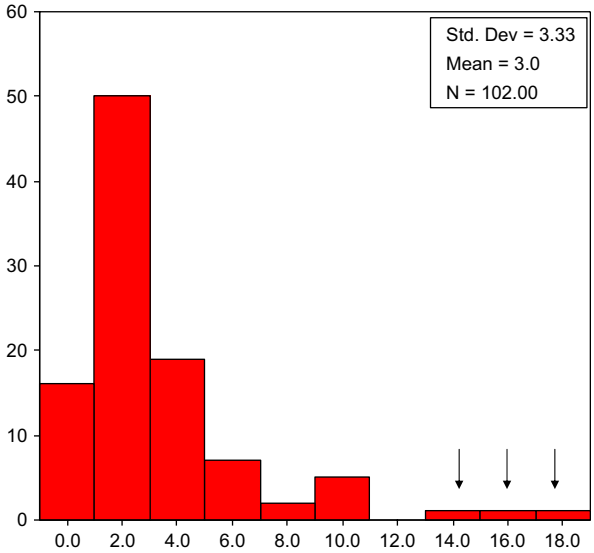

Fig. 4. Total number of TCD detected emboli during the second postoperative hour after transformation. (Frequency vs Sqrt total number of emboli). Outliers are marked with an arrow.

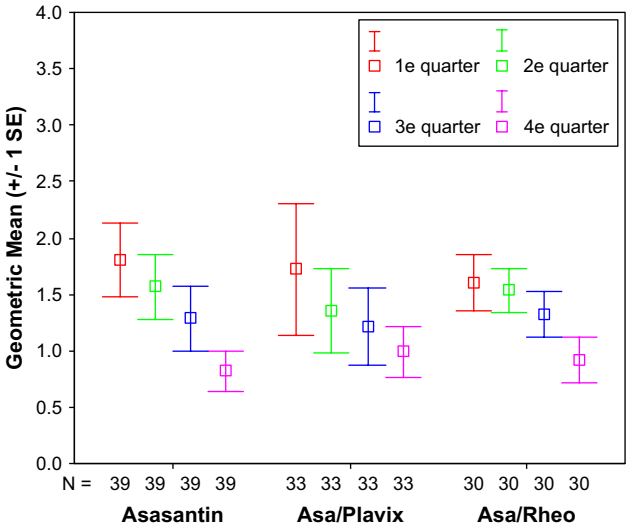

Fig. 6. Postoperative number of TCD detected emboli for complete study group after splitting up for different medication sub-groups. (Red = first quarter, green = second quarter, blue = third quarter, pink = fourth quarter).

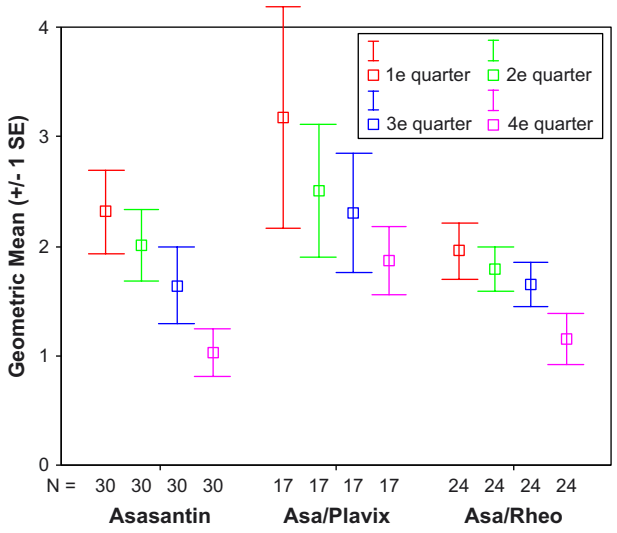

Fig. 7. Postoperative number of TCD detected emboli for patients with ≥1 emboli, after splitting up for different medication sub-groups. (Red = first quarter, green = second quarter, blue = third quarter, pink = fourth quarter).

underlying medial collagen and adventitia. This injury to the arterial wall leads to platelet adherence on the denuded vessel immediately after CEA in humans.[26] The thrombogenic endarterectomy zone can subsequently become the source of emboli following flow restoration.

Stroke due to post-operative carotid thrombosis (POCT) still complicates 2–3% of CEA's and has long been thought to be unpreventable. With the evidence of increasing postoperative embolisation preceding any neurological deficit[4,8–13] this view has changed. These TCD detected MES can serve as a marker of stroke risk and as a surrogate marker to evaluate and monitor antiplatelet agents.[8,10,11] Administration of Dextran has been shown to both reduce high-grade postoperative embolization and prevent thromboembolic stroke, providing further evidence of the important association between these two events.[4,13,20] Following the introduction of TCD-directed Dextran therapy, the rate of thrombotic stroke after CEA was shown to fall from 2.7 per cent to zero.[4,27] Although several authors have proposed a threshold of MES for increased risk of adverse cerebral events,[4,10,12,13,28] their outcome was highly variable and thus at present no consensus exists on which threshold to use.

Table 4. Bleeding complications in the three medication groups

	Group I	Group II	Group II	
Variable	Asasantin ($n = 39$)	Clopidogrel ($n = 33$)	Rheomacrodex ($n = 30$)	p
Transfusion	1	1	0	NS
Reexploration	1	2	2	NS

Several hours of postoperative TCD monitoring is impractical outside a research programme; however, the technique appears to work in smaller periods without loss of clinical yield.[23] In our previous work one hour monitoring appeared to be effective to select patients in whom the number of microemboli did not spontaneously decrease.[23] In the present study, patients thus underwent 1-hour of monitoring which had a sufficiently alarming function, since in 8 patients with sustained embolization (range 49–354/hour; mean 149/hour) Rheomacrodex was successful in lowering the embolic rate, and none of these 8 developed adverse cerebral events after leaving the recovery room. These 8 patients should be considered as failures within their own APT group (4 group I, 4 group II). Unfortunately, retrospectively, we found no relation between embolization during woundclosure (0 emboli (5), 1 emboli (2), 2 emboli (1)) and development of high-grade postoperative embolization. Identification of embolization during woundclosure therefore does not seem to be helpful in selecting patients who need pharmacological intervention.

Targeted modification of pre-operative APT will probably be a promising alternative way in the prevention of perioperative MES and subsequent devastating cerebral events. Ideally, a "one-size-fits-all" APT could be designed. It is important to note that commonly used pretreatment regimens with antiplatelet agents, in most cases aspirin, do not abolish thrombo-embolization in the early postoperative period.[17] Aspirin inhibits only 1 of the several pathways of platelet activation, and platelet activation through an aspirin insensitive pathway may be more important in the occurrence of thrombo-embolization. Furthermore, a significant proportion of patients taking aspirin do not show laboratory evidence of platelet inhibition[18] although resistance to other antiplatelet regimens also must be considered.

Dual therapy with aspirin may prove more effective in reducing thrombo-embolic complications.[15,19,29] Ex-vivo experiments have confirmed the synergistic antithrombotic effects of a combined therapy and showed the early benefit obtained with a loading dose of Clopidogrel.[15] Hayes et al. have also shown that in CEA patients, the preoperative response of platelets to adenosine diphosphate (ADP) was predictive of postoperative embolization, concluding that platelet ADP-receptor antagonism could prevent perioperative cerebral embolization.[16] More recent evidence showed a significant reduction in postoperative embolization by the administration of a single 75 mg dose of Clopidogrel the night prior to

surgery (in addition to regular aspirin).[19] Clopidogrel also showed significant reduction in expression of markers of platelet activation in response to ADP compared to aspirin or aspirin with dipyridamole.[30] Clopidogrel therefore seems more efficacious than other APTs at a molecular level but its clinical role remains controversial.[4] In our study, the number of postoperative MES was lower in the Clopidogrel group compared to group I and III but this difference was not statistically significant (Fig. 6). When comparing patients with $\geq$1 emboli, the number of emboli was even higher in the group of patients receiving Clopidogrel, but also this effect was not statistically significant (Fig. 7).

In vivo, combined therapy with Clopidogrel and aspirin significantly increased the bleeding time.[31] In our study, re-explorations were performed in 5 patients for bleeding complications which is in excess of expectations following CEA. APT groups were too small to find a relationship between bleeding complication and APT (Table 4). Therefore, future studies have to search for APT that balance between minimal embolization rate and minimum of bleeding complications. In particular we need to know: 1) are certain patients at increased risk of postoperative embolization and thrombosis, and if so how can we identify them?; 2) what is the best treatment for patients with sustained embolization?; 3) what is the optimal preoperative APT in lowering both postoperative MES and adverse cerebral deficit?

The correlation of microemboli during wound closure with ongoing postoperative embolization is pathophysiologically interesting and theoretically of help in identifying patients at risk for sustained embolization.[14] However, as described above, our 8 patients that were provided additional Rheomacrodex hardly showed embolization during woundclosure. Stork et al. identified 3 factors associated with postoperative MES: female sex, left-sided CEA, and absence of preoperative APT.[14] Two of these are non-modifiable risk factors, leaving only preoperative APT as a modifiable factor influencing outcome.

Our study has several potential limitations. First, >60 minutes monitoring might be needed to identify differences in embolic rate. Second, it is important to note that the analysis reported here was a pilot with small group size. The study may therefore have been underpowered. Third, plaque characteristics were not studied in the present population. Fourth, aggregation tests were not performed, but heparin effect was checked by ACT. Based on ACT measurements, no additional heparin was provided in this study population. Fifth, a surrogate (MES) served as a marker for clinical outcome (stroke). We believe that this surrogate marker reliably predicts clinical outcome following CEA.[4,27] However, it is harder to show that the desired outcome (reduced thromboembolic stroke incidence) is based on the drug effect on the surrogate. Although the dramatic reduction in embolic events in patients treated with Dextran or Rheomacrodex is encouraging, the fact that one of our patients without warning signals on TCD still experienced postoperative minor stroke is discouraging.

Despite, inhibiting postoperative embolization seems to represent a therapeutic strategy in reducing stroke after CEA. Nevertheless, the role and clinical efficacy of TCD detected microemboli as a surrogate measure for stroke after CEA remains to be better validated. First, further well-powered studies need to be undertaken to determine the optimum perioperative APT in reducing postoperative embolization. Future research has to focus on potentially more effective combinations of ASA with other antiplatelet drugs. Although TCD may still be used to identify patients at high risk in the early postoperative period, it seems likely that the optimal role for TCD will be to develop novel targeted modification of pre-operative APT, so that, ultimately, no postoperative monitoring is necessary at all.

Conclusion

In the present study no significant difference between the number of postoperative emboli and different antiplatelet regimens was found. In all study subgroups, linear regression of emboli in the second postoperative hour was observed. TCD directed Rheomacrodex infusion showed successful in lowering MES rate.

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