



Original Research Article

Abolition of micro embolic signals in symptomatic carotid stenosis using dual antiplatelet therapy

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ABSTRACT

BackgroundIntroduction : Micro-Embolic Signals (MES) detected by Trans-Cranial Doppler (TCD) in symptomatic carotid stenosis (CS) are considered a marker of subsequent stroke. We aimed to investigate the role of antiplatelet and antithrombotic agents in abolishing the MES in recently symptomatic CS.

Materials and Methods: Transient ischemic attack/stroke patients with 50% CS or unstable carotid plaque, who were prospectively enrolled within 48 hours of symptom onset, underwent bilateral middle-cerebral artery one-hour TCD emboli monitoring within 48 hours. Those with MES underwent second monitoring at 48 hours of the initial study. Treatment given during the interval period was recorded.

Results: Out of 73 patients enrolled from April 2016 to March 2019, 22 (17 males, mean age 67.4 years) had ipsilateral MES on initial TCD (30.1%). Ten were on a single-antiplatelet agent (aspirin/clopidogrel) and one was on dual (aspirin&clopidogrel) therapy prior to this. Single-antiplatelet agent was started after TCD in seven, dual-agents in six and unfractionated-heparin in seven patients. Second TCD showed no MES in 14 patients. Only one out of three on a single antiplatelet agent alone had abolition of MES while all ten patients on dual-antiplatelet agents had a complete suppression ($p=0.027$, Chi-square test). Although heparin suppressed MES in 5/7 patients, all five had additional dual-agent therapy. MES was not abolished in one patient treated with heparin alone and another one on a combination of heparin and single-antiplatelet agent.

Conclusion: Aspirin/Clopidogrel combination is very effective in suppressing arterial emboli in recently symptomatic carotid stenosis whereas unfractionated-heparin, single-antiplatelet agent or their combination is not useful for the same.

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1. Introduction

Trans-Cranial Doppler (TCD) is a simple bedside tool for the evaluation of stroke in both acute and chronic settings.¹ It is technically feasible in most patients and it provides clinically useful information about future stroke risk for patients with carotid disease.² Micro-Embolic Signals (MES) detected by TCD emboli detection monitoring³ is a marker of stroke and TIA in symptomatic carotid stenosis (SCS) as well as asymptomatic carotid stenosis (ACS)^{4,5} and hence the strategies to abolish the MES are important. Dual antiplatelet therapy with aspirin

and clopidogrel significantly reduces the MES compared with aspirin alone in symptomatic intracranial carotid and middle cerebral artery stenosis.⁶ A similar effect was seen with a reduction in both MES positivity and MES frequency per hour in extra-cranial SCS patients treated with aspirin and clopidogrel versus aspirin alone.⁷ However, different antiplatelet regimens were not found to be useful to abolish MES in the setting of post carotid endarterectomy.⁸ Further, the effectiveness of antiplatelet agents especially clopidogrel is being questioned in Indian patients.⁹ Hence we aimed to investigate the role of antiplatelet and antithrombotic agents in abolishing MES in recently symptomatic Carotid stenosis patients in our center.

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2. Materials and Methods

The study was conducted from 1st April 2016 to 31st March 2019 in a tertiary care teaching hospital in Kerala, South India. Patients with Transient Ischemic Attack (TIA) or ischemic stroke, having 50% stenosis of the extra-cranial carotid artery in Magnetic Resonance Angiography (MRA) or duplex ultrasonography, were prospectively enrolled for the study, within 48 hours of symptom onset. In our center, we routinely perform urgent non-contrast MRA or duplex ultrasonography for all our stroke patients. Though we do Digital Subtraction Angiography (DSA), typically it is delayed and is usually done in the setting of planned endovascular interventions. Computerized Tomographic Angiography (CTA) is not being performed routinely in our center. As per protocol, all enrolled patients underwent bilateral Middle Cerebral Artery (MCA) TCD emboli detection monitoring, as soon as possible for a duration of one hour.³ Those with positive MES underwent second monitoring at 48 hours of the initial study. Treatments given during the interval period were carefully recorded. Treatment protocol was not standardized and the practice included using single antiplatelet agents, dual antiplatelet agents, heparin and combination of single or dual antiplatelet agents and heparin. Results were analyzed using descriptive method. Abolition/reduction in the MES during the second study with single antiplatelet treatment versus dual antiplatelet treatment was compared using the Chi-square test.

3. Results

Out of a total 3256 ischemic stroke admissions during the study period, 73 patients (2.2%) with SCS were enrolled in the study; 61 were males and 12 were females and the median age was 72 years. Among them, 22 patients (30.1%) were positive for ipsilateral MES on initial TCD evaluation. They included 17 males and five females, with a median age of 70 years. Sixteen of them were hypertensive, eight diabetic, eight dyslipidemic and three were smokers; overall 21 out of the 22 patients (95.5%) had at least one of these classical vascular risk factors. Eight of them had prior ischemic stroke / TIA, eight had coronary artery disease and three had peripheral artery disease of the lower limb vessels; altogether 12 out of 22 (54.5%) had any of the three which suggests prior macro-vascular disease.

Half of the MES positive patients were already on antiplatelet therapy; ten on a single antiplatelet agent (aspirin or clopidogrel) and one on dual antiplatelet agents (aspirin and clopidogrel) prior to the first TCD monitoring. They received a combination of drugs and the remaining patients received a single agent or combination of drugs after the initial TCD monitoring. The decision was purely at the discretion of the treating physician.

Second TCD showed complete suppression of MES in 14 patients. Only one out of three patients on a single antiplatelet agent alone had abolition of MES while all ten patients on dual antiplatelet agents had a complete suppression of MES ($p=0.027$, Chi-square test). Although heparin suppressed MES in five out of seven patients, all five had additional dual agent therapy. MES was not abolished in one patient treated with heparin alone and in another one on a combination of heparin and single antiplatelet agent.

4. Discussion

The current standard of care in SCS is carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS).¹⁰ Micro-Embolus Signals (MES) detected by Trans-Cranial Doppler (TCD) help in risk stratification¹¹ and so it may aid in triaging. MES predict recurrent cerebral ischemic events in acute stroke/TIA patients¹² and an overall poor outcome.¹³ A large number of emboli in TCD is a marker of risk in patients with emboli of carotid origin and so prompt research strategies to triage for carotid revascularization.⁵ Therapeutic reduction of MES will reduce the chance of stroke¹⁴ and so may have a role in bridging for CEA or CAS. Further, it has a potential to aid the 'aggressiveness' in the aggressive medical management of carotid stenosis.¹⁵

Dual antiplatelet therapy with aspirin and clopidogrel significantly reduces the MES compared with aspirin alone in symptomatic intracranial carotid and middle cerebral artery stenosis.⁶ A similar effect was seen with a reduction in both MES positivity and MES frequency per hour in extra-cranial SCS patients treated with aspirin and clopidogrel versus aspirin alone.⁷ This has not been studied well in Indian patients. We felt that investigating the effects of antiplatelet and antithrombotic agents in abolishing MES in our population is very important especially in the scenario of high rates of clopidogrel resistance.⁹

Symptomatic Carotid Stenosis was considered to the cause of stroke in a minority (2.2%) of our stroke admissions, which appears to be less than that of the western countries.¹⁶ TCD evaluation in the initial hours of admission showed ipsilateral positive MES in a third of these cases. All except one (95.5%) had any one of the vascular risk factors with hypertension being the commonest factor and 54.5% (12/22) had evidence of macro-vascular disease. This suggests that SCS with MES, which is a surrogate of plaque instability¹⁷ can be considered as a marker of generalized atherosclerotic vascular disease as well. Another point suggesting high atherosclerotic load in these patients is the fact that 50% of them had the MES while on antiplatelet therapy.

Before the second TCD monitoring, aspirin, clopidogrel, heparin or their combinations were added or initiated in all patients. In the second monitoring at 48 hours after the initial TCD evaluation, out of three patients on a single antiplatelet agent, only one had total abolition of MES,

whereas all ten patients on dual antiplatelet agents (aspirin and clopidogrel) had complete suppression of their MES. This difference was statistically significant suggesting that the combination of aspirin and clopidogrel is required to suppress the MES in SCS patients. A similar observation in other recent studies underscores this inference.^{5,6} Our study was unique since it proved the same in Indian context especially in the background of high clopidogrel resistance in our country. Unfractionated heparin was used in seven patients. It didn't abolish the MES in one patient on heparin alone and another one on a combination of heparin and aspirin. Although heparin abolished MES in remaining five patients, all of them were on additional aspirin and clopidogrel suggesting that it is the dual antiplatelet agents and not the heparin, which is important in suppressing the MES in SCS. This is in contrary to the reported usefulness of heparin to reduce MES in the setting of cervical carotid dissection.¹⁸ Hence it is reasonable to infer that the structure of emboli in carotid dissection is different from that of carotid stenosis, though further confirmatory studies are required for the same.

All our patients received the therapy on a bridging basis before the definitive procedure of CEA/CAS. So the role of dual antiplatelet agents in long-term management of sCS could not be commented. Adding to the limitations, the study had a small sample size, was non-blinded and was from a single center. Feasibility and safety of long-term aspirin and clopidogrel in sCS utilizing both TCD and diffusion MRI monitoring should be investigated in future, with large multi-centric trials.

5. Conclusion

Dual antiplatelet therapy with aspirin and clopidogrel abolishes Micro-Embolic Signals (MES) in recently symptomatic carotid stenosis. Unfractionated heparin alone or in combination with a single antiplatelet agent cannot effectively suppress MES. So dual antiplatelet therapy with aspirin and clopidogrel should be considered as the standard of care in recently symptomatic carotid stenosis.

6. Source of funding

None.

7. Conflict of interest

None.

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