Comparison of Clinical and Radiological Outcome of Carotid Angioplasty and Stenting after Direct Navigation Versus Exchange Methods: a Randomized Clinical Trial

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Abstract

Background—The purpose of this study was to compare the frequency of microembolic brain infarcts after direct navigation method versus exchange method in carotid artery stenting and vertebral artery origin angioplasty.

Methods and Material—This is a prospective study conducted at Shiraz University of Medical Sciences in southern Iran. Consecutive patients undergoing "carotid angioplasty and stenting" and "vertebral artery origin stenting" were randomly assigned into two groups with "direct navigation method" and "exchange method." Subsequently, postprocedural magnetic resonance imaging (MRI) including diffusion weighted imaging and apparent diffusion coefficient were obtained within the first 24 hours after completion of the procedure.

Results—In total, 89 patients were recruited (67% male, mean age: 72 years). Cases comprised of 38 left internal carotid arteries (ICAs), 38 right ICAs, 6 left vertebral artery origin, and 7 right vertebral artery origin. Forty patients underwent exchange method, while 49 underwent direct navigation method. There was only one clinical stroke that occurred in "exchange method" group. Fifteen patients (37.5%) in exchange group and 23 patients (46.9%) in direct navigation group developed diffusion restricted lesions. In exchange group, 13 patients (32.5%) had at least one diffusion restricted lesion ipsilateral to the target vessel, and three patients (7.5%) had at least one diffusion restricted lesion contralateral to the target vessel. In direct navigation group, these measures were 19 (38.8%) and 9 (18.4%). However, no statistically significant intergroup differences were observed. The only significant difference was bilateral infarct percentile, which was more common in the direct navigation method (0.032).

Conclusion—Diffusion restricted lesions were more common in the direct navigation method, both ipsilateral and contralateral to the target vessel, and in both carotid and vertebral artery study subgroups. However, differences were not statistically significant.

Keywords

Stroke; ischemic; carotid artery stenting; microembolic brain infarcts; diffusion restriction

Introduction

Stroke is a worldwide critical health problem [1]. Large arterial stenosis is one of the treatable causes of ischemic stroke [2]. Carotid artery stenting (CAS) and vertebral artery origin stenting (VAOS) have been increasingly applied as an alternative to invasive carotid endarterectomy (CEA) in cases with cervical artery stenosis [3,4]. Nonetheless, transient ischemic attack (TIA), ischemic strokes, intracerebral hemorrhage (ICH), myocardial infarction, hemodynamic depression, and death are the most serious complications of these procedures [5]. Micro embolic brain infarcts have been considered as a major concern for CAS and their detrimental effects

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on cognition are well-established [6]. Although usually silent, symptomatic microembolic brain infarcts are present in 2–17% of such patients [7]. Difficult aortic arch, unfavorable supra-aortic takeoff, pre- or poststenotic vascular tortuosity and acute angle between parent and offspring arteries are among the factors. These pose special challenges during the advancement of guiding catheters near carotid bifurcation, and consequently, increase the rate of symptomatic and asymptomatic brain infarcts [8].

There are two methods for advancement of guiding catheter. In "direct navigation method," guiding catheter is directly engaged to supra-aortic arteries and advanced on a hydrophilic wire. Meanwhile, the "exchange method" is based on using a stiff wire anchored to external carotid artery (ECA) for further advancement of guiding catheter [9]. There are pros and cons regarding these techniques [10,11]. In this prospective study, the risk of postprocedural strokes and silent brain infarcts was compared between direct navigation and exchange methods.

Methods and Materials

Patients and settings

This study was conducted from January 2016 to January 2017 at Kowsar Hospital, a major referral center for stroke patients in southern Iran, affiliated to Shiraz University of Medical Sciences (SUMS). The study consists of two subgroups. In CAS subgroup, we included symptomatic patients with ischemic stroke/TIA with greater than 70% stenosis of the ipsilateral internal carotid artery (ICA), as well as asymptomatic patients with more than 80% stenosis of ICA, who were at standard or high risk for CEA. The severity of stenosis was calculated according to the North American Symptomatic CEA Trial criteria [12]. VAOS was performed for patients with greater than 70% stenosis of vertebral artery origin and contralateral occlusion, stenosis or atresia, and posterior circulation stroke or TIA, need for coronary artery bypass graft, bilateral anterior circulation disease, and ipsilateral posterior inferior cerebellar artery TIA/stroke with no other embolic source [3]. The stenosis in vertebral artery origin was verified by computed tomography angiography or magnetic resonance angiography before stenting. Patients with ICH, lacunar stroke, vasculitis, arterial dissection, and fibromuscular dysplasia were excluded. Patients with Modified Ranking Scale of equal or greater than 3 after a stroke were also excluded.

The trial was approved by Medical Ethics for Researches and Institutional Review Board (95-00-00-12978) affiliated to SUMS. Each patient was individually informed about the process of experiment and a written informed consent was obtained.

Patients were pretreated with clopidogrel 75 mg/day and aspirin 80 mg/day. During the procedure, the patients received heparin 80 units/kg of body weight after successful femoral artery puncture to maintain an activated clotting time longer than 250 seconds.

Patients were randomly assigned into direct navigation method or exchanging method using block randomization. In direct navigation method, 7F right Judkins guiding catheter, Zenyte (Asahi Intecc, Aichi, Japan) or Launcher (Medtronic, MN, USA) was used to engage supra-aortic arteries and advanced on a 0.035 hydrophilic wire (Glidewire, Terumo, NJ, USA). The guiding catheter was parked close to common carotid artery (CCA) bifurcation or vertebral artery origin. In exchanging technique, a 5F diagnostic catheter (Glidecath JB1, Terumo, NJ, USA) was advanced into the ipsilateral ECA or superior carotid artery (SCA) using a 0.035 hydrophilic wire. Afterward, the hydrophilic wire was withdrawn and substituted with a stiff (0.038, 260 cm) wire (Emerald, Cordis, Baar, Switzerland). Next, the 5F catheter was also withdrawn and a 7F guiding catheter was advanced (as above) on the anchored stiff wire in the CCA or SCA for the purpose of stenting.

Distal embolic protection devices such as Filter EZ (Boston scientific, Marlborough, MA, USA) or Spider X (Medtronic, MN, USA) were used for carotid stenting. Self-expanding stents such as Wallstent (Boston scientific) or Cristalloideale (Medtronic, MN, USA) were used for carotid stenting.

For VAOS, balloon-mounted drug eluted stents were deployed without protection device. Pre- and/or postdilation were performed in suitable cases. Postdilation was done with the same balloon to flare the proximal part of the stent in SCA. Coronary stents such as Orsiro (Biotronick, Bülach, Switzerland), Xience (Abbott, Chicago, IL, USA), or Promus (Boston Scientific, Marlborough, mA, USA) were used for VAOS.

All patients were followed up over the next several days and were thoroughly evaluated by the interventionist neurologist for any potential ischemic or hemorrhagic stroke and any other peri- and postprocedural complications immediately after the procedure, as well as on days 1, 7, and 30.

Data collection

Postprocedural magnetic resonance imaging (MRI) was taken within the first 24 hours after completion of the

procedure using Simens MR 1.5 Tesla machine. The studied MRI sequences included 5.5–6-mm slice thickness axial diffusion weighted imaging (DWI), and apparent diffusion coefficient (ADC) with TR/TE: 100/1000, flip angle: 90.

Maximum spatial gradient of 3.3 Tesla/meter and a maximum whole body averaged specific absorption rate of 2.0 W/kg for 15 min of MRI were considered for all procedures.

In order to determine any new ischemic lesion during the trial time window and to differentiate them from old ones, only lesions with diffusion restriction (hyperintense in DWI and hypointense in ADC) were recognized as to be relevant to the outcome interpretation. Presence or absence of new lesions, number of lesions, the largest existing diameter of a lesion, accumulated lesion surface area, and the average surface area (accumulated lesion surface area/ number of lesions) were measured. Location (cortical versus subcortical) and laterality (ipsilateral versus contralateral to the target vessel) were also recorded. In order to measure the lesion surface area, two perpendicular lesion diameters matched with the largest diameter of lesions were measured by means of computerized tools from Infinite PACS software (Infinite Healthcare, Seoul, South Korea), assuming elliptical geometry of cerebral infarctive lesion studied in the literature [12]. In an attempt to ensure acuity of the results, images were studied by two independent neuroradiologists who were blinded to the patients' clinical status and grouping, and discrepancies were later reviewed and reconciled.

Outcome definition

Primary clinical outcome was defined as development of any new stroke event after CAS or VAOS. Secondary clinical outcomes were ischemic stroke ipsilateral or contralateral to the target vessel. All clinical outcomes in one month were ascertained.

Primary radiologic outcome was the presence of any DWI restricted lesion, while the presence of DWI restricted lesions ipsilateral or contralateral to the target vessel, number of these lesions and surface area of the lesions were considered as the secondary radiologic outcomes.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous values are presented as mean ± SD and categorical variables as frequency and percentage.

Fisher's exact test or Student's t-test were used when appropriate.

Results

In this randomized trial study, 89 patients were recruited (67% male, age: 72.09 ± 8.1). Thirty-eight LICA, 38 RICA, 6 LVAO, and 7 RVAO were stented. Regarding major risk factors of atherosclerosis, 69 (77.5%), 39 (43.8%), 35 (39.3%), and 31 (34.8%) of patients had hypertension, hyperlipidemia, smoking and diabetes mellitus, respectively. Preprocedural stenosis and residual stenosis were 78.6% ± 17.8% and 17.8% ± 14.6%. Seventy-four percent of all lesions were ulcerated and 48% calcified.

In total, 40 patients underwent exchange method and 49 patients underwent direct navigation method. After the stenting procedures, 38 patients (42.7%) had diffusion restricted lesions. In DWI+ patients, on average each patient had 1.7 ± 2.7 lesions. Largest lesion diameter, accumulated lesion surface area, and average surface area were 10.8 ± 7.5, 99.2 ± 217, and 52.43 ± 211, respectively. In these patients, 15.7% of lesions were cortical and 84.3% were subcortical. Meanwhile, 77.2% of lesions were ipsilateral and 22.8% were contralateral to the target vessels.

Percentage of DWI + patients, number of lesions, lesion surface area, average surface area, largest lesion diameter, percentage of cortical infarcts, and percentage of contralateral infarct were not significantly different between direct navigation method and exchange method (Table 1). The percentile of contralateral, ipsilateral, and bilateral infarct was defined as the percentage of patients with at least one infarct in the corresponding areas. Ipsilateral infarct percentile and contralateral infarct percentile were not significantly different between the two methods. Bilateral infarct percentile was observed in one patient in exchange method (2.5%), and eight patients in direct navigation method (16.39%). This difference was statistically significant ($P = 0.032$).

CAS subgroup

Seventy-six patients were assigned in the CAS subgroup (67.1% male, age: 72.6 ± 8); 38 LICA and 38 RICA were stented. EPD was used in 64 (84.2%) of patients. Also, predilation was performed in 30 (39.5%) patients and postdilation in 64 (84.2%) patients.

There was no significant difference between two groups regarding mean age, gender, major risk factors of atherosclerosis, hemoglobin concentration, platelet count and

Table 1. Comparison of MRI derived factors describing microinfarcts in the general population

	CAS + VAOS (N = 89)		
	Direct navigation method N = 49	Exchange method N = 40	P value
Percent of DWI + patients	61.22%	47.5%	0.14
Number of lesions (n)	1.89 ± 3.28	1.32 ± 2.09	0.34
Lesion surface area (mm^2)	93.38 ± 99.71	71.18 ± 42.67	0. 42
Average surface area (mm^2)	22.91 ± 14.42	21.7 ± 9.2	0.77
Largest lesion diameter (mm^2)	11.5 ± 9.29	9.5 ± 2.71	0.34
Cortical infarct (%)	15.9%	15.47%	0.95
Contralateral infarct (%)[†]	33.5%	16.66%	0.19
Contralateral infarct percentile[††]	22.5% (N = 11)	10% (N = 4)	0.10
Ipsilateral infarct percentile[††]	55% (N = 27)	40% (N = 16)	0.11
Bilateral infarct percentile[††]	16.39% (N = 8)	2.5% (N = 1)	0.032

[†] The percentage of contralateral infarcts indicates the ratio of infarct numbers contralateral to the target stented vessel in the form of percentage.

[††] The percentile of contralateral, ipsilateral, and bilateral infarct indicates the number of patients with at least one infarct in the corresponding areas.

Table 2. Comparison of MRI derived factors describing microinfarcts in CAS study subgroup

	CAS (N = 76)		
	Direct navigation method N = 43	Exchange method N = 33	P value
Percent of DWI + patients	65.11% (N = 28)	57.57% (N = 19)	0.33
Number of lesions (n)	2 ± 3.42	1.6 ± 2.19	0.52
Lesion surface area (mm^2)	97.85 ± 103.66	71.18 ± 42.67	0.35
Average surface area (mm^2)	23.08 ± 14.9	21.7 ± 9.2	0.75
Largest lesion diameter (mm^2)	13.16 ± 10.42	9.86 ± 2.58	0.17
Cortical infarct (%)	10%	19.6%	0.16
Contralateral infarct (%)[†]	30.35%	16.66%	0.28
Contralateral infarct percentile[††]	21% (N = 9)	12.12% (N = 4)	0.23
ipsilateral infarct percentile[††]	60.5% (N = 26)	48.5% (N = 16)	0.20
Bilateral infarct percentile[††]	16.3% (N = 7)	3% (N = 1)	0.064

[†] The percent of contralateral infarcts indicates the ratio of infarct numbers contralateral to the target stented vessel in the form of percentage.

[††] The percentile of contralateral, ipsilateral, and bilateral infarcts indicates the number of patients with at least one infarct in the corresponding areas.

creatinine level, mean pre-procedural stenosis, lesion ulceration, lesion calcification, mean residual stenosis, procedural time and rate of pre-dilation, post-dilation, and EPD usage (all P values >0.05).

In this subgroup, 33 patients (46%) had diffusion restricted lesions, while 79% of the lesions were ipsilateral and 21% were contralateral to the target carotid. There was only one clinical stroke, which occurred after LICA stenting by direct navigation method in occipital lobe ipsilateral to the stented carotid artery. Due to inconsiderable number of clinical strokes, statistical comparison was not possible.

In patients with exchange method, 19 patients (57.57%) developed diffusion restricted lesions. Meanwhile, 28 patients (65.11%) were DWI+ in the direct navigation method group. There was no statistically significant difference between these groups (P = 0.33). Table 2 shows there was no statistically significant difference between the two groups regarding the presence of diffusion restricted lesions, number of lesions, the largest lesion diameter, the accumulated lesion surface area , and the average surface area.

Considering the laterality to target vessel, in "exchange method" 16 patients (48.5%) had at least one diffusion restricted lesion ipsilateral to the target vessel and four patients (12.12%) had at least one diffusion restricted lesion contralateral to the target vessel, and one patient in both ipsilateral and contralateral areas (3%). In direct navigation method, these measures were 26 (60.5%), 9 (21%), and 7 (16.3%), respectively. The differences between the two groups were not significant (Table 1). The mean number of contralateral lesions in exchange method was 0.4 ± 0.9 (16.6% of total lesions), and in direct navigation method 1.2 ± 1.9 (30.3% of total lesions). This difference was not significant (P = 0.13).

VAOS subgroup

In VAO subgroup, 13 patients (69.2% male, age: 69 ± 8.3) were assigned amongst which 6 LVAO, and 7 RVAO were stented.

In the exchange method group (N = 7), no infarcts were detected after stenting. While there were two patients with new infarcts after the procedure (33%) in the direct navigation group, but was not statistically significant (P = 0.19). The comparison of other factors derived from DWI studies was not possible due to lack of new infarction in the exchange method group. Table 3 shows DWI derived microinfarct features in this study subgroup. A total of 60% of the lesions (three out of five total lesions) were contralateral to the targeted vessel in the VAOS study subgroup. All the lesions had occurred after

Table 3. Comparison of MRI derived factors describing microinfarcts in vertebral stenting study subgroup

	VAOS(N = 13)		
	Direct method $N = 6$	Exchange method $N = 7$	P value[†††]
Percent of DWI + patients	33% ($N = 2$)	0% ($N = 0$)	0.19
Number of lesions (n)	0.83 ± 1.32	NA	-
Lesion surface area (mm^2)	48 ± 15	NA	-
Average surface area (mm^2)	21 ± 12	NA	-
Largest lesion diameter (mm^2)	9.2 ± 4.5	NA	-
Cortical infarct (mm^2)[†]	33%	NA	-
Contralateral infarct (mm^2)[††]	60%	NA	-
Contralateral infarct (mm^2)[††]	33% ($N = 2$)	NA	-
ipsilateral infarct percentile[††]	16% ($N = 1$)	NA	-
Bilateral infarct percentile[††]	16% ($N = 1$)	NA	-

[†]The percent of contralateral infarcts indicates the ratio of infarct numbers contralateral to the target stented vessel in the form of percentage.

[††]The percentile of contralateral, ipsilateral and bilateral infarct indicates the number of patients with at least one infarct in the corresponding areas.

[†††]Due to the absence of microembolic signals in the exchange method, statistical analysis could not be performed.

LVAO stenting in direct navigation method, even though considerable, was not possible to be analyzed statistically.

Discussion

The biggest drawback in endovascular treatments of cervicocephalic large arterial disease is higher rate of minor strokes in comparison with CEA [13]. The frequency of microembolic infarcts after CAS is reported to be 20–55% [6]. Although the rate of symptomatic presentation of these infarcts ranges 2–17%, their detrimental effects on cognition are well established [6,7]. Any technical modification that can decrease the rate of postprocedural symptomatic or asymptomatic brain infarcts is encouraged to be employed by the interventionists.

In the current study, diffusion restricted lesions were more common in the direct navigation method both ipsilateral and contralateral to the target vessel and in both carotid and vertebral artery study subgroups, but the differences were not statistically significant. The only significant difference was bilateral infarct percentile, which was more common in direct navigation method.

Although exchange method may facilitate the advancement of guiding catheter on an ECA-anchored stiff wire, it lengthens the procedure, and in turn increases the risk of embolization due to the application of a thrombogenic wire [14]. Retrograde embolization through ECA to brain was also presumed [14]. Some interventionists have used guiding sheath instead of guiding catheter [9], yet its disadvantages are the increase in procedural time, the risk of parent artery dissection and anatomical bifurcation change.

We randomized our patients regardless of vessel anatomy. However, some interventionists advocate this factor in patient selection. Exchange method is favorable in treatment of patients with tortuous or aneurismal aorta, elongated aortic arch, poor angulation of innominate, LCCA or LSCA or tortuosity of CCAs or SCAs. Occlusion or severe stenoses of ECA or SCA after VAO are indications for direct navigation method [15–17].

The presence of diffusion restricted lesions contralateral to the target vessel is generally due to embolization from arch of aorta. The presence of atheromatous plaques and particularly thrombus in the arch of aorta increase the risk of embolization during CAS. The arch of aorta CT angiography or trans-esophageal echocardiography might be useful in patient selection for CAS [17]. Complex aortic arch anatomy is associated with increased risk of embolic lesions [15] and clinical complications [16].

The most important shortcoming of our study was loss of volumetric evaluation of the DWI lesions. Although the presence or absence of lesions, number of lesions, and largest lesion diameter can be obtained with nonvolumetric method (naked-eye method), accumulated or average surface area could have been evaluated, and we used volumetric assessment.

Acknowledgment

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