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Efficacy of carotid artery stenting on stroke prevention of octogenarians

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ABSTRACT

Objectives: Octogenarians account for a third of ischemic stroke (IS) patients and applying endovascular carotid artery stenting (CAS), as a secondary prevention, in these patients is challenging. The aim of this study was to evaluate peri-procedural and long term clinical and angiographic impact of CAS on octogenarians.

Patients and methods: In a prospective study, 102 patients aged over 80 years old with symptomatic internal carotid artery (ICA) stenosis presenting by non-disabling IS or transient ischemic attack and having undergone CAS were evaluated prospectively from January 2012 to July 2016. All patients received standard stroke care during the study follow up period. Peri-procedural complication, cerebrovascular accidents, restenosis in target vessel and mortality rate were recorded and the collected data were analyzed to evaluate safety and durability of CAS in octogenarians.

Results: 48 (47.06%) males and 54 (52.9%) females with the mean age of 83.39 ± 2.53 (range, 80–88) years were followed in a mean period of 24.5 ± 14.1 months (6–50 months). Success rate of CAS was 100%; whereas, the peri-procedural complication rate was 5.8% (only one patient experienced acute ischemic stroke during the procedure). Restenosis and recurrent cerebrovascular accidents were observed in 3.9% and 9.8% of the cases, respectively. Recurrent cerebrovascular accident leading to death was seen in 2.9% of the cases. The median patient event-free survival was 20 months.

Conclusion: Endovascular CAS seems to be a safe and durable method for secondary prevention in ischemic stroke following symptomatic carotid artery stenosis in octogenarians.

1. Introduction

Octogenarians make up a third of ischemic stroke (IS) cases; this in turn accounts for a large number of IS related morbidity and mortality cases [1–3].Secondary IS prevention in this group of patients is challenging because of multiple associated comorbidities and loss of specific medical evidences [4].

Carotid artery stenosis or occlusion due to arterial atherosclerosis is a major etiology of IS [5]. Different modalities are available to reduce the risk of IS by relieving stenosis and preventing thromboembolic events, including but not limited to medical treatment or carotid revascularization therapies (endarterectomy, endovascular angioplasty etc.) [1,4,5]. Although carotid endarterectomy (CEA) has been established as the gold standard for the treatment of high-grade (≥ 70%) internal carotid artery (ICA) stenosis, octogenarians are usually labeled as "high risk" patients and normally not considered for this procedure [5–7]. Excessive risk of complications and limited post-procedural long-term survival are the commons concerns [8–10].Although some non-randomized studies indicate the safety of CEA in octogenarians, there are not sufficient evidences for the safety and efficacy of this approach

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[11–17]. Hence, less invasive alternative approaches such as endovascular carotid artery stenting (CAS) are mostly preferred in these "high risk" patients [5,11,18].CAS is increasingly being used as a safer and more applicable approach for carotid stenosis [19–23]. Initial studies demonstrated further peri-procedural complications like IS in octogenarians than their younger counterparts [19]; nevertheless, these complications are decreasing with the advent of newer and safer devices and methods [23–25]. Yet, some controversies still exist and even some clinical studies alarm that CAS might cause further exaggerated adverse events in octogenarians [5,18].

The aim of this study was to evaluate peri-procedural and long term clinical and angiographic impact of CAS on octogenarians.

2. Material and methods

2.1. Patients & clinical evaluation

The present investigation is a single-center, real observational prospective database analysis of CAS as a method of stroke prevention in octogenarians. Eligible patients, with symptomatic internal carotid artery (ICA) stenosis presented by non-disabling ischemic stroke [based on a focal neurological deficit with corresponding ischemic lesions in brain magnetic resonance imaging (MRI)] or transient ischemic attack (TIA) [defined as transient focal neurological deficit (less than 24 h) with no change in brain MRI], referred to the interventional Neuro-Radiology service of Shams hospital, Tabriz, Iran, were recruited. Later, patients underwent CAS and were evaluated for study outcomes prospectively from January 2012 to July 2016.

The inclusion criteria of this study were: 1. Age of 80–90 years old; 2. Confirmed acute IS or TIA by expert neurologists; 3. Presence of at least 50% stenosis in the cervical ICA by the NASCET criteria (based on Screening using ultrasound and confirmation with angiography) [26]. The exclusion criteria were: 1. Non-atherosclerosis related carotid stenosis (e.g. artery dissection, fibromascular dysplasia, vasculitis, radiation therapy and etc.); 2. Accompanying neurological deficits not correlated with ICA stenosis; 3. Having modified Rankin scale (mRS) score of > 2 or National Institutes of Health stroke scale (NIHSS) score [27] of > 5 after recent acute IS; 4. Not signing the written informed consent or willingness to exit the study sooner than 6 months; 5. Disabling or chronic (renal, hepatic, pulmonary, cardiac or etc.) diseases; 6. Sever loss of consciousness or confirmed dementia; 7. History of CEA or CAS; 8. Life expectancy of less than 6 months; 9. Contraindications for angiography or angioplasty (e.g. renal failure, coagulopathy and contrast allergy); 10. Inevitable cardiac surgery after CAA; 11. Anatomical complex aortic arch; and 12. Carotid occlusion or thrombosis.

A comprehensive interview and neurological and vascular examination were performed on admission for all patients. A consultant neurologist always confirmed the clinical diagnosis as TIA or minor stroke (NIHSS ≤ 5). Considering the defined criteria, 102 patients entered the study and ultimately underwent CAS. Expert neurologists recorded demographic data and risk factors of the vascular diseases. Also, the related and necessary para-clinic tests were performed and recorded. Later, patients were discharged within 1 week with Clopidogrel 75 mg once a day up to the end of follow up period. Also it is mentioned that all of the study patients were on dual antiplatelet therapy (ASA 80 mg and Clopidogrel 75 mg) for three mounts. Patients were evaluated 24 h before procedure and also in a programmed monthly visits for clinical and risk factors assessment. The follow up time terminated when the last engaged patient was followed for 6 months.

Primary endpoint of this study considered as recurrence of any types of stroke or TIA in the targeted territory of CAS. Also secondary endpoints were defined as post-procedure outcomes included: death, coronary artery disease (CAD), need for re-intervention, and re-stenosis of the target vessel. Modified Rankin scale (mRS) was used to assess clinical outcome at hospital and every clinical evaluation by expert neurologists. Throughout the follow up period, risk factor controlling through a lifestyle modification program was continued. All of the patients, including 3 who expired, completed their clinical follow up. The protocol of the current study was approved by the ethical board committee of Tabriz University of Medical Sciences, Tabriz, Iran, and is in accordance with the Declaration of Helsinki and its later amendments.

2.2. Procedure & angiographic follow up

Expert cardiologists performed perioperative cardiac work-up to exclude cases with severe coronary artery diseases. A 300-mg loading dose of oral Clopidogrel and 5000 IU intra-venues heparin were administered for all patients before and during CAS, respectively. Angiography of aortic arch and their major branches, renal artery angiography and diagnostic four-vessel angiography assessing the collateral vascular supply was performed under local anesthesia and conscious sedation. Also, endovascular CAS was performed with self-expandable stent placement (*Carotid WALLSTENT™ - Boston Scientific*) at the target lesion of ICA without distal filter protection devices. If required, dilatation by inflating the balloon (in about 8–16 atmosphere for 10–20 s to deploy the stent into the inner arterial wall) was performed by the same interventional neuroradiologist. Technical success was defined as the ability to access the target lesion at carotid artery and successfully stenting the lesion with residual stenosis of no more than 20%. Access was provided at the common femoral artery in all patients. Repeated procedure was performed after 6 weeks for those with significant stenosis (at least 50% stenosis in the symptomatic cervical ICA and more than 70% in the contralateral non-symptomatic extracranial ICA by the NASCET criteria) in their both carotids. For carefully monitoring the patients after the procedure, patients were admitted to the Neurology Intensive Care Unit. Carotid ultrasound study was performed in all patients on 30th day and every 6 months during follow-up. Control angiography was applied every 6 months during follow up period. In the control angiography, the main intra and extracranial arteries were evaluated focusing on the detection of restenosis or occlusion in the target stented artery. In-stent restenosis was described as a > 30% visual stenosis by carotid Doppler ultrasound and confirmed by carotid angiography. Restenosis degree and location was determined based on criteria suggested by Setacci et al. [28].

2.3. Statistical method

Observation period was defined as the time from the inclusion to the study to occurrence of death, loss to follow-up, or the completion of the study. Data are expressed as mean ± SD and percentage. Kaplan-Meier survival graph was plotted to estimate and compare time to failure (recurrent cerebrovascular accident, CAD or death. log-rank statistic was performed to compare time to failure in both gender. Wilcoxon Signed Ranks Test was used to comparison patient's mRS Scores. Cox proportional-hazard regression model was performed to determine potential predictors of time to recurrent cerebrovascular accident or death. The proportional hazard assumption was checked for the fitted models. Statistical analysis was performed using STATA 12 software (STATA Corp, College Station, TX). All p values were 2-tailed and statistical significance was considered as $P < 0.05$.

3. Results

In a 55-month period of investigation, 102 patients entering the study underwent CAS and were followed up for the mean of 24.5 ± 14.1 (6–50 months). Mean age of the patients was 83.39 ± 2.53 (range, 80–88) years and female gender was predominant (52.9%). Age distribution of patients was shown in Fig. 1. Percentage of hypertension, as the most common vascular risk factors in the current study, was 41.2%. In presenting symptoms, TIA was the

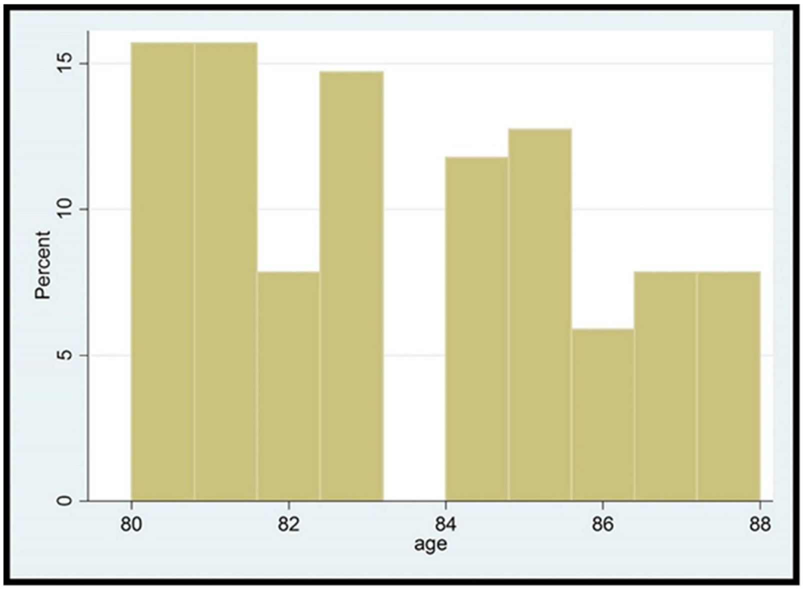

Fig. 1. The age distribution of patients included in the study.

Table 1
Patient's characteristics.

Characteristics	102(100%)
Gender	48 (47.06%)
Male	
Female	54(52.9%)
Age (years)	83.39 ± 2.53 (80–88)
Vascular risk factors:	
Cigarette smoking	29(28.4%)
Diabetes	28(27.5%)
Dyslipidemia	9(8.8%)
Hypertension	42(41.2%)
Presenting symptoms:	
TIA	82(80.4%)
Ischemic Stroke	20(19.6%)
Modified Rankin Scale:	
Baseline score	0.49 ± 0.79 (0–3) [0.0, 0.0 and 1 for 25th, 50th (median) and 75th Percentiles]
After procedure score	0.50 ± 0.83 (0–3) [0.0, 0.0 and 1 for 25th, 50th(median) and 75th Percentiles]
Final score	0.38 ± 0.95(0–6) [0.0, 0.0 and 0.25 for 25th, 50th(median) and 75th Percentiles]
National Institutes of Health Stroke Scale:	
Baseline score	1.08 ± 1.60 (0–7)
After procedure score	1.10 ± 1.66 (0–7)

Data are presented as mean ± SD or n (%).

Table 2
Procedural and follow up data of patients who underwent endovascular procedure.

Characteristics	N (%)
Treated Artery:	
Left Carotid	35(34.3%)
Right Carotid	37(36.3%)
Bilateral Carotid*	30(29.4%)
Total combined lesions of cerebral circulation:	
Left vertebral	32 (31.3%)
Right vertebral	18 (17.6%)
Bilateral vertebral	17 (16.6%)
Bilateral Carotid†	50 (49.1%)
Middle cerebral artery stenosis	9 (8.8%)
Anterior cerebral artery stenosis	6 (5.8%)
Posterior cerebral circulation stenosis	7 (6.8%)
Concomitant peripheral arterial lesion:	
Renal artery stenosis	12 (11.7%)
Subclavian artery stenosis	9 (8.8%)
Iliac artery stenosis	7 (6.8%)
Periprocedural complication:	
Hematoma	3 (2.9%)
Bradycardia	3 (2.9%)
Ischemic Stroke	1 (1%)
Follow up results	
Restenosis	4 (3.9%)
Recurrent cerebrovascular accident:	
Transient ischemic attack	4 (3.9%)
Ischemic stroke	1 (1%)
Coronary artery disease	5 (4.9%)
Death	3 (2.9%)
Follow up(months)	24.5 ± 14.1 (6-50)

* Significant carotid arteries stenosis.
† Significant and non-significant carotid arteries stenosis; Data are presented as mean ± SD or n (%).

most frequent (80.39%) and the related baseline mRS and NIHSS scores were 0.49 ± 0.79 (range, 0–3) and 1.07 ± 1.6 (range, 0–7), respectively. Demographic and basic variables of the patients were summarized in Table 1. Right ICA was the most frequent (36.27%) treated site; whereas, in 29.4% of patients, treatment was performed for both ICAs. The frequency of the concomitant lesions at the other main vessels supplying brain circulation (carotid or vertebral arteries), except of the target vessel, were 67 (65.7%). The concomitant involvement of the peripheral artery disease was found in 28 (27.45%); renal artery stenosis was the most frequent (11.7%). All patients underwent CAS, whereas the periprocedural complication rate was 5.8%; access-site local hematoma and bradycardia during CAS occurred each in 2.94% of patients. Only did one case (1%) suffered acute ischemic Stroke during the wiring procedure: acute hemiparesis of the left side and speech disturbance were observed during procedure in an 81-year-old man with the history of diabetes and hypertension. We found a small emboli having occluded one of the lenticostrait branches of the right middle cerebral artery. Intra-arterial recombinant tissue plasminogen activator was immediately injected to the target vessel and the occlusion resolved completely. He was followed up for 30 months without any disability. No other complications such as loss of consciousness, cardiac dysrhythmia or significant arterial oxygen desaturation were found during

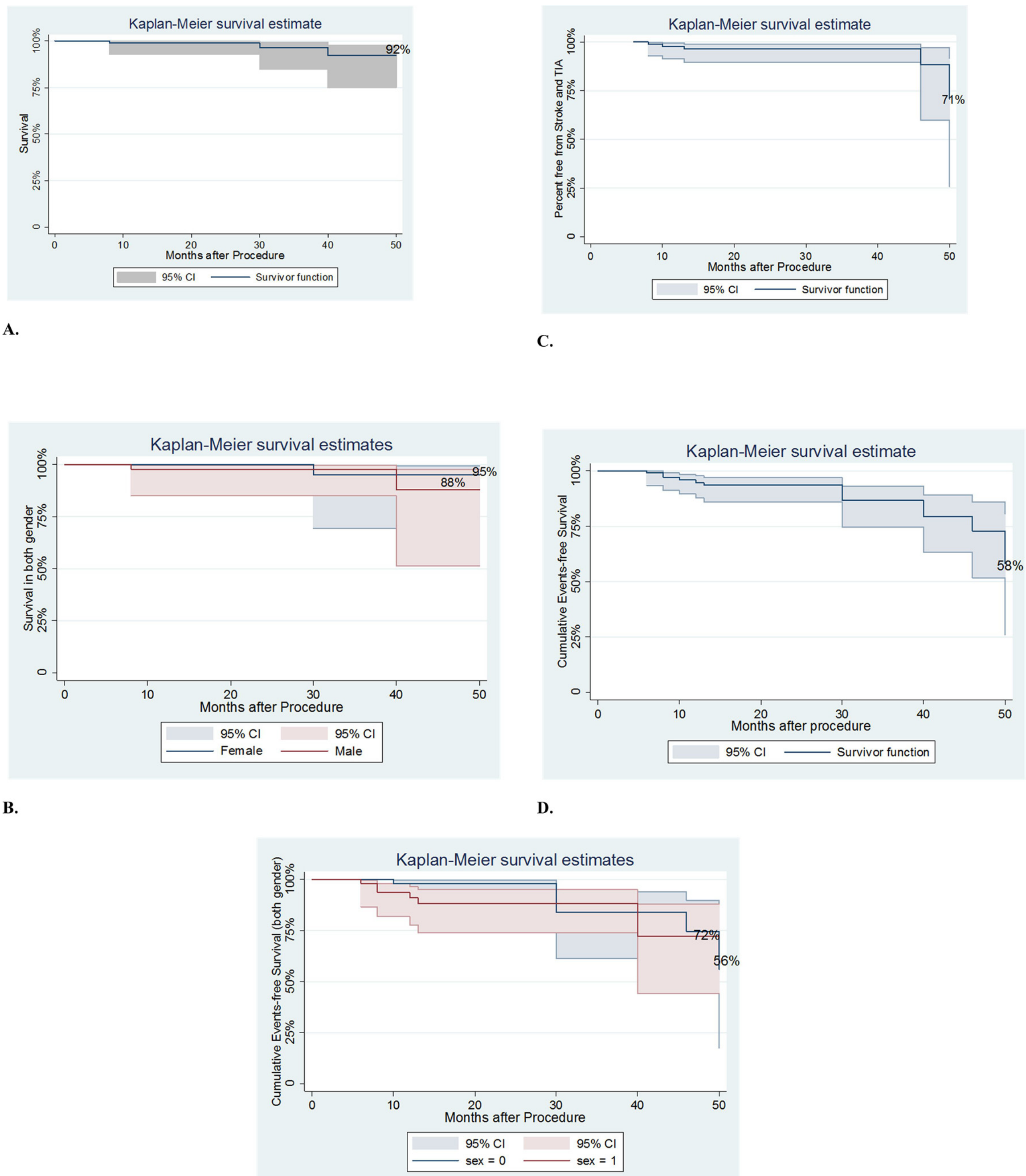

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Fig. 2. Kaplan-Meier curve of cumulative events-free survival rate at 50 months in all patients with 95% confidence interval (CI); **A.** Survival rate in all patients; **B.** Survival rate with considering gender segregation; **C.** Stroke and TIA - free survival in all patients; **D.** Event – free (stroke, TIA, CAD and death) survival rate of all patients; **E.** Event – free (stroke, TIA, CAD and death) survival rate of all patients considering gender segregation.

the procedure. Procedural and follow up data are summarized in Table 2. The procedural (technical) success rate was 100% and the mean post procedure mRS and NIHSS scores were 0.5 ± 0.82 (range, 0–3) and 1.09 ± 1.66 (range, 0–7), respectively. There was no significant difference between pre and post procedure scores, neither in NIHSS nor in mRS. Also, mRS alteration during the study follow up was not statistically significant. In the follow up period, restenosis occurred in 3.9% (4/102) of the patients after a mean of 21.5 (range, 14–24 months). Based on Setacci et al. criteria [28], three of these cases had mild degree restenosis and only did one have moderate degree restenosis. Medical treatment was successfully implemented in all of these patients. The proportion of recurrent cerebrovascular accident was 4.9% (5 cases); while, TIA occurred in 3.9% (4 cases) at a mean duration of 23.7 ± 13.8 months and IS happened in 1% (1 case) of patients on the 6th follow-up month. All of these incidents occurred in regions other than the treated vessels. Also, 5 patients (4.9%) experienced CAD at a mean duration of 21.4 ± 15.4 months. The proportion of fatal recurrent cerebrovascular accidents was 2.9% (myocardial infarction in 2 and IS in one patients) with mean of 15.3 months (6–26). The mean duration of patient event-free survival was 20 months (Fig. 2). Kaplan-Meier curves showed survival rate of all study patients is equal to 92% (95% CI: 75%–98%) in 50 months follow up period. Also they demonstrated the rate of Event - free survival (stroke, TIA, CAD and death) and stroke and TIA – free survival of all patients are equal to 58% (95% CI: 26%–81%) and 71% (95% CI: 26%–91%) respectively. In addition, they showed the rate of Cumulative Event - free survival (stroke, TIA, CVD and Death) of Male and Female patients are equal to 72% (95%CI: 44%–89%) and 56%(95%CI: 18%–82%) respectively in 50 months follow up period.

Clinical follow-up was performed for all patients while 75.4% of them completed at least a 1-year follow-up. The mean final mRS score was 0.38 ± 0.95 (range, 0–6) while all of survivors (100%) had favorable outcome (mRS 0–2). The final mRS was significantly lower than baseline mRS ($P = 0.01$)

4. Discussion

This prospective study showed that proper administration of interventional endovascular angioplasty (performing CAS) in the elderly with symptomatic carotid stenosis could be considered as a safe and tolerable method for preventing the stroke recurrence. Furthermore, the lower recurrence incidence of cardiovascular events, restenosis and mortality throughout the long-term follow up period of these patients is an evidence of this approach being durable and beneficial.

Secondary prevention of stroke in the elderly with symptomatic carotid stenosis has been associated with numerous challenges. In one hand, the multiple associated comorbidities of this disease have made it difficult to access an ideal medical treatment. On the other hand, inappropriate physical capacities of these patients have made it impossible to use the conventional surgical interventions used in other age ranges [4,29]. Furthermore, although advanced age and its associated comorbidities is associated with limited life expectancy in the octogenarian, most clinicians tend to select efficacious secondary prevention strategies to avoid stroke recurrence. Higher probability of stroke recurrence and associated morbidity and mortality and also the immense burden the affected patients impose on the society turn this modality into a valuable yet difficult opportunity. Nevertheless, unfortunately there is no strong evidence confirming a selective medical approach in this regard [4,30].The risk of carotid endarterectomy is high in octogenarian [31,32]; on the other hands, CAS has been reported to be associated with higher stroke incidence [33].

SAPPHIRE trial provided valuable answers. Based on this study, in the elderly with severe symptomatic carotid stenosis and simultaneous comorbidities, the more advanced the age, the more undesirable results with both CAE and CAS approaches [34].

Rango et al., in a retrospective study, reviewed 10 year results from carotid revascularization (CAE and CAS) in patients older than 80 years and compared the perioperative and log-term outcomes. Perioperative stroke/death following stenting was reported 6.2% vs. 4.8% for CAS vs. CEA. In addition, throughout a 36 month follow up, 5-year Kaplan-Meier stroke-free was reported in 49.4% of the cases. The authors concluded that perioperative stroke/death was lower in CAS and invasive surgical approaches are not recommended, especially in the female and asymptomatic patients [35].

The results of the CREST, CAPTURE and SAPPHIRE trials revealed that advanced age is a negative prognostic factor for the incidence of stroke/death in CAS patients [25,34,36,37]. In contrast, some other studies suggest that there is no significant difference in CAS outcomes in the octogenarian compared to the younger counterparts [28,37–39].In a meta-analysis, Antoniou et al. evaluated 44 studies reporting data on 512,685 CEA and 75,201 CAS patients. They concluded that CAS has an increased risk of adverse cerebrovascular events in elderly patients but mortality is equivalent to younger patients. Also, carotid endarterectomy is associated with similar neurologic outcomes in elderly and young patients, at the expense of increased mortality [40]. In a study by Dzierwa and colleagues, the results of tailored-CAS in patients older than 75 years old and younger patients were compared. In symptomatic patients aged ≥75 years, 30-day stroke and death rate was 7% versus 1.9% in symptomatic patients aged < 75. It was concluded that symptomatic elderly is a group of highest CAS risk and the use of “tailored CAS” algorithm does not equalize CAS risk in this patient group [41]. In another study conducted by Werner and associates on CAS patients, the authors suggested that despite achieving a 99.2% total success rate for stenting, intra-hospital stroke/death ratio was 4 times higher in the octogenarian compared to the younger patients. Later, the authors concluded that anatomical conditions and octogenarian age were associated with an increased rate of neurologic adverse events during CAS [42].

In the present study, despite a high primary success rate (100%) for the procedure, with a mean of 24.5-month follow-up, the mortality rate was 2.9% in our patients (1% due to stroke recurrence and 1.9% due to CAD) in about the mean of 15.3 months. The median patient event-free survival was 20 months. These findings indicate an acceptable morbidity and mortality rate in this age range which could suggest this preventive approach in the octogenarians.

Chaturvedi et al., in the CAPTURE 2 study, evaluated periprocedural risk predictors for stroke and suggested that, for their overall cohort, death/stroke rate was 3.3% and stroke rate was 2.7% (0.8% major and 1.9% minor). Death/stroke rates were significantly higher for octogenarians than non-octogenarians (4.5% vs. 3.0%) as were stroke rates (3.8% vs. 2.4%). Symptomatic status, embolic protection device dwell time, and lesion length were risk predictors for periprocedural stroke in octogenarians. Octogenarians were also found to be of a higher periprocedural events incidence [43]. Grant and associates, in a study on a large clinical series of CAS in the elderly, found that the overall 30-day incidence of stroke and death was 2.8% (11/389). The cumulative incidence of major cardiovascular events (stroke, death, or myocardial infarction) during that time period was 3.3% (13/389). Authors later concluded that octogenarians can safely undergo CAS with stroke and death rates comparable to younger patients. The key to achieve these excellent results is CAS to be performed by high volume, experienced operators who exercise restraint regarding patient selection [44].

In the current study, the incidence of stroke throughout the procedure was only 1%. Furthermore, the incidence of recurrent CVA was 4.9% (TIA 3.9% and IS 1%) all of which happened after a few months (mean of 23.7 months) and in the blood supply region other than the artery having undergone angioplasty. Furthermore, CAD incidence was 4.9% with a mean of 21.4 months.

In the prospective study of CaRESS, Zarins et al. evaluated four-year outcome in patients with symptomatic carotid stenosis. The authors found that the risk of death/stroke or death/stroke/MI appears to be higher following CEA than CAS among patients < 80 years of age, yet there is no statistically significant relationship between death, stroke, or MI among octogenarians [45]. Linfante and associated, in a retrospective study conducted on 24 patients older than 80 years, evaluated the results of CAS and suggested that success rate was 100% with residual stenosis of < 20%. In 30 day follow-up, there was 4.2% non-Q wave MI, 4.2% TIA, and 4.2% femoral occlusion in the symptomatic group [46]. Some studies suggest that performing CAS using embolic-protection devices (EPDs) could be associated with more confidence and turn CAS into a comparable method with CAE [34]. Nonetheless, the use of this technique could be associated with some risks such as spasm or dissection [47]. One of the characteristics of our study was that all interventions and angioplasties were performed without using any EPD.

One of the other concerns in CAS of the elderly is elongation and calcification of aortic arch and also carotid tortuosity [48] which demands the expertise of the interventionist and proper case selection. There are also other solutions to this concern. For instance, in a primary study by Christopoulos et al., the authors suggested that the trans-cervical approach with flow reversal during the insertion of the protecting filter allows CAS with minimal interruption of cerebral circulation and is simple and safe in patients unsuitable for CEA and transfemoral CAS for anatomic reasons [49]. In the present study, selection of the patients was performed using the same criterion and patients were followed up for almost a long period. Re-stenosis (mostly mild re-stenosis) rate of 3.9% was observed which, in association with other findings, also indicates that this stroke prevention approach is of appropriate efficacy and durability. Furthermore, access-site local hematoma and bradycardia during CAS each occurred in only 2.94% of the cases and only one intra-procedure stroke happened which was treated appropriately and promptly.

5. Limitations

The current study could be affected by the presence of limitations i.e. single-center study, single arm study, open label assessment, lack of control group and restriction of the follow-up period.

6. Conclusion

All these findings might be indicative of the fact that CAS is an effective method for secondary prevention of IS in octogenarians with symptomatic carotid artery stenosis. Considering the low rate of the peri-procedural complication as well as the restenosis during more than 2 years follow up, demonstrates this method could be safe, effective and relatively durable for these patients.

Final message

CAS seems to be a safe and relatively durable method for secondary prevention in IS following symptomatic carotid artery stenosis in octogenarians.

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Competing interest statement

Authors declare no conflict of interest in this original article.

Statement of authors' contribution to this manuscript

R Mohammadian and **E Sharifipour** designed the study protocol. **R Mohammadian** contributed to the conduction of trial, interpretation of results, and preparation of the manuscript. **A Taheraghdam** contributed to the conduction of trial. **E Sharifipour** and **S Golzari** contributed to the conduction of trial, interpretation of results, and writing of the manuscript. **R Mansourizadeh**, **D Altafi**, **G Fattahzadeh**, **P Sariaslani**, **P Yousefshahi** and **K Ebrahimzadeh** contributed to the conduction of trial and interpretation of results. **M Vahedian** contributed to the interpretation of results, and preparation of the manuscript.

Data sharing

There is no data sharing for this original article.

Ethical standards and patient consent

We declare that the current study has been approved by the ethics committee of Tabriz University of Medical Sciences and has therefore been performed in accordance with the ethical standards of 1964 Declaration of Helsinki and its later amendments. Also, we declare that written informed consents were obtained from all patients prior to their inclusion in this study.

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