

Safety of Dual Antiplatelet Therapy After Carotid Endarterectomy for Prevention of Restenosis: A Single Center Experience

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Abstract

Introduction—The incidence of recurrent carotid stenosis after carotid endarterectomy varies from 1% to 37% with only 0–8% symptomatic restenosis. Safety of short-term (30 days) dual-antiplatelet therapy has not been established in this type of procedure.

Aims—To investigate the safety of dual antiplatelet therapy after carotid endarterectomy to prevent restenosis.

Methods—We retrospectively identified all the patients who underwent carotid endarterectomy (symptomatic or asymptomatic) treated at our center between July 2010 and July 2013 according to local protocols. All patients received a dose of 100 mg of aspirin daily immediately after carotid endarterectomy, with subsequent 100 mg of aspirin daily for the rest of the study period, and some patients received 75 mg of Clopidogrel for 30 days starting immediately after surgical procedure (dual therapy group), assigned according to medical criteria. Duplex carotid ultrasound and clinical assessments were performed at 30 days and 1 year after the procedure.

Results—A total of 44 patients (71.2 ± 7.9 years old; 77.2% symptomatic) were analyzed; 35 of them with dual therapy (79.54%). At 30 days, two patients from the mono-therapy group developed restenosis (22.2%), compared to none in dual therapy group ($p=0.04$). At one year follow-up, only one patient from the dual group showed restenosis ($p=0.10$). No deaths, major bleeding or new strokes were reported in both groups.

Conclusions—Short-term dual antiplatelet therapy with aspirin and clopidogrel after carotid endarterectomy might be associated with a lower incidence of restenosis. This observation must be validated in a prospective trial.

Keywords

carotid endarterectomy; dual antiplatelet therapy; cerebrovascular disease; atherosclerotic carotid disease

Introduction

Carotid endarterectomy (CEA) is the standard treatment for the revascularization of symptomatic severe atherosclerotic carotid stenosis [1–4]. Current guidelines recommend that CEA should be performed within first 14 days after a transient ischemic attack or nondisabling ischemic stroke [2,4,5].

One of the main concerns after surgery is restenosis rate and the risk of subsequent stroke. The incidence of recurrent carotid stenosis ranges from 1% to 37%, with only 0% to 8% of patients having restenosis-related symptoms [6,7]. Some of the factors associated with a lower incidence of restenosis are the use of surgical

patch, perioperative use of statins and the absence of tobacco use [7]. However, only few studies have described the association between peri-procedural antiplatelet use and frequency of restenosis. Platelet deposition within the endarterectomy zone begins within minutes of flow restoration [9,10]. Platelets of patients considered high risk of embolization are more sensitive to ADP (a pathway of the platelet activation not affected by aspirin) [11].

The present study aimed to establish the safety of short-term (30 days) dual antiplatelet therapy with aspirin + clopidogrel after carotid endarterectomy (CEA) in high-

risk patients and analyze the frequency of ischemic cerebral events and mortality.

Methods

We retrospectively identified all the patients who underwent CEA at our hospital from July 2010 to July 2013. All cases included should have at least one-year follow-up and clinical records must be available to include all the variables from the study: demographic, vascular risk factors [smoking, diabetes mellitus, hypertension, dyslipidemia, previous stroke or transient ischemic attack (TIA)], clinical findings, laboratory, and imaging results, as well as complications and functional outcomes at discharge, 30 days and 1 year after the procedure, also the indication for carotid surgery and decision for the antiplatelet therapy should be written on the medical record. Symptomatic patients were defined according to ASCOD classification system as A1: they should be under the assumption of ipsilateral atherosclerotic stenosis between 50–99% in an intra- or extracranial artery (internal carotid vessel in this case) supplying the ischemic field [12].

We defined ischemic stroke (IS) as the presence of an acute neurological deficit lasting longer than 24 h, confirmed by a positive imaging (brain computed tomography or magnetic resonance) for ischemia; or clinical assessment by neurologist for transient ischemic attack (TIA).

Asymptomatic patients were recruited for CEA if the stenosis degree was >70% and shared at least one high-risk criteria for thromboembolic complications and post-procedural restenosis: heavy smoker, high plaque surface irregularity or peripheral vascular disease and diabetes.

All the patients were assessed by color flow Doppler ultrasound scanning (General Electric Vivid-e®) by an accredited specialist in vascular surgery and vascular ultrasound in our Neurosciences Department. The same operator performed the initial and follow-up carotid duplex examination. The degree of carotid stenosis of the common and internal carotid vessel was assessed using the criteria from von Reutern et al; [13] degree of stenosis was classified in the following criteria: <50%, 50–69%, 70–89%, 90–99%, and occlusion. Restenosis was defined as a >50% diameter reduction on the surgical zone according to ultrasound criteria.

All CEA's were performed under general anesthesia, without shunt and the arteriotomy was closed with a patch placement. All patients had a follow-up protocol

in the stroke outpatient clinic, with clinical assessment (National Institute of Health Stroke Scale [NIHSS] and modified Rankin scale [mRs]), assessment of new symptoms, stroke recurrence or any adverse reaction to the medications. The clinical evaluation was performed at discharge, 30 days and 1 year with concomitant carotid ultrasound.

The decision for dual antiplatelet therapy (DAT) with aspirin 100 mg/daily + clopidogrel 75 mg/daily for the first 30 days (starting day one after surgery), was made according to medical criteria considering the risk of restenosis as defined by: heavy history of smoking (>40 pack/year), symptomatic early procedure (<2 weeks), high plaque surface irregularity and the absence of statin prior to surgery [7,14,15]. The rest of patients received only 100 mg aspirin for the first 30 days (starting day one after surgery), as monotherapy group (MT). After 30 days, both group patients received 100 mg aspirin/daily for the rest of the year as monotherapy.

As this was a retrospective observational study from medical records, no informed consent was performed; the study analysis was approved by the Local Ethics Committee.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS (Statistical Package for the Social Sciences, version 20.0, IBM Inc., Armonk, NY). Continuous values were expressed as mean \pm standard deviation (SD), and nominal variables were expressed as count and percentages. For the comparison of categorical data (considered as risk factors in the incidence of restenosis or unfavorable outcome), two-tailed chi-square with Yates correction was performed. Differences between categorical variables were expressed as odds ratios (OR) with confidence intervals (CI) of 95%; *p* value <0.05 was considered statistically significant.

Results

A total of 64 consecutive subjects were identified in a 3-year period recruitment time: seven patients did not have follow-up carotid duplex assessment, five patients did not complete the follow-up period, five patients continued their follow-up in another hospital, and in three patients, medical files were not available. The final sample included 44 patients who met the inclusion criteria. The mean age was 71.2 ± 7.9 years, with 15 [42.1%] patients less than 70 years old, including 32 (72.7%) male patients. Basal characteristics of the patients are

Table 1. Baseline characteristics of patients.

	Aspirin+clopidogrel n=35 (%)	Aspirin n=9 (%)	<i>p</i>
Age, years (mean, SD)	71.34 ± 6.6	70.7 ± 12.3	0.82
Male	25 (71.4)	7 (77.8)	0.25
<i>Comorbidities</i>	14 (40.0)	2 (22.2)	0.23
Diabetes	32 (91.4)	8 (88.9)	0.89
Hypertension	19 (54.2)	4 (44.4)	0.39
Dyslipidemia (previous statin use)	6 (17.1)	2 (22.2)	0.76
Ischemic cardiac disease	8 (22.8)	2 (22.2)	0.78
Previous stroke			
Smoking history	21 (60.0)	5 (55.6)	0.45
Symptomatic	27 (77.1)	7 (77.7)	0.61
TIA	14 (40.0)	3 (37.5)	0.41
Stroke	14 (40.0)	4 (44.4)	0.53
CEA within 2 weeks of the qualifying event	14 (40.0)	6 (66.6)	0.09
Recurrent Stroke or TIA	0	0	-
Major bleeding (CNS, surgical zone, GIT)	0	0	-
Death	0	0	-

TIA: transient ischemic attack, CEA: carotid endarterectomy, CNS: central nervous system, GIT: gastrointestinal tract

Table 2. Thirty-day and 1-year outcomes in restenosis prevention.

	30-day restenosis			1-year restenosis		
	OR	CI 95%	<i>p</i>	OR	CI 95%	<i>p</i>
Smoking >40 p/y	1.21	0.84–1.72	0.06	1.21	0.84–1.72	0.06
Hypertension	0.95	0.88–1.02	0.64	0.92	0.84–1.01	0.56
Symptomatic carotid disease	0.94	0.86–1.02	0.45	2.0	0.16–24.9	0.58
Acute CEA	0.91	0.78–1.04	0.22	0.91	0.78–1.04	0.22
Male	0.94	0.85–1.02	0.39	0.90	0.81–1.03	0.29
>70 years old	1.07	0.97–1.19	0.29	1.07	0.90–12.4	0.95
Dual antiplatelet therapy	0.78	0.55–1.11	0.04	0.10	0.08–1.13	0.10
Ischemic cardiac disease	1.06	0.97–1.19	0.42	1.10	0.98–1.22	0.32
Absence of statin	1.10	0.96–1.24	0.17	1.81	0.15–21.6	0.63
Diabetes	0.52	0.03–8.92	0.64	1.07	0.09–12.9	0.95

shown on Table 1 for both groups (DAT vs. MT). For the overall population hypertension was present in 39 patients (88.6%), dyslipidemia in 23 (52.3%, all of them under oral statin therapy preoperatively), and previous stroke in eight (18.2%) cases. Smoking history was present in 26 (59.4%), with 15 cases (57.7%) smoking 10–39 pack/year; no recurrent smoking after the CEA was recorded during the study time. In the vast majority of the subjects presented with a symptomatic severe atherosclerotic stenosis, CEA was performed within 2 weeks from the qualifying event. The degree of stenosis at diagnosis was moderate in 30.8%, severe in 47.7% and critical in 22.7%. High degree irregularity (by duplex assessment) in plaque surface was reported in 28 (63.6%) of all cases.

All subjects presented with a premorbid mRs of 0 points. The mean value for NIHSS at presentation was four points in the subjects presenting with cerebral infarction.

A total of 35 (79.5%) patients received DAT and nine (20.4%) patients MT. The DAT group was assigned based on medical criteria of the treating physician, to prevent restenosis development according to criteria for high-risk patients.

There was no major bleeding in surgical zone. Only one subject in the DAT group, and two subjects in the MT

group developed a minor postoperative hematoma at the surgical site. No central nervous system, gastrointestinal, or genitourinary hemorrhages were detected during the follow-up period. Other transient uncommon postoperative complications included hypertensive crisis and spontaneous resolving hoarseness. No recurrent stroke or TIA was recorded in any of the groups during the follow-up period. The mean modified Rankin scale at 30 days and 1 year was 1 point. Early restenosis (at 30-days follow-up) occurred in two subjects in the MT group (22.2%) and no cases were detected in the DAT group ($p=0.04$; OR 0.78; 95% CI: 0.55–1.10). Late restenosis at 1 year occurred in one subject of the DAT and in two of the MT group. Bivariate analysis was performed for the main risk factors (summarized on Table 2), and no clinical significance was found for any of them for their effects on restenosis at 30-day and 1-year follow-up. Based on the inequality of the sample in both arms, no multivariate analysis was performed.

Discussion

Restenosis is a well-known complication after CEA and can potentially increase the risk of subsequent ipsilateral ischemic stroke. The restenosis after CEA is a complex process and platelets play a pivotal role. One of the main concerns for antiplatelet drugs in this context is the

higher incidence of perioperative bleeding complications including the wound hematoma that potentially might require re-exploration [17]. Our study demonstrated that short-term DAT with aspirin + clopidogrel was a safe intervention with no incidence of significant hemorrhagic complications in the DAT group. In a meta-analysis by Gouya et al., DAT with aspirin and clopidogrel in comparison with aspirin monotherapy reduced the relative risk of total stroke by 20% without increase in intracranial hemorrhage [17].

Many strategies have been implemented to prevent restenosis and stroke after CEA including high patient-risk identification, the use of loco-regional anesthesia and patch in the surgical zone, the minimizing of clamping time, optimal peri-procedural hemodynamic management, as well as the use of intraoperative transcranial Doppler ultrasound to detect embolization during manipulation of the plaque and the use of potent antiplatelet drugs including tirofiban [19] and abciximab [20].

Platelet aggregation was measured in response to adenosine diphosphate (ADP), collagen and arachidonic acid in patients undergoing carotid endarterectomy. It was found that the platelet in response to ADP was significantly higher in patients with peri-procedural embolic complications [11]. The ADP receptor inhibitors like clopidogrel have been proposed as an option to decrease the disposition of platelet activity and expression in surgical zone.

Our study found a significant association with lower restenosis rate at 30 days. This early restenosis did not correlate with late restenosis at 1 year in our study. We did not find an association between the commonly established risk factors and the frequency of restenosis in our study period, but the model must be validated in a prospective clinical trial. Certain limitations should be acknowledged in the present study: our model includes the design as a retrospective analysis from a predetermined sample according to medical criteria to decide which patients should undergo DAT. The small sample size is another limitation in our study, as well as the inequality of both arms that leads to a cautious interpretation of the therapeutic effect of one versus two antiplatelet drugs. A longer-term follow-up is needed to assess if the finding observed at one year are sustained over time.

Conclusion

The short-term (30 days) use of a combination of aspirin and clopidogrel immediately after CEA appears to be a safe therapeutic approach and may result in a lower inci-

dence of restenosis. This strategy seems to be a reasonable option to decrease recurrent ischemic events. This observation needs to be validated in a prospective trial.

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Tables

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