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INVITED COMMENTARY

Influence of Antiplatelet Therapy on Cerebral Micro-emboli After Carotid Endarterectomy Using Postoperative Transcranial Doppler Monitoring

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This well-written paper describes a randomised trial with negative outcomes. Essentially, no difference was shown in the rate of microembolisation as detected by Transcranial Doppler (TCD) in relation to three different antiplatelet regimes employed during carotid endarterectomy. Baring in mind the potential for negative publication bias for trials without positive outcomes, there is perhaps a good incentive to share the data proffered with an audience of vascular specialists.

The authors quite rightly point out that the study is underpowered to detect a relationship between clinical adverse cerebral events and antiplatelet regimes. The study instead hinges on the use of a surrogate marker of neurological injury utilised in place of clinical endpoints, namely the rate of TCD- detected microemboli in the middle cerebral artery ipsilateral to the carotid artery being treated by endarterectomy. This surrogate is being increasingly used in studies of carotid intervention by both carotid endarterectomy and carotid stenting. Whilst it may be reasonable to do so, it must be recognised that the absolute numbers of microemboli detected during carotid endarterectomy and stenting are discrepant perhaps by a significant order of magnitude (a reasonable body of work suggests significantly more microemboli when either carotid angioplasty or indeed, state-of-the-art carotid stenting is performed, compared with carotid endarterectomy). Under these circumstances, with the relative paucity of signals detected during endarterectomy, perhaps the trial as presented is underpowered for the use of this surrogate marker in a way that would not be relevant for a study of carotid stenting. As a pilot study, though, it provides food for thought.

A number of other points may be raised. Ordinarily, there may be intuitive concerns about the use of dual antiplatet agents employed during endarterectomy, particularly with respect to the greatly feared bleeding complication rate. Indeed, the rate of bleeding complication requiring re-exploration of the neck in this study is 4.9% (5/102), which seems a little high. Two patients suffering this complication were treated with asasantin and clopidogrel and two with asasantin and Rheomacrodex. It is unfortunate, then, that the use of these two additional antiplatelet strategies did not result in benefit as judged by a significant reduction in microembolic signals. Furthermore, the dosing schedule for Group II, in which clopidogrel was administered in addition to asasantin is not clearly rationalised. Clopidogrel was provided at a dose of 75 mg three days prior to endarterectomy. Certainly for carotid stenting, which we must accept is not the primary focus of this study, there is Level 1 evidence to support a much more stringent dual antiplatelet regime. This comprises either 75 mg clopidogrel daily one week prior to intervention to supplement aspirin at a dose of at least 75 mg daily with both drugs to continue for at least 28 days post-stenting or alternatively, in a more urgent setting, for clopidogrel to be administered at a dose of 300–600 mg at least 15 hours prior to the procedure, assuming that the patient, invariably an arteriopath, is taking aspirin at a dose of at least

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75 mg daily. Clearly, a recently endarterectomised artery will in most cases expose a thrombogenic surface to the circulation and this may be compounded by the use of a synthetic patch (albeit selectively applied in this series). The authors reference the Leicester experience in which one hundred patients on 150 mg of aspirin were randomised to 75 mg of clopidogrel or placebo the night before surgery (reference 27). A significant reduction in platelet response to adenosine diphosphate with a 10-fold reduction in the relative risk of those patients having >20 emboli on TCD in the postoperative period was demonstrated. Whilst the number recruited in the Leicester study is comparable to the trial presented here, the Leicester work highlights a two-way randomisation process and the current study a three-way randomisation. The reduced number in each randomised limb of the current trial perhaps explains the negative results. However, it does beg the question; ''Are the authors convinced of the validity of their chosen antiplatelet dosing schedule?''

Penultimately, the influence of the heparin regime selected within this trial on the antiaggregant effect on the antiplatelets employed is worthy of elaboration. It is stated simply that 5,000 international units (IU) of heparin were administered prior to cross-clamping, that protamine reversal was not used, that platelet aggregation tests were not performed and that the heparin dose-response relationship was calculated by the activated clotting time (ACT). The readership must assume that unfractionated heparin was utilised within this trial and yet the Leicester group elegantly demonstrated that administration of unfractionated heparin during the procedural time-frame of carotid endarterectomy significantly increases platelet aggregation in response to arachidonic acid, despite adequate inhibition by aspirin administered preoperatively.[1] This apparent reversal of antiplatet activity persists into the immediate post-operative period. Taken to its logical conclusion, the use of unfractionated heparin within this trial may jeopardize the results of a trial relying on the effect of asasantin as a supplement to additional antiplatelet agents. Intriguingly, the Leicester group's work is referenced on seven occasions but both the potentially harmful effect of unfractionated heparin and the relatively protective effect of the (as yet unlicensed) use of intravenous *FRACTIONATED* heparin during carotid endarterectomy is overlooked.[2]

Finally, we must not neglect the issue of aspirin (and/or asasantin) resistance − this is hinted at in the discussion section of the paper. Indeed, the aspirin-resistant population may be at increased risk of clopidogrel-resistance. The authors have a noble aim − that of a ''one-size-fits-all'' antiplatelet regime but without accurate point-of-care testing for aspirin, asasantin and/or clopidogrel resistance (which unfortunately remains elusive) this aim may not realistically be achieved.

In summary, this trial has failed to show any difference in the rate of embolisation in the first two hours after endarterectomy in patients treated with one of three different antiplatet regimes. This may be because there is no difference, or it may be because the trial was underpowered and/or flawed by inappropriate choice of pharmacological regime and the dosing schedule.

References

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