ORIGINAL ARTICLE

Factors associated with recurrent stroke and recanalization in patients presenting with isolated symptomatic carotid occlusion

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Background and purpose: Patients with symptomatic internal carotid artery (ICA) occlusion constitute a small proportion of stroke/transient ischaemic attack patients who are at increased risk of early stroke recurrence and poor outcome. The optimal medical treatment for patients with symptomatic ICA occlusion who are ineligible for thrombolysis or thrombectomy is unknown.

Methods: Consecutive patients presenting at a single center with newly diagnosed symptomatic ICA occlusion (not involving the circle of Willis) were retrospectively reviewed. Those treated with intravenous thrombolysis or intra-arterial thrombolysis/thrombectomy were excluded. Patients were divided into two groups based on whether they experienced recurrent in-hospital stroke.

Results: The selected study population (n = 33) represented a small (20.4%) proportion of all newly symptomatic carotid occlusions, who nevertheless had an elevated risk of recurrent stroke during admission (24.2%). Of the variables examined (age, gender, admission National Institutes of Health Stroke Scale score, vascular risk factors, atrial fibrillation, prior stroke/transient ischaemic attack and anticoagulation within 48 h of presentation), only anticoagulation was significantly associated with a lower risk of in-hospital recurrent stroke. Anticoagulated patients showed a decreased incidence of stroke recurrence within the first week (6.7% vs. 38.9%, P = 0.032) and fewer strokes or deaths at 1 month (13.3% vs. 47.1%, P = 0.040). Hemorrhagic transformation was not observed in any patient. On follow-up imaging, ICA recanalization was significantly more frequent in anticoagulated patients (46.2% vs. 9.1%, P = 0.047).

Conclusion: Patients with newly diagnosed symptomatic ICA occlusion (not involving the circle of Willis) represent a small but high risk subgroup of patients with carotid occlusion. Early anticoagulation was associated with fewer recurrent strokes and increased ICA recanalization. Larger scale prospective studies may be justified.

Introduction

Whilst patients presenting with symptomatic carotid occlusion constitute a relatively small proportion of stroke admissions, they have a higher risk of recurrent in-hospital stroke and early death compared with otherwise undifferentiated acute ischaemic stroke (AIS) or transient ischaemic attack (TIA) patients. An analysis of 4144 patients from the Canadian Stroke Network found symptomatic occlusion of the extracranial internal carotid artery (ICA) in 6.8% of patients; this group experienced significantly higher rates of recurrent in-hospital stroke (6.7% vs. 2.8%) and death (12.0% vs. 3.8%) [1]. Similar findings were seen in 4157 AIS/TIA patients presenting to the German Stroke Collaboration: 6.5% had symptomatic extracranial carotid occlusion, with significantly ele-

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vated rates of recurrent stroke within 72 h (7.4% vs. 3.5%) and death within 100 days (21.2% vs. 10.3%) [2]. Population-based studies (Olmsted County, Minnesota, USA) have also shown elevated risks of early stroke recurrence after symptomatic carotid occlusion: 8% within the first 30 days, nearly half occurring within the first week of diagnosis [3]. Whilst intravenous thrombolysis and endovascular therapy can help improve outcomes in AIS due to carotid occlusion [4,5], optimal medical treatment of patients ineligible for such interventions is unknown. Factors associated with lack of in-hospital recurrent stroke in patients who presented to our institution with a newly symptomatic isolated carotid occlusion [not involving the circle of Willis and anterior/middle cerebral arteries (ACA/MCA)] who were deemed ineligible for intravenous thrombolysis or endovascular intervention were therefore evaluated.

Methods

This study is a Research Subjects Review Board (the institutional review board committee) approved retrospective analysis of consecutive patients presenting with a diagnosis of AIS/TIA at a single quaternary referral center (designated as a Comprehensive Stroke Center by the Joint Commission) from July 2008 to April 2014. Clinical charts and imaging of all patients who had a discharge diagnosis of AIS/TIA were reviewed. Patients with an acute anterior circulation AIS/TIA in whom a newly diagnosed (i.e. never previously documented) ipsilateral ICA occlusion was found on initial vascular imaging were included. All isolated ICA occlusions were diagnosed using computed tomography angiography (CTA), magnetic resonance angiography (MRA) and/or conventional angiography of the head and neck. Patients were excluded who (a) presented more than 24 h after last known to be well, (b) received intravenous thrombolytic treatment or endovascular intervention at presentation, (c) had initial CT/MRI showing intracerebral hemorrhage, (d) had initial vascular imaging showing occlusion of the circle of Willis or intracranial large vessel [defined as the first segment of the ACA (A1) or first/second segment of the MCA (M1/M2)] ipsilateral to the symptomatic hemisphere and/or (e) had initial vascular imaging showing severe symptomatic intracranial stenosis.

Imaging and medical records of patients were reviewed to abstract relevant information, including but not limited to demographics, stroke severity [as measured by the National Institutes of Health Stroke Scale (NIHSS)], vascular risk factors, in-hospital treatment with antiplatelets or anticoagulation, and follow-up imaging to examine the status of the occluded artery. Anticoagulation consisted of therapeutic weight-based dosage of heparin, dalteparin or enoxaparin (dosages targeting prophylaxis against venous thromboembolism did not qualify), started within 48 h of presentation. Choice of anticoagulation or antiplatelets was at the discretion of the treating physician. Patients were divided into two groups: those who suffered recurrent stroke during their admission (defined as worsening of NIHSS score $\geq$4 points and new infarct on follow-up imaging in the territory of the occluded carotid) and those who did not. Clinical worsening (change in NIHSS score $\geq$4 points) was investigated as per clinical practice with CT and/or MRI, and was not attributable to edema in our series. Occurrence of death, recurrent stroke and hemorrhagic transformation found on repeat imaging within 7 days and 1 month was recorded, as were results of any repeat vascular imaging within 1 year after initial diagnosis of carotid occlusion. Initial and final infarct volumes on CT/MRI images were verified and measured (using an automated, validated algorithm – ITK SNAP software version 3.2.0 www.itksnap.org) by a board-certified neuroradiologist [6,7]. Univariate analyses were performed using JMP® (Cary, NC, USA) 11.0.0 statistical software and a P value <0.05 was considered as significant. Data are presented as mean $\pm$ SE unless otherwise specified.

Results

Of 2670 patients presenting with stroke/TIA during the study time period, 195 patients (7.3%) were identified as having an ICA occlusion. Of those 195 patients, 33 patients had known prior carotid occlusion and were excluded. Of the remaining 162 patients with newly diagnosed ICA occlusion on their initial neurovascular imaging, patients were excluded who (i) were last known well $\geq$24 h (n = 10), (ii) had received intravenous and/or intra-arterial thrombolysis/thrombectomy (n = 20), (iii) had proximal MCA and/or ACA occlusion in addition to their ICA occlusion (n = 86) and (iv) had severe symptomatic intracranial stenosis (n = 3) or other exclusion criteria (hemorrhage on initial imaging, bilateral or posterior circulation stroke, incomplete imaging; n = 10). A total of 33 patients met the final inclusion criteria, none of whom were deemed candidates for intra-arterial thrombolysis/thrombectomy due to lack of intracranial large vessel occlusion and low NIHSS score [median of 4, interquartile range (IQR) = 1–9]. A review of initial neurovascular imaging found all ICA occlusions to begin at or a few centimeters above

the cervical bifurcation and extend to the intracranial petrous/cavernous segment, with supraclinoid reconstitution proximal to the intracranial ICA terminus. Acute ischaemic changes were seen in 31/33 patients on initial neuroimaging (25 on MRI, six on CT where MRI was not available); the remaining two patients had mild stroke (NIHSS score 4 and 2), both of whom underwent CT scan only.

Recurrent stroke was seen in eight (24.3%) of the included patients during their admission, all of which occurred within the first week. In univariate analysis of factors including age, presenting NIHSS score, vascular risk factors and medical treatment (Table 1), only early anticoagulation was significantly associated with a lower risk of recurrent in-hospital stroke. Specifically, there was a significant decrease in the incidence of stroke recurrence within 1 week in anticoagulated patients (6.7% vs. 38.9%, $P = 0.032$). All recurrent strokes occurred early (≤7 days), were during the same admission and were within the territory of the occluded carotid artery.

As univariate analysis found only anticoagulation to be significantly associated with lower risk of recurrent in-hospital stroke (Table 1), patients were divided into those treated with anticoagulation and those who did not receive anticoagulation, and subsequently differences between these two groups were examined (Table 2). There was no difference in the initial stroke volume in patients who underwent anticoagulation versus no anticoagulation (4.3 ± 2.2 vs. 9.6 ± 3.1 ml, $P = 0.164$). Non-anticoagulated patients with recurrent stroke showed a significant increase in stroke volume from that seen on initial imaging (7.2 ± 2.0 vs. 68.6 ± 25.3 ml, $P < 0.02$). Hemorrhagic transformation was not seen in either group. At 1 month, 1/15 (6.7%) of anticoagulated patients experienced a recurrent stroke (on day 6 post-stroke) and one died (day 25 post-stroke); none was lost to follow-up. During the same period, 7/18 patients (38.9%) who were not anticoagulated developed recurrent stroke (median 3 days after initial stroke, IQR = 1–4), one died (day 13 post-stroke) and one was lost to follow-up (5.6%). Death or stroke at 1 month was significantly less in anticoagulated patients (13.3% vs. 47.1%, $P = 0.040$). Our sample size did not permit further multivariate analysis. However, univariate analysis did not reveal any significant difference in other potential predictors of outcome (age, presenting NIHSS score, vascular risk factors) between anticoagulated versus non-anticoagulated patients (Table 2). In patients with repeat vascular imaging, ICA recanalization was seen more often in anticoagulated patients (46.2% vs. 9.1%, $P = 0.047$).

Table 1 Recurrent stroke during the same admission

Variables	Recurrent stroke ($n = 8$), N (%)	No recurrent stroke ($n = 25$), N (%)	P value
Demographics			
Age[a]	71.5 (56.3–77.5)	66 (54–83.5)	0.721
Female	3 (37.5)	13 (52)	0.475
White or Caucasian	8 (100)	24 (96)	0.566
NIHSS score on admission[a]	2 (0–6.3)	4 (1.5–9.5)	0.237
Past medical history			
Stroke/TIA	2 (25)	6 (24)	0.954
HTN	7 (87.5)	23 (92)	0.700
HLD	7 (87.5)	15 (60)	0.151
DM	2 (25)	5 (20)	0.763
CAD	2 (25)	5 (20)	0.763
AF	0 (0)	5 (20)	0.170
Current smoker	6 (75)	17 (68)	0.707
Anticoagulation	1 (12.5)	14 (56)	0.032[b]
Outcomes			
NIHSS score on discharge[a]	3 (1–11.8)	1 (0–4)	0.148
Hemorrhagic transformation	0 (0)	0 (0)	–

NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack; HTN, hypertension; HLD, hyperlipidemia; DM, diabetes mellitus; CAD, coronary artery disease; AF, atrial fibrillation.

[a]Median, interquartile range; [b]significant P value.

Discussion

Patients with symptomatic carotid occlusion represent a small but potentially high risk subgroup of AIS patients [1,2]. In our study, 7.3% of our stroke/TIA patients presented with newly diagnosed symptomatic intracranial or extracranial ICA occlusion, similar to previous studies [1,2]. These prior series found symptomatic carotid occlusion to be associated with more than double the baseline risk of early stroke recurrence [1,2]. Our data suggest an even higher stroke recurrence rate in patients with isolated symptomatic carotid occlusion (i.e. not involving the circle of Willis). This may be due to (i) excluding patients who were treated with intravenous thrombolysis or endovascular therapy in our cohort and (ii) including only patients who did not have concomitant intracranial occlusion affecting the circle of Willis (and thus had low stroke burden; median NIHSS score 4; IQR = 1–9). Our study population therefore represents a more specific and smaller fraction of newly symptomatic carotid occlusions (20.4%) and of the general stroke population (1.2%) than prior investigations, who nevertheless harbor a markedly elevated risk of early stroke recurrence (24.3%). It is possible

Table 2 Characteristics and outcomes of anticoagulated patients

Variables	Anticoagulated (n = 15), N (%)	Not anticoagulated (n = 18), N (%)	P value
Demographics			
Age[a]	71 (61–83)	58.5 (53.5–80)	0.515
Female	9 (60)	8 (44.4)	0.373
White or Caucasian	14 (93.3)	18 (100)	0.266
NIHSS score on admission[a]	4 (1–9)	3.5 (1–9.3)	1.000
Stroke volume on initial imaging (ml)	4.3 (±2.2)	9.6 (±3.1)	0.164
Past medical history			
Stroke/TIA	4 (26.7)	4 (22.2)	0.767
HTN	14 (93.3)	16 (88.9)	0.658
HLD	9 (60)	13 (72.2)	0.458
DM	4 (36.7)	3 (16.7)	0.484
CAD	3 (20)	4 (22.2)	0.876
AF	3 (20)	2 (11.1)	0.478
Current smoker	9 (60)	14 (77.8)	0.269
DVT/PE (prior)	0 (0)	1 (5.6)	0.354
DVT/PE (during admission)	0 (0)	0 (0)	–
Renal insufficiency	0 (0)	1 (5.6)	0.354
Malignancy	2 (13.3)	5 (27.8)	0.312
Dementia	1 (6.7)	0 (0)	0.266
Outcomes			
NIHSS score on discharge[a]	1 (0–2)	3.5 (0–9.3)	0.071
Hemorrhagic transformation	0 (0)	0 (0)	–
Recurrent stroke within 7 days[c]	1 (6.7)	7 (38.9)	0.032[b]
Stroke and/or death at 1 month	2 (13.3)	8 (47.1)	0.040[b]
(Lost to follow-up at 1 month)	0 (0)	1 (5.6)	0.354
ICA recanalization by 1 year[d]	6 (46.2)	1 (9.1)	0.047[b]
(Lost to follow-up imaging)	2 (13.3)	7 (38.8)	0.100

NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack; HTN, hypertension; HLD, hyperlipidemia; DM, diabetes mellitus; CAD, coronary artery disease; AF, atrial fibrillation; DVT/PE, deep vein thrombosis and pulmonary embolism; ICA, internal carotid artery.

[a]Median, interquartile range; [b]significant P value; [c]all recurrent strokes were during the same initial admission; [d]in patients with repeat carotid imaging.

that recurrent stroke may be more readily detectable in these patients (who have a low admission NIHSS score), and/or clot propagation or stump emboli from an occluded carotid may pose a graver risk to patients whose intracranial circulation is initially patent.

Our study suggests that early anticoagulation is associated with a lower incidence of recurrent stroke during initial admission and a lower incidence of death and/or stroke at 1 month in this highly selected group of AIS patients. In contrast, large randomized trials of anticoagulation in AIS (including FISS, TOAST, HAEST and IST) have not shown a significant benefit with respect to outcomes at discharge or stroke related morbidity and mortality [8–12], and a recent meta-analysis of the five largest acute stroke trials to include heparins also failed to find a subgroup of AIS patients that might benefit from acute anticoagulation [13]. However, this meta-analysis (and most trials) of anticoagulation in AIS has not accounted for stroke heterogeneity seen on acute vascular imaging (such as CTA or MRA of the head and neck), which is increasingly obtained at time of presentation in AIS patients. It is therefore possible that a small subgroup of AIS patients, defined by their initial vascular imaging, may benefit from early anticoagulation. For example, subgroup analysis from both the TOAST and FISS-tris trials suggested a benefit for anticoagulation in AIS patients with large artery occlusive disease [9,14].

The mechanism by which patients with acute symptomatic isolated carotid occlusion (not reaching the circle of Willis) might benefit from anticoagulation is unclear. It is hypothesized that early anticoagulation may help (i) by preventing ICA clot extension into circle of Willis end-arteries (i.e. MCA or ACA), which would deprive them of collateral supply from the anterior/posterior communicating arteries, and (ii) by preventing stump emboli from the occluded carotid [15,16].

It is important to acknowledge that anticoagulation is not without risk of hemorrhagic transformation. In

our study, none of the patients in either group experienced hemorrhagic transformation, perhaps due to low initial stroke burden (median NIHSS score 3–4).

Increased carotid recanalization was noted in anticoagulated patients. Prior investigations have reported spontaneous recanalization following carotid occlusion in 5%–67% [17–21] of cases, and the recent Dutch Acute Stroke Study (DUST) found early recanalization in approximately 40% of patients [22]. However, prior series have not excluded patients undergoing acute thrombolysis or thrombectomy (54.7% of patients in DUST received intravenous tissue plasminogen activator) [22] and have not differentiated between choice of medical therapy. None of our patients had undergone intravenous thrombolysis or thrombectomy, and spontaneous recanalization was found in 46.2% of anticoagulated patients, versus 9.1% of non-anticoagulated patients ($P = 0.047$).

A major weakness of our paper is the retrospective, observational, non-randomized nature of our data. In particular, the decision to use anticoagulation was dictated by the treating physicians, whose selection bias could have affected our results by making the two groups not comparable. No significant difference (such as age, race, presenting NIHSS score, infarct volume, deep vein thrombosis and pulmonary embolism (DVT/PE) during admission, dementia, renal insufficiency, malignancy) was found between anticoagulated and non-anticoagulated patients, decreasing the chances that physician selection bias alone may explain the association between anticoagulation and decreased stroke recurrence in our patients; however, unmeasured confounding remains possible. Additionally, none of the patients had known reasons other than carotid occlusion for anticoagulation (such as PE or DVT) that could have further biased our results. Other weaknesses in our data include a lack of prespecified intervals for imaging or clinical follow-up which, whilst similar across both groups, made the data nevertheless incomplete. Anticoagulated patients were more likely to undergo repeat vascular imaging, although this was not significantly different from patients who were not anticoagulated. Lastly, it was not possible to confirm the cause or chronicity of ICA occlusions on initial neurovascular imaging, and study inclusion was based solely on whether ICA occlusion was a new diagnosis or not.

Conclusion

Patients with newly symptomatic isolated carotid occlusion represent a small minority of AIS patients, yet are at high risk of early stroke recurrence. Anticoagulation was associated with fewer recurrent strokes and increased carotid recanalization in our series. Larger prospective studies for this specific patient population may be justified.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

References

1. Burke MJ, Vergouwen MD, Fang J, *et al*. Short-term outcomes after symptomatic internal carotid artery occlusion. *Stroke* 2011; **42:** 2419–2424.
2. Weimar C, Goertler M, Harms L, Diener HC. Distribution and outcome of symptomatic stenoses and occlusions in patients with acute cerebral ischemia. *Arch Neurol* 2006; **63:** 1287–1291.
3. Flaherty ML, Flemming KD, McClelland R, Jorgensen NW, Brown RD Jr. Population-based study of symptomatic internal carotid artery occlusion: incidence and long-term follow-up. *Stroke* 2004; **35:** e349–e352.
4. Berkhemer OA, Fransen PS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; **372:**11–20.
5. Demchuk AM, Goyal M, Yeatts SD, *et al*. Recanalization and clinical outcome of occlusion sites at baseline CT angiography in the Interventional Management of Stroke III Trial. *Radiology* 2014; **273:** 202–210.
6. Yushkevich PA, Piven J, Hazlett HC, *et al*. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *NeuroImage* 2006; **31:** 1116–1128.
7. Boers AM, Marquering HA, Jochem JJ, *et al*. Automated cerebral infarct volume measurement in follow-up noncontrast CT scans of patients with acute ischemic stroke. *AJNR Am J Neuroradiol* 2013; **34:** 1522–1527.
8. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet* 1997; **349:** 1569–1581.
9. The Publications Committee for the TOAST Investigators. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. *JAMA* 1998; **279:** 1265–1272.
10. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. *Lancet* 2000; **355:** 1205–1210.
11. Duke RJ, Bloch RF, Turpie AG, Trebilcock R, Bayer N. Intravenous heparin for the prevention of stroke

progression in acute partial stable stroke. *Ann Intern Med* 1986; **105:** 825–828.
12. Wong KS, Chen C, Ng PW, *et al.* Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. *Lancet Neurol* 2007; **6:** 407–413.
13. Whiteley WN, Adams HP Jr, Bath PM, *et al.* Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. *Lancet Neurol* 2013; **12:** 539–545.
14. Wang QS, Chen C, Chen XY, *et al.* Low-molecular-weight heparin versus aspirin for acute ischemic stroke with large artery occlusive disease: subgroup analyses from the Fraxiparin in Stroke Study for the treatment of ischemic stroke (FISS-tris) study. *Stroke* 2012; **43:** 346–349.
15. Delcker A, Diener HC, Wilhelm H. Source of cerebral microembolic signals in occlusion of the internal carotid artery. *J Neurol* 1997; **244:** 312–317.
16. Lakshminarayan R, Scott PM, Robinson GJ, Ettles DF. Carotid stump syndrome: pathophysiology and endovascular treatment options. *Cardiovasc Intervent Radiol* 2011; **34** (Suppl. 2)**:** S48–S52.
17. Gohel MS, Hamish M, Harri JI, Davies AH. Symptomatic late recanalization of an occluded internal carotid artery: a case report and review of the literature. *Vasc Endovascular Surg* 2008; **42:** 486–488.
18. Meves SH, Muhs A, Federlein J, Buttner T, Przuntek H, Postert T. Recanalization of acute symptomatic occlusions of the internal carotid artery. *J Neurol* 2002; **249:** 188–192.
19. Nguyen-Huynh MN, Lev MH, Rordorf G. Spontaneous recanalization of internal carotid artery occlusion. *Stroke* 2003; **34:** 1032–1034.
20. Shah PS, Hingorani A, Ascher E, Shiferson A, Patel N, Gopal K. Spontaneous recanalization of an occluded internal carotid artery. *Ann Vasc Surg* 2010; **24:** 954 e1–e4.
21. Som S, Schanzer B. Spontaneous recanalization of complete internal carotid artery: a clinical reminder. *J Surg Tech Case Rep* 2010; **2:** 73–74.
22. Luitse MJ, Velthuis BK, Dauwan M, *et al.* Residual high-grade stenosis after recanalization of extracranial carotid occlusion in acute ischemic stroke. *Stroke* 2014; **46:** 12–15.