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Outcomes of carotid artery stenting at a high-volume Brazilian interventional neuroradiology center

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OBJECTIVES: Carotid artery stenting is an emerging revascularization alternative to carotid endarterectomy. However, guidelines have recommended carotid artery stenting only if the rate of periprocedural stroke or death is $< 6\%$ among symptomatic patients and $< 3\%$ among asymptomatic patients. The aim of this study is to evaluate and compare clinical outcomes of symptomatic and asymptomatic patients who had undergone carotid artery stenting as a first-intention treatment.

METHOD: A retrospective analysis of patients who underwent carotid artery stenting by our interventional neuroradiology team was conducted. Patients were divided into two groups: symptomatic and asymptomatic patients. The primary endpoints were ipsilateral ischemic stroke, ipsilateral parenchymal hemorrhage and major adverse cardiac and cerebrovascular events at 30 days. The secondary endpoints included ipsilateral ischemic stroke, ipsilateral parenchymal hemorrhage, ipsilateral transient ischemic attack and major adverse cardiac and cerebrovascular events between the 1- and 12-month follow-ups.

RESULTS: A total of 200 consecutive patients were evaluated. The primary endpoints obtained in the symptomatic vs. asymptomatic groups were ipsilateral stroke (2.4% vs. 2.7%, $p = 1.00$), ipsilateral parenchymal hemorrhage (0.8% vs. 0.0%, $p = 1.00$) and major adverse cardiac and cerebrovascular events (4.7% vs. 2.7%, $p = 0.71$). The secondary endpoints obtained in the symptomatic vs. asymptomatic groups were ipsilateral ischemic stroke (0.0% vs. 0.0%), ipsilateral parenchymal hemorrhage (0.0% vs. 0.0%), ipsilateral TIA (0.0% vs. 0.0%, $p = 1.00$) and major adverse cardiac and cerebrovascular events (11.2% vs. 4.1%, $p = 0.11$).

CONCLUSIONS: In this retrospective study, carotid artery stenting was similarly safe and effective when performed as a first-intention treatment in both symptomatic and asymptomatic patients. The study results comply with the safety requirements from current recommendations to perform carotid artery stenting as an alternative treatment to carotid endarterectomy.

KEYWORDS: Carotids angioplasty stenting; Symptomatic carotid artery stenosis; Asymptomatic carotid artery stenosis; Carotid endarterectomy.

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INTRODUCTION

Carotid artery stenosis is associated with approximately 15% of all ischemic strokes (1,2). Carotid endarterectomy (CEA) is indicated for the revascularization of carotid stenosis, with the goal of stroke prevention (3). Carotid artery stenting (CAS) is an emerging alternative to CEA; however, safety requirements from current guidelines have recommended CAS only if the rate of periprocedural stroke or death is $< 6\%$ among symptomatic patients or $< 3\%$ among asymptomatic patients (1,2). Despite the increasing indication of CAS procedures following publication of the CREST trial results (4), evaluating safety data on CAS outside of randomized trials is necessary to externally validate the procedure in daily clinical practice. Moreover, since the publication of the CREST trial results, no study has been published that focused specifically on CAS safety outcomes in Brazil. The aim of the present study is to evaluate and compare the clinical outcomes of symptomatic

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and asymptomatic patients who had undergone CAS performed by the interventional neuroradiology team of a high-volume Brazilian tertiary university hospital.

MATERIALS AND METHODS

Study design, clinical assessment and workflow

This is a single-center retrospective study. The study protocol and written informed consent were approved by the institutional review board, and all patients or their legal representatives signed the consent forms. We retrospectively evaluated the clinical and radiological data of patients who underwent CAS for atherosclerotic carotid stenosis from July 2010 to December 2012. Patients had undergone CAS if they fulfilled the institutional eligibly criteria, which are summarized in Table 1. Patients were divided into two groups: the first group comprised patients presenting symptomatic carotid stenosis, and the second group comprised patients presenting asymptomatic carotid stenosis. Data on patients who had not undergone CAS and were clinically managed were not collected.

All patients were examined by certified vascular neurologists in hospital at the 1-month and at the 12-month follow-ups. The neurologists measured the neurological deficit and outcomes using validated Portuguese versions of the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) (6). The mRS scores were obtained at hospital admission, 1 month after treatment, and at the 12-month follow-up. A stroke was defined as an ischemic neurological deficit (NIHSS score $\geq$ 4) or aphasia that persisted for more than 24 hours, and TIA was defined as an ischemic neurological deficit (NIHSS' score $\geq$ 4) or aphasia that persisted for less than 24 hours. The patients who missed a follow-up were contacted by telephone.

The primary endpoints were the incidences of ipsilateral ischemic stroke, ipsilateral parenchymal hemorrhage (iPH) and major adverse cardiac and cerebrovascular events (MACCEs) at 30 days. MACCEs are defined as any stroke, symptomatic myocardial infarction, vascular complication or death. The secondary endpoints included ipsilateral ischemic stroke, iPH, ipsilateral TIA and MACCE occurring between the 1- and 12-month follow-ups.

Carotid artery stenting procedure

All procedures were performed by the interventional neuroradiology team of our institutional stroke team, which comprises both training fellows and staff. The CAS procedure protocol was identical to the procedure that has already been published (7). We used cerebral embolic protection devices whenever possible. The recommended antiplatelet regimen was aspirin (300 mg daily) and clopidogrel (75 mg daily) at least five days before treatment or aspirin (300 mg per attack) and clopidogrel (300 mg per attack) at least four hours before the procedure and continuing for three months afterward. Aspirin (300 mg daily) was maintained indefinitely. When an anticoagulant was indicated for secondary stroke prevention, only 300 mg daily aspirin was recommended in combination with the anticoagulant drug; clopidogrel was not indicated. All patients were discharged 24 hours after treatment if no contraindication occurred.

Statistical analysis

The continuous variables were presented as the mean (range, $\pm$ SD) or median, and Student's t test or the Mann-Whitney U test was used, as appropriate. The categorical variables were presented as numbers and percentages and compared among groups using the Chi-square or Fisher's exact tests, as appropriate. One independent blinded investigator processed all collected data for the statistical analysis. SPSS software version 20.0 (Chicago, IL, USA) was used for the statistical analysis.

RESULTS

A total of 233 patients who had undergone CAS were screened; 33 were excluded, and 200 were included. Among the excluded patients, 28 had undergone CAS during mechanical thrombectomy for acute ischemic strokes, 2 were treated for carotid stenosis related to radiotherapy, 1 had undergone staged CAS open-heart surgery, and 2 were lost to follow-up and could not be contacted. Among the 200 patients included, 127 were symptomatic, and 73 were asymptomatic.

The baseline characteristics of the patients according to group are summarized in Tables 2 and 3. All the CAS procedures were successful. Only two patients (1.0%), one

Table 1 - Eligibility criteria.

Inclusion criteria
Patient age $\geq$ 18 years
Life expectancy $\geq$ 1 year
Symptomatic ICA stenosis $\geq$ 50%*
Asymptomatic ICA stenosis $\geq$ 60%*
Symptoms were defined as ischemic stroke, transient ischemic attack, hypoperfusion or retinal ischemia
Exclusion criteria
Total occlusion of the target carotid artery
Patients who underwent CAS and mechanical thrombectomy for acute ischemic stroke
Carotid-related severe disabling ischemic stroke (mRS $\geq$ 5)
Severe chronic renal insufficiency under non-dialytic management (creatinine clearance $\leq$ 40 ml/min)
Untreatable bleeding diathesis, hypercoagulable state or refusal of blood transfusion
Contraindication for antiplatelet therapy
Impending major surgery

*Based on the criteria defined by the American Heart Association Stroke Council and defined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (1,5).

Table 2 - Patients' baseline clinical data in each group.

	Total (N = 200)	Symptomatic group (N = 127)	Asymptomatic group (N = 73)	p value
Male (n, %)	126 (63)	84 (66.1)	42 (57.5)	0.229
Age (mean, range, SD)	68.5 (35-88, SD: ±8.82)	68.1 (35-88, SD: ±9.42)	69.3 (42-84, SD: ±7.67)	0.31
70 years or older (n, %)	89 (44.5)	53 (41.7)	36 (49.3)	0.306
80 years or older (n, %)	25 (12.5)	17 (13.4)	8 (11)	0.664
Carotid-related stroke (n, %)	102 (51)	102 (80.3)	0 (0)	<0.001
Transient ischemic attack (n, %)	20 (10)	20 (15.7)	0 (0)	<0.001
Retinal infarction (n, %)	5 (2.5)	5 (3.9)	0 (0)	0.161
Previous unrelated stroke (n, %)	73 (36.5)	31 (24.4)	42 (57.5)	<0.001
Coronary heart disease (n, %)	47 (23.5)	21 (16.5)	26 (35.6)	0.003
Congestive heart failure (n, %)	22 (11)	15 (11.8)	7 (9.6)	0.815
Atrial fibrillation (n, %)	10 (5)	6 (4.7)	4 (5.5)	1.000
Peripheral artery disease (n, %)	25 (12.5)	15 (11.8)	10 (13.7)	0.825
Chronic renal insufficiency (Creatinine clearance ≤ 60 ml/min)	39 (19.5)	24 (18.9)	15 (20.5)	0.853
Chronic obstructive pulmonary disease (n, %)	15 (7.5)	9 (7.1)	6 (8.2)	0.785
Tobacco smokers (n, %)	119 (59.5)	78 (61.4)	41 (56.1)	0.550
High blood pressure (n, %)	185 (92.5)	117 (92.1)	68 (93.2)	1.000
Hypercholesterolemia (n, %)	148 (74)	94 (74)	54 (74)	1.000
Diabetes mellitus (n, %)	76 (38)	47 (37)	29 (39.7)	0.763
Baseline mRS (mean, SD)	1.7 (0-4, SD: ±1.31)	1.9 (0-4, SD: ±1.25)	1.3 (0-4, SD: ±1.36)	0.009

from each group, presented asymptomatic carotid restenosis (>70%) at the 6- and 12-month follow-ups that required retreatment. As the two groups were divided based on the symptomatic status of the patients, a few baseline variables, carotid related stroke, TIA and mRS, were significantly different between the groups, as expected. The asymptomatic group did not present any carotid-related stroke or TIA, and the mRS grade of this group was significantly lower than that of the symptomatic group (Table 2). The other baseline variables that varied significantly between the two groups were the prevalence rates of coronary heart disease, contralateral carotid occlusion, and previous unrelated stroke. Compared with the symptomatic group, the asymptomatic group had higher prevalence rates of coronary heart disease (35.6% vs. 16.5%, p = 0.003), previous unrelated stroke (57.5% vs. 24.4%, p<0.001), and contralateral carotid occlusion (23.3% vs. 7.9%, p = 0.004). A flow-reversal protection device was used in 12 patients of the symptomatic group, which was was significantly higher than that in the asymptomatic group (0 patients, p = 0.004).

All 200 patients were included in the primary analysis. The overall incidence of ipsilateral stroke was 3.0% (6/200), and the overall rate of MACCE was 4.0% (8/200) at the 30-day follow-up (Table 4). The incidence of the primary endpoints did not differ significantly between the two groups (Table 4). The incidences of ipsilateral ischemic stroke, iPH and MACCE for the symptomatic vs. asymptomatic groups were 2.4% vs. 2.7% (p = 1.000), 0.8% vs. 0.0% (p = 1.000), and 4.7% vs. 2.7% (p = 0.713), respectively.

Among the 4 strokes observed in the symptomatic group, 3 were ipsilateral ischemic strokes, and 1 was iPH. The first ipsilateral stroke occurred immediately after the procedure, causing significant functional disability (mRS = 4) at the 12-month follow-up. The second ischemic stroke occurred 6 hours after the procedure, causing moderate patient disability at the 12-month follow-up (mRS = 3). The third ischemic stroke occurred after carotid angioplasty and was caused by an occlusion of the M1 segment of the ipsilateral middle cerebral artery; the patient presented a moderate neurological deficit (mRS = 3) at the 12-month follow-up. The iPH occurred 2 days after the procedure, and the patient died 10 months later from pneumonia.

The 2 deaths observed in the symptomatic group were caused by hospital-acquired pneumonia and acute myelodysplastic syndrome. Both of these deaths were unrelated to cardiovascular complications or to the CAS procedures.

The incidence of clinical secondary outcomes did not significantly differ between the two groups (Table 4). During the period between the 1- and 12-month follow-up, no ipsilateral ischemic stroke, iPH or ipsilateral TIA were observed. One patient of the symptomatic group had a cerebellar hemorrhage requiring surgical intervention 7

Table 3 - Patients' baseline radiologic and procedural data in each group.

	Total (N = 200)	Symptomatic group (N = 127)	Asymptomatic group (N = 73)	p value
CAS procedure successfully accomplished (n, %)	200 (100)	127 (100)	73 (100)	-
Left carotid stenosis (n, %)	98 (49)	61 (48)	37 (50.7)	0.770
Carotid stenosis grade (mean, range, SD, NASCET %)	74.5 (50-95, SD: ±14.7)	75.5 (50-95, SD: ±16.3)	72.8 (60-95, SD: ±11.44)	0.118
Contralateral carotid occlusion (n, %)	27 (13.5)	10 (7.9)	17 (23.3)	0.004
Cerebral embolic protection (n, %)	191 (95.5)	122 (96.1)	69 (94.5)	0.726
Filter protection device (n, %)	179 (89.5)	110 (86.6)	69 (94.5)	0.095
Flow-reversal device (n, %)	12 (6.0)	12 (9.5)	0 (0.0)	0.004
Pre-dilatation	85 (42.5)	59 (46.5)	26 (35.6)	0.141
Restenosis that was retreated (n, %)	2 (1.0%)	1 (0.8%)	1 (1.3%)	1.000

Table 4 - Clinical outcomes *per* group at the 1- and 12-month follow-ups.

During the 30-day follow-up	Total (N = 200)	Symptomatic group (N = 127)	Asymptomatic group (N = 73)	One-tailed p value	Two-tailed p value
Ipsilateral ischemic stroke (n, %)	5 (2.5)	3 (2.4)	2 (2.7)	0.602	1.000
Ipsilateral parenchymal hemorrhage (n, %)	1 (0.5)	1 (0.8)	0 (0.0)	0.635	1.000
Any stroke (n, %)	6 (3.0)	4 (3.1)	2 (2.7)	0.618	1.000
Ipsilateral transient ischemic attack (n, %)	3 (1.5)	3 (2.4)	0 (0.0)	0.254	0.301
Symptomatic myocardial infarction (mean, %)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Deaths (n, %)	2 (1.0)	2 (1.6)	0 (0.0)	0.412	0.534
MACCE (n, %)	8 (4.0)	6 (4.7)	2 (2.7)	0.389	0.713
mRS (mean, range, SD)	2.03 (0-6, SD: ±1.51)	2.03 (0-6, SD: ±1.51)	1.49 (0-6, SD: ±1.45)	-	0.030
Between the 1- and 12-month follow-ups	**Total (N = 198)**	**Symptomatic group (N = 125)**	**Asymptomatic group (N = 73)**	**One-tailed p value**	**Two-tailed p value**
Ipsilateral ischemic stroke (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Ipsilateral parenchymal hemorrhage (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Any stroke (n, %)	1 (0.5)	1 (0.8)	0 (0.0)	0.635	1.000
Ipsilateral transient ischemic attack (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Symptomatic myocardial infarction (mean, %)	2 (1.0)	2 (1.6)	0 (0.0)	0.412	0.534
Deaths (n, %)	16 (8.0)	13 (10.4)	3 (4.1)	0.094	0.175
MACCE (n, %)	17 (8.5)	14 (11.2)	3 (4.1)	0.068	0.115
mRS (mean, range, SD)	2.15 (0-6, SD: ±1.70)	2.29 (0-6, SD: ±1.74)	1.53 (0-6, SD: ±1.54)	-	0.006

(mRS) modified Rankin Scale; **(MACCE)** major adverse cardiac and cerebrovascular events (MACCE), defined as any stroke, symptomatic myocardial infarction, vascular complication or death.

months after CAS, and this patient presented a moderate neurological deficit (mRS = 3) at the 12-month follow-up. Sixteen patients died, of whom 13 were symptomatic and 3 were asymptomatic. The 3 deaths in the asymptomatic group were not related to the CAS procedure or to cerebrovascular or cardiovascular events. In contrast, in the symptomatic group, one patient who had iPH at the 30-day follow-up died from pneumonia 10 months later, 2 patients died from acute myocardial infarction, and the other 10 patients died from causes unrelated to the CAS procedures or to cerebrovascular or cardiovascular events.

Despite having had strokes that involved only small areas of infarcted brain tissue, 10.5% (21/200) of the patients had significant functional disability (mRS = 4) before the procedures; 16 of these patients belonged to the symptomatic group, and 5 belonged to the asymptomatic group (p = 0.238). Among the 16 patients (mRS = 4) of the symptomatic group, 4 patients (25%) died between the 1- and 12-month follow-ups, whereas no one among the 5 patients of the asymptomatic group died (p = 0.532).

DISCUSSION

In this study, we reported the clinical outcomes of patients presenting carotid stenosis who underwent CAS as a first-intention treatment since the publication of the CREST trial results (3). All procedures were performed by the interventional neuroradiology staff and fellows at a high-volume tertiary university hospital that receives patient referrals from local and regional health facilities.

Our results revealed that the overall incidences of ipsilateral stroke (3.0%, 6/200) and MACCE (4.0%, 8/200) at the 30-day follow-up were in accordance with the recommended safety rates for carotid revascularization procedures (1,2). Moreover, both the primary and secondary endpoints did not differ significantly between the two groups (Table 4). Compared with the asymptomatic group, the symptomatic group had a slightly higher rate of MACCE at the 30-day follow-up (4.7% vs. 2.7%, p = 0.71), although this difference was not significant. These MACCE rates were lower than the recommended safety rates for performing CAS in symptomatic (< 6%) and asymptomatic (< 3%) patients (1-3). The higher MACCE rate in the symptomatic group was expected because compared with CAS for asymptomatic patients, CAS for symptomatic patients has been associated with a twofold higher risk of major complications (1-3). However, the higher MACCE rates in the symptomatic group were due to 2 deaths that were not related to the CAS procedures. Therefore, excluding the 2 unrelated deaths, the rate of ipsilateral stroke or death between the symptomatic vs. asymptomatic groups was 3.1% vs. 2.7% (p = 1.000), respectively. The secondary endpoints also showed a higher (but not significantly higher) rate of MACCE in the symptomatic group compared with the asymptomatic group (11.2% vs. 4.1%, p = 0.11). This finding was mainly due to the higher rate of death unrelated to cardiovascular or cerebrovascular complications among the symptomatic patients during the follow-up period (8.8% vs. 4.1%, p = 0.26).

An analysis of the baseline variables showed that carotid-related stroke or TIA, as per the definition, were present in the symptomatic group and absent in the asymptomatic group, which explained the higher mRS scores among the symptomatic patients (Table 2). Moreover, the following variables: previous unrelated stroke, contralateral carotid occlusion, and coronary heart disease had significantly higher prevalence rates in the symptomatic group than in the asymptomatic group. The higher mRS scores of the symptomatic patients suggests that recent ischemic strokes lead to higher functional disability scores than do chronic unrelated strokes or contralateral carotid occlusions (Table 2). Another interesting finding was that despite the higher frequency of coronary heart disease in the asymptomatic group, no patient of that group suffered a myocardial infarction, whereas in the symptomatic group with a lower frequency of baseline coronary heart disease, 2 deaths from myocardial infarction were observed during the 12-month follow-up.

Our results revealed that CAS was safe when indicated as a first-intention revascularization strategy performed during daily clinical practice at a high-volume center outside of a

randomized trial. Importantly, previous carotid revascularization randomized trials, which served as the inspiration for the current procedural safety limits, had more restricted eligibility panels than those of our institutional protocol (1,3) (Table 1). In other words, we observed similar periprocedural safety outcome rates to those of previous controlled carotid trials in a real clinical care context in which CAS was indicated as the first-intention treatment. The policy of indicating CAS as a first-intention therapy plays a relevant methodological role in the interpretation of the results obtained because important selection biases were avoided (8). In addition, because patients were evaluated by certified vascular neurologists, the incidence of stroke observed in this study was likely not influenced by clinical assessment bias as reported in other surgical studies (9).

The good results obtained in this study may be explained by a sum of the following factors: the use of embolic protection devices (10,11), the use of a double antiplatelet regimen (1-3), and the high-volume center setting (12,13). Our findings underscore the value of performing a high volume of CAS procedures and a more experienced neurointerventional team on the outcomes obtained. Moreover, we stress the importance of a CAS reference center for achieving good outcomes as opposed to the common Brazilian reality of care, in which CAS procedures are performed at multiple distantly arranged low-volume hospitals.

The major limitations of the study are the small sample size, the non-randomized and retrospective design, and the lack of clinical data on patients who were clinically managed and did not undergo CAS.

In this retrospective study conducted at a high-volume Brazilian interventional neuroradiology center, CAS was similarly safe and effective when performed as a first-intention treatment in both symptomatic and asymptomatic patients. The study results comply with the safety requirements from the current recommendations to perform CAS as an alternative treatment to CEA.

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AUTHOR CONTRIBUTIONS

Castro-Afonso LH conceived the study; participated in its design, coordination, and data collection; and drafted the manuscript. Nakiri GS, Monsignore LM, Santos D, Camilo MR, Dias FA, Cougo-Pinto PT, Barreira CMA, Alesio-Alves FF, and Fabio SRC participated in the study design and data collection. Pontes-Neto OM participated in the study design and helped draft the manuscript. Abud DG conceived the study, participated in its design and coordination, and helped draft the manuscript.

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