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Chronic oral anticoagulant therapy in carotid artery stenting: The un-necessity of perioperative bridging heparin therapy

Rodolfo Pini, Gianluca Faggioli *, Raffaella Mauro, Sara Gallinucci, Antonio Freyrie, Mauro Gargiulo, Andrea Stella

Vascular Surgery, Department of Specialistic Surgeries and Anesthesiological Sciences, University of Bologna, Policlinico S. Orsola, via Massarenti 9, 40138 Bologna, Italy

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ABSTRACT

Introduction: Chronic oral anticoagulant therapy (OAT) is of widespread use, and usually its management in patients undergoing carotid artery stenting (CAS) is through perioperative bridging heparin therapy. Aim of the present study is to analyze a single center experience of CAS in patients maintaining OAT without perioperative bridging heparin therapy.
Materials and methods: A retrospective evaluation of consecutive patients submitted to CAS was performed. Clinical anatomical characteristics and chronic OAT were evaluated to find a correlation with stroke, death, myocardial infarction and bleeding from the access site by Chi-square, Fisher's tests and regression analysis.
Results: 502 CAS were performed in a 5-year period. Twelve (2.4%) strokes, 1 (0.2%) death, no myocardial infarctions and 4 (0.8%) access site bleeding occurred in the perioperative period. In the overall population the presence of type 3 or bovine aortic arch was associated with stroke (5.5% vs. 1.5% $p = 0.02$), and preoperative neurological ischemic symptoms were correlated with higher incidence of the composite event of stroke/death (4.8% vs. 1.4%, $p = 0.05$). Twenty patients (4.0%) under chronic OAT were submitted to CAS without perioperative bridging heparin therapy with no complications. Overall, patients under OAT had no significantly different outcome compared with patients without OAT.
Conclusions: OAT without perioperative bridging heparin therapy is safe and effective. This data could be useful in the management of patients with chronic OAT submitted to CAS.

Introduction

Approximately 4 million patients are currently receiving oral anticoagulant therapy (OAT) to prevent thromboembolism from atrial fibrillation, mechanical heart valves or deep vein thrombosis in western countries [1]. The management of patients in OAT undergoing surgical procedures requires usually a perioperative bridging heparin therapy, with substitution of OAT by heparin infusion few days before the surgical procedure and perioperatively [2].

The management of this bridging therapy causes, patients discomfort, costs - ranging from 672 $ to 5196 $ for patient [3–5] - and risks of thrombosis/hemorrhage due to an incorrect dosage or adverse heparin reaction, even with low-molecular-weight and with unfractionated heparin [6–9]. OAT patients candidate to endovascular procedures, usually undergo to perioperative bridging heparin therapy, in order to prevent possible bleeding complications, however some authors report safe and effective results in percutaneus coronary interventions or pacemaker/defibrillator implantation without interrupting OAT thus avoiding the necessity of heparin bridging therapy [10–13].

Carotid artery revascularization by stenting (CAS) is nowadays an alternative to standard surgical therapy [14]; in this setting, OAT patients are usually managed with bridging heparin therapy, but there are no data establishing the effective value of this management compared with unstopped OAT. We have therefore reviewed a single center experience of CAS in patients with unstopped OAT, in order to assess its safety and effectiveness.

Materials and methods

Patients

All consecutive CAS performed in a five years period in a single centre were retrospectively reviewed. From 2005 to 2008 CAS were chosen as an alternative to CEA according patients' clinical and anatomical characteristics ("hostile neck" or pulmonary or cardiac diseases) or surgeon's experience in endovascular carotid artery revascularization. The first operator for all the CAS procedures were an expert surgeon (FG) with more than 500 procedures performed. From early 2009 CAS indications were

Abbreviations: CAS, carotid artery stenting; OAT, oral anticoagulant therapy; MI, myocardial infarction.

* Corresponding author at: Chirurgia Vascolare, Università di Bologna, Policlinico S. Orsola, Via Massarenti 9, 40138 Bologna, Italy. Tel.: +39 051 6364244; fax: +39 051 6363288.
E-mail address: gianluca.faggioli@unibo.it (G. Faggioli).

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modified according SVS recommendations: endovascular carotid revascularization was performed in symptomatic with high surgical or anesthesiologic risk patients [14,15]. Clinical and anatomical characteristics were recorded in a database software for the statistical analysis.

Clinical characteristics considered were: hypertension (presence of systolic blood pressure >140 or/and diastolic >90 mmHg, or specific therapy), dyslipidemia (total cholesterol >200 mg/dl or low density lipoprotein >120 mg/dl or specific therapy), diabetes mellitus (prediagnosed in therapy with oral hypoglycemic drugs or with insulin), current smoking, coronary artery disease (CAD) considered as history of angina pectoris or myocardial infarction or coronary revascularization. Pre-operative ischemic neurological symptoms were considered any hemispheric events (stroke, transient ischemic attack, amaurosis fugax) ipsilateral with the carotid stenosis within 6 months of the revascularization. Anatomical characteristics considered were: aortic arch type – arches have been divided into "simple aortic arch" [i.e. type I or II] and "difficult aortic arch" [type III and "bovine"], as previously described [16] and carotid plaque echogenic structure - evaluated as ipo-echogenic, iso-echogenic and iper-echogenic/calcified according to Tromso classification (type I, II and III/IV) [17]. The events considered in perioperative (30-day) period were: stroke, clinically evaluated by an in hospital neurologist and new acute ischemic lesion identified by cerebral CT scan, myocardial infarction (with hospital cardiologist and electrocardiography and serologic evaluation) and death and bleeding at the access site requiring surgical evacuation that corresponds to the mild GUSTO [18] bleeding classification or minimal of TIMI [19] classification.

Patients under OAT were submitted to CAS without interrupting the therapy and maintaining the assigned target INR according to their pathology (atrial fibrillation, mechanical prosthesis or deep vein thrombosis); in these patients, the usual heparin administration during the CAS procedure was avoided. Single antiplatelet therapy were administered to all patients in OAT in the perioperative period.

CAS procedure

CAS procedure was conducted as follows and as described in previous papers [20]. Briefly, patients were taken to the angiographic suite after appropriate informed consent and cardiological evaluation and medicated with aspirin 100 mg and clopidogrel 75 mg for 3 days before the procedure. Clopidogrel therapy was maintained for a month. All procedures were performed under local anaesthesia, systemic unfractionated heparinisation according the ACT values and an 8 F groin introducer. Common carotid cannulation was achieved with 40° Boston Scientific® or Medtronic® HS I and II catheters over a Terumo® stiff guide wire. When cannulation was not achievable by these means, several different alternative techniques were used (i.e., buddy wire, coaxial). Brachial or carotid access was not attempted in any case. Routine cerebral protection was by Filterwire EZ (Boston Scientific®) and stenting by closed-cell (Wallstent, Boston Scientific®). 'Technical success' was defined as the ability of treating the stenosis with less than 30% residual stenosis.

Haemostasis of the point of access was achieved with vascular closure device platform (Angio-Seal™ St. Jude Medical Inc., St. Paul, Minnesota, USA.) or manual and elastic groin compression.

Neurological outcome was evaluated both at the end of the procedure and in the following 24 h by a neurologist according to the NIH stroke scale and the modified Rankin scale.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as numbers with percentage. Chi-squared and Fisher's test and logistic regression were used to compared different frequencies between groups. The value of $p<0.05$ was considered significant. Statistical tests were performed using Statistical Package for Social Sciences for Windows® (SPSS® 13.0) computer software (SPSS, Chicago, IL, USA).

Results

From 2006 to 2010, 502 CAS procedures were performed. Mean patients age was 75.7 ± 6.7 years. The overall clinical and anatomical characteristics and perioperative events are summarized in Tables 1 and 2. In the population study, 145 (29.1%) patients were symptomatic: there were 57 (11.4%) ipsilateral strokes, 69 (13.9%) TIA and 19 (3.8%) amaurosis fugax. The aortic arch was type I in 259 (51.6%) cases, type II in 121 (24.1%) cases, type III in 40 (8.0%) cases and bovine or other anomalies in 69 (13.7%) cases. In 34 procedures technical success was not achieved due to unstable common carotid access in 28 cases and severe tortuosity of the common carotid artery in 6 cases; all these patients were submitted to carotid endarterectomy afterwards. An arterial closure device (Angioseal) was used in 483 (96.2%) cases and manual and elastic compression of the femoral point of access in 19 (3.8%) cases. The latter kind of hemostasis was used in 1 OAT patients and was not correlated with any adverse events.

In the perioperative period 12 strokes (3 major and 9 minor stroke) occurred; there was one death at 30 day and 4 cases of bleeding requiring surgical intervention. In the overall population the elements associated with adverse events were the aortic arch type and the preoperative neurological ischemic symptoms, as shown in Table 3.

Twenty patients under OAT (4.0%) underwent to CAS in this series. Indication for OAT with appropriate INR is shown in Table 4. The clinical and anatomical characteristics of patients in OAT were homogeneous with the overall patients' populations (Table 1). Patients under OAT did not experience any adverse event in term of strokes, death, myocardial infarction or hemorrhage/hematoma. There were not significant differences in clinical outcome between patients in OAT and the overall population underwent to CAS.

Discussion

Our data show that no thrombotic or hemorrhagic events occurred in CAS patients under uninterrupted OAT; thus to maintain OAT unmodified could be a valid alternative to bridging heparin therapy. Currently, bridging heparin therapy for endovascular procedures in

Table 1
Clinical and anatomical characteristics of the study population. CAD: coronary artery disease.

	N (Tot: 502)	%
Age ≥ 80 years	142	28.5
Male gender	326	65.5
Clinical risk factors		
Pre-operative ischemic neurological symptoms	145	29.1
Stroke	57	11.4
Transient Ischemic Attack	69	13.9
Amaurosis Fugax	19	3.8
Hypertension	437	87.8
Dislipidemia	184	36.9
Diabetes	133	26.5
Smoke	92	18.8
CAD	185	37.1
Oral Anticoagulant Therapy	20	4.0
Anatomical characteristics		
Type III or bovine aortic arch	109	21.9
Carotid plaque at duplex scan		
Iper-echogenic/calcified	314	62.5
Ipo-echogenic	116	23.1
Iso-echogenic	72	14.3

Table 2
Perioperative events after carotid artery stenting. Stroke (clinically evaluated by an in hospital neurologist and with new acute ischemic lesion identified by cerebral CT scan); MI: myocardial infarction (with hospital cardiologist and electrocardiography and serologic evaluation); bleeding (at the access site requiring surgical evacuation that corresponds to the mild GUSTO [18] bleeding classification or minimal of TIMI [19] classification); S/D: Stroke/Death; S/D/MI: Stroke/Death/Myocardial Infarction; S/D/MI/B: Stroke/Death/Myocardial Infarction/Bleeding.

	N	%
Technical failure	34	6.7
Arterial closure device	483	96.2
Manual/elastic compression	19	3.8
Events		
Stroke	12	2.4
Death	1	0.2
MI	0	0.0
Bleeding	4	0.8
Composite events		
S/D	13	2.6
S/D/MI	13	2.6
S/D/MI/B	17	3.4

OAT patients is widely employed during coronary artery procedures; however this strategy is not supported by specific randomized controlled trials. Bridge heparin therapy needs at least five days to be effective, causing a delay in carotid revascularization. In recently symptomatic carotid stenosis this revascularization delay could increase the risk of stroke since it is higher in the first period after neurological symptoms. Being aware of the possibility of performing endovascular treatments outside the carotid areas with ongoing OAT we elicited to leave OAT unmodified during CAS in order to perform an expeditious carotid revascularization.

Moreover the bridging heparin therapy is not completely safe: the overlap of heparin and OAT therapy can increase the anticoagulant effect of either one of the two medications; warfarin re-initiation may be associated with a transient pro-thrombotic state since anticoagulant factors with short half-lives are depleted prior to the decrease of vitamin K-dependent clotting factors [21–24]. In their literature review, Spyropoulos et al. reported an incidence of thromboembolic events of 1.22% and an incidence of major bleeding of approximately 3% in patients undergone to bridging heparin therapy [7]. This gives an overall complication risk of more than 4%, which compares unfavorably with the data of unstopped OAT shown above.

Some authors reported the safety of a temporary OAT interruption during less invasive procedures [25] to reduce hemorrhagic risk and maintain the anticoagulant effect, however the temporary OAT interruption with sub-therapeutic anticoagulation effect is associated with the potential increase of thrombo-embolic events [26].

The present study had an important limitation since it is a retrospective nonrandomized case cohort study, without a comparative group of patients medicated with bridging heparin therapy. A prospective trial on this topic is therefore needed. Next, the low number of OAT patients and the low overall event rate reduce the statistical strength of the results. However our data suggest that bridging therapy in OAT patients undergoing CAS may be un-necessary than unstopped OAT, which seems to be safe and effective.

Table 3
Perioperative carotid artery stenting events and clinical and anatomical characteristics. Stroke (clinically evaluated by an in hospital neurologist and with new acute ischemic lesion identified by cerebral CT scan); MI: myocardial infarction(with hospital cardiologist and electrocardiography and serologic evaluation); bleeding (at the access site requiring surgical evacuation that corresponds to the mild GUSTO [18] bleeding classification or minimal of TIMI [19] classification); S/D: Stroke/Death; S/D/MI/B: Stroke/Death/Myocardial Infarction/Bleeding *: neurological symptoms: defined as cerebral neurological ischemic symptoms, ipsilateral to the carotid artery stenosis, occurred within six months before the carotid revascularization.

	N (%)	Stroke N: 12 (%)	p	Death N: 1 (%)	p	MI N: 0 (%)	p	Bleeding N: 4 (%)	p	S/D N: 12 (%)	p	S/D/HH N: 16 (%)	p
Clinical characteristics													
Age													
≥ 80 years	142 (28.5)	6 (4.4)	.11	0 (0)	.51	0 (0)	.52	2 (1.4)	.36	6 (4.4)	.18	8 (5.6)	.10
< 80 years	360 (71.5)	6 (1.6)		1 (0.2)		0 (0)		2 (0.5)		6 (1.6)		8 (2.2)	
Male gender	326 (65.5)	8 (3.3)	0.91	1 (0.3)	.47	0 (0)	.45	2 (0.6)	.50	9 (2.7)	.78	11 (3.3)	.92
Female gender	176 (34.5)	4 (2.2)		0 (0)		0 (0)		2 (1.1)		3 (1.7)		5 (2.8)	
Neurological symptoms*													
Yes	145 (28.8)	6 (4.1)	.11	1 (0.6)	.12	0 (0)	.23	0 (0)	.19	7 (4.8)	.04	7 (4.8)	**.04**
No	357 (17.2)	6 (1.6)		0 (0)		0 (0)		4 (1.1)		5 (1.4)		9 (2.5)	
Hypertension	437 (87.0)	11 (2.5)	.73	1 (0.2)	.72	0 (0)	.46	4 (0.9)	.47	12 (2.7)	.67	16 (3.6)	.46
Not-hypertension	65 (13.0)	1 (1.5)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	
Dislipidemia	184 (36.6)	6 (3.2)	.35	0 (0)	.44	0 (0)	.38	1 (0.5)	.61	6 (3.2)	.35	7 (3.8)	.73
Not-dislipidemia	318 (63.3)	6 (1.8)		1 (0.3)		0 (0)		3 (0.9)		6 (1.8)		9 (2.8)	
Diabetes	133 (26.5)	5 (3.8)	.25	0 (0)	.54	0 (0)	.53	2 (1.5)	.30	5 (3.8)	.25	7 (5.2)	.18
Not-diabetes	369 (73.5)	7 (1.9)		1 (0.2)		0 (0)		2 (0.5)		7 (1.8)		9 (2.4)	
Smoke	92 (18.8)	1 (1.0)	.91	0 (0)	.74	0 (0)	.53	1(1.0)	.34	1 (1.0)	.91	2 (2.0)	.48
Not-smoke	317 (63.1)	11 (2.6)		1 (0.2)		0 (0)		3 (0.7)		11 (2.6)		14 (3.4)	
CAD	185 (36.8)	5 (2.7)	.76	1 (0.5)	.19	0 (0)	.26	2 (1.0)	.60	6 (3.2)	.51	8 (4.3)	.40
Not-CAD	317 (63.1)	7 (2.2)		0 (0)		0 (0)		2 (0.6)		6 (1.8)		8 (2.5)	
Anatomical characteristics													
Type III or bovine aortic arch	109 (21.9)	6 (5.5)	**.02**	0 (0)	.59	0 (0)	.23	2 (1.8)	.18	6 (5.5)	**.03**	8 (7.3)	**.01**
Type I or II aortic arch	393 (78.1)	6 (1.5)		1 (0.2)		0 (0)		2 (0.5)		6 (1.5)		8 (2.0)	
Carotid plaque													
Iper-echogenic	314 (62.5)	11 (3.5)	.12	0 (0)	.20	0 (0)	.33	3 (0.9)	.75	11 (3.5)	.23	14 (4.5)	.19
Ipo-echogenic	116 (23.1)	1 (0.9)		1 (0.9)		0 (0)		1 (0.8)		2 (1.7)		3 (2.6)	
Iso-echogenic	72 (14.3)	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	
Oral anticoagulant therapy													
Oral Anticoagulant Therapy	20 (4.0)	0 (0)	.47	0 (0)	.83	0 (0)	.46	0 (0)	.68	0 (0)	.45	0 (0)	.39
Not-oral anticoagulant therapy	482 (96.0)	12 (2.4)		1 (0.2)		0 (0)		4 (0.8)		12 (2.4)		16 (3.3)	

Table 4
Clinical indication to Oral Anticoagulant Therapy and International Normalized Ratio (INR) values in the study population.

	N	%	INR
			Mean ± SD
Atrial fibrillation	14	70	2.59 ± 0.7
Mechanical valve prosthesis	5	25	2.61 ± 0.4
Deep vein thrombosis	1	5	2.36

Conclusions

Bridging heparin therapy is not associated with better results in CAS compared with unmodified OAT. Leaving OAT uninterrupted throughout the perioperative period is a safe and effective alternative.

Conflict of interest statement

None.

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None.

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