Clopidogrel Load for Emboli Reduction in Patients With Symptomatic Carotid Stenosis Undergoing Urgent Carotid Endarterectomy

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Background and Purpose—Microembolic signals (MES) on transcranial Doppler are an independent risk factor for recurrent stroke in patients with extracranial symptomatic/asymptomatic carotid artery stenosis (CARAS). Clopidogrel load (300 mg) combined with dual antiplatelet therapy has been shown to reduce MES in patients with symptomatic CARAS. We sought to determine feasibility of clopidogrel load in decreasing asymptomatic embolization in patients with symptomatic CARAS undergoing urgent carotid endarterectomy within the first 2 weeks from the index event.

Subjects and Methods—Consecutive patients with symptomatic CARAS (70%–99%) and presence of MES on 1-hour baseline (<24 hours from the index event) transcranial Doppler monitoring of ipsilateral middle cerebral artery were treated with clopidogrel load followed by clopidogrel (75 mg) aspirin (100 mg) during the elapsed time period between hospital admission and urgent carotid endarterectomy at 3 tertiary-care stroke centers. Repeat 1-hour transcranial Doppler monitoring was performed the day before surgery. Bleeding complications during surgery and recurrent strokes or transient ischemic attacks during the first month of ictus were prospectively recorded.

Results—A total of 11 symptomatic CARAS patients (mean age, 66 ± 7 years; 73% men; 64% acute ischemic strokes) were treated with clopidogrel load followed by dual (67%) or single (33%) antiplatelet therapy. MES count was significantly reduced between baseline (median count, 8 MES/h; interquartile range, 6–19) and repeat transcranial Doppler monitoring (0 MES/h; interquartile range, 0–3; P=0.003). No bleeding complications, recurrent strokes, or transient ischemic attacks were documented.

Conclusions—Our pilot observational study provides preliminary nonrandomized data regarding the potential efficacy of clopidogrel load to reduce asymptomatic embolization in patients with symptomatic CARAS before urgent carotid endarterectomy. (Stroke. 2012;43:00-00.)

Key Words: clopidogrel load | emboli reduction | urgent carotid endarterectomy | carotid artery stenosis

Microembolic signals (MES) on transcranial Doppler (TCD) are an independent risk factor for recurrent stroke and neurological deterioration in patients with extracranial symptomatic and asymptomatic carotid artery stenosis (CARAS).1–3 MES have been used for risk stratification and assessment of therapeutic efficacy in these conditions.4 Clopidogrel load (300 mg) combined with dual antiplatelet therapy reduces asymptomatic embolization in patients with symptomatic CARAS in 2 phase IIb randomized clinical trials.5,6 To the best of our knowledge, the safety of aggressive antiplatelet therapy in patients with acute cerebral ischemia caused by symptomatic CARAS with active microembolization before emergent carotid endarterectomy (CEA) has never been investigated. We sought to determine feasibility of clopidogrel load in decreasing asymptomatic embolization in patients with symptomatic CARAS undergoing urgent CEA within the first 14 days from the index event.

Methods

We prospectively evaluated patients presenting with symptoms of acute ischemic stroke or transient ischemic attack caused by symptomatic CARAS in 3 university, tertiary-care stroke centers fulfilling the following inclusion criteria during the study period (October 2009–September 2011):

1. ≥70% stenosis in symptomatic carotid artery diagnosed on baseline carotid duplex evaluation using the Society of Radiologists in Ultrasound Consensus Criteria7 and confirmed by subsequent magnetic resonance angiography, computed tomography angiography, or digital subtraction angiography.

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2. MES detected in ipsilateral to symptomatic CARAS middle cerebral artery in baseline 1-hour TCD monitoring (<24 hours).
3. Emergent CEA performed for revascularization of symptomatic CARAS within 2 weeks from stroke onset.
4. Repeat 1-hour TCD monitoring performed 1 day before CEA.
5. Absence of other potential sources of embolism (eg, cardiac sources, aortic arch atheroma)

Demographic characteristics and stroke risk factors were recorded as previously described.8 Stroke severity on hospital admission and at discharge was evaluated using the National Institutes of Health Stroke Scale score. Patients with absent temporal artery windows, symptomatic carotid artery occlusion, and prehospital functional disability (defined as modified Rankin Scale score of ≥2) were excluded from additional evaluation.

TCD monitoring of the M1-middle cerebral artery ipsilateral to the symptomatic CARAS was performed at 50 to 60 mm depth using previously described methodology5,6 with motion-mode TCD (PMD-ST3, Spencer Technologies or SONARA, VIASYS Healthcare) equipped by a 2-MHz transducer that was stabilized by a head frame. Standard TCD settings were set according to the International Consensus Criteria: 4 to 5 mm sample volume and 4 to 5 seconds sweep speed. Experienced sonographers at each center (G.T., A.K., C.K., K.Y., I.H., A.V.A.) reviewed the TCD recordings in real-time to identify the presence of MES according to International Consensus Criteria on MES detection (Figure 1).9

Bleeding complications during surgery and recurrent acute ischemic stroke/transient ischemic attacks during the first month following the index event were prospectively documented. Patients were treated with single antiplatelet therapy (aspirin 81–325 mg or clopidogrel 75 mg) following CEA. Functional status at 3 months was evaluated using modified Rankin Scale score.

The present study was approved by the Ethics Committee/Institutional Review Board of our institutions, where clopidogrel load (300 mg) is used as standard of care in addition to aspirin for patients who have large artery atherosclerotic (LAA) stroke mechanism and are scheduled to undergo urgent extra- or intracranial revascularization procedure. Data were collected under Institutional Review Board-approved protocol that captured all pretreatment variables, treatments, and outcomes among consecutive stroke patients admitted to our institutions as part of ongoing research and quality/outcomes improvement processes. All patients signed standard informed consent forms for carotid endarterectomy and were informed about potential bleeding risks. Given that this was a pilot/standard of care observational study, no a priori stopping rules were implemented. Serious adverse events were reported by local investigators and there was no independent data safety and monitoring board.

Statistical Analyses
Continuous variables with normal and skewed distribution are presented as mean (SD) or as median (interquartile range [IQR]). The difference in frequency of embolization between baseline and repeat TCD monitoring was evaluated using Wilcoxon rank-sum test given the skewness in MES distribution.

Results
A total of 11 symptomatic CARAS patients (mean age, 66±7 years; 73% men; 64% acute ischemic stroke) were treated with clopidogrel load followed by dual (67%) or single (33%) antiplatelet therapy during the study period (Table). The

Table. Baseline Characteristics of the Study Population (n=11)

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>66 (7)</td>
</tr>
<tr>
<td>Male</td>
<td>73%</td>
</tr>
<tr>
<td>Index event</td>
<td></td>
</tr>
<tr>
<td>AIS</td>
<td>64%</td>
</tr>
<tr>
<td>TIA</td>
<td>36%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>100%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>64%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>91%</td>
</tr>
<tr>
<td>Current smoking</td>
<td>27%</td>
</tr>
<tr>
<td>Stroke before index event</td>
<td>9%</td>
</tr>
<tr>
<td>Median admission NIHSS score (range)</td>
<td>5 (0–11)</td>
</tr>
<tr>
<td>Median elapsed time between admission and CEA, d (range)</td>
<td>7 (5–10)</td>
</tr>
</tbody>
</table>

AIS indicates acute ischemic stroke; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; CEA, carotid endarterectomy.
median elapsed time between hospital admission and CEA was 7 days (range, 5–10). MES count was significantly reduced between baseline (median count, 8 MES/h; IQR, 6–19) and repeat TCD monitoring (0 MES/h; IQR, 0–3; \( P = 0.003 \) by Wilcoxon rank-sum test). The median absolute and relative decrease in MES detection following clopidogrel load was 8 (IQR, 5–13) and 100% (IQR, 67%–100%), respectively. Error bars of MES counts at baseline and repeat TCD monitoring are depicted in Figure 2. A total of 6 patients were free of MES at repeat TCD monitoring (54%; 95% CI:, 28%–79%).

No bleeding complications, recurrent strokes, or transient ischemic attacks were documented during the first month after the index event. No patient required blood transfusion during or after CEA. The median National Institutes of Health Stroke Scale score at hospital discharge was 0 points (interquartile range, 0–4). The mean decrease in National Institutes of Health Stroke Scale score during hospitalization was 2.1±0.7 points. All patients were functionally independent (modified Rankin Scale scores of 0–1) at 3 months.

**Discussion**

Cerebral embolization can be detected by TCD in real-time in up to 71% of patients with acute cerebral ischemia. The prevalence of MES is by far the highest in patients with LAA and may be used for risk stratification of patients at elevated risk of recurrent acute ischemic stroke. In a recent meta-analysis, MES presence increased the risk of recurrent stroke by almost 10-fold in patients with symptomatic CARAS. Similarly, Hao and colleagues have documented an association of MES with worsening of neurological deficit in patients with LAA. Moreover, Iguchi et al have also reported that the presence of MES at 48 hours after symptom onset was associated with recurrence of cerebral ischemia on diffusion-weighted imaging in patients with LAA.

Our findings are consistent with European and Asian randomized clinical trials evaluating the safety and efficacy of clopidogrel load followed by dual antiplatelet therapy in patients with asymptomatic microembolization caused by symptomatic CARAS or symptomatic extra- or intracranial LAA. The reduction of MES detection at day 7 following aggressive antiplatelet therapy was 67% in the Asian and 54% in the European study. We documented a similar 54% reduction at repeat TCD monitoring performed at a median of 6 days (range, 4–9) from symptom onset. Our findings are also in line with the observations of a single-center study, indicating that the addition of clopidogrel to aspirin before CEA resulted in a 10-fold reduction in the relative risk of those patients having >20 emboli in the postoperative period. Notably, no increase in bleeding complications or blood transfusions during or after CEA was noted in patients treated with dual antiplatelet therapy. However, substantial methodological differences between our and the former study need to be acknowledged, including the fact that clopidogrel load was not used, and both symptomatic and asymptomatic CARAS patients were included. In addition, dual antiplatelet therapy was administered only the night before CEA.

Our study has limitations, including the observational design and the absence of central reading of TCD recordings. Moreover, our findings should be interpreted with caution given the nonrandomized setting of our study and the absence of independent data safety and monitoring board for evaluation of potential serious adverse events. In addition, as we describe in our methodology, we implemented no prespecified stopping rules, and no formal sample size estimation was performed before study initiation. Finally, dual antiplatelet therapy following clopidogrel load was administered in 2 of the 3 participating centers (Alexandroupolis and Alabama), whereas in the remaining center (Bochum), patients were treated with antiplatelet monotherapy (clopidogrel 75 mg) after clopidogrel load because of the fear of bleeding complications.

In conclusion, our pilot observational study provides preliminary nonrandomized data regarding the potential efficacy of clopidogrel load to reduce asymptomatic embolization in patients with symptomatic CARAS before urgent CEA. The present findings are subject of a larger ongoing multicenter study investigating whether clopidogrel load followed by dual antiplatelet therapy is associated with lower risk of recurrent stroke in patients with symptomatic CARAS scheduled to undergo urgent CEA.

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None.

**Disclosures**

None.

**References**


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