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Safety and efficacy of mechanical thrombectomy with stent-retrievers in anticoagulated patients with anterior circulation stroke

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AIM: To assess the safety and efficacy of mechanical thrombectomy (MT) with stent-retrievers in anterior circulation stroke (ACS) patients due to the occlusion of major cerebral arteries, and to compare the results achieved in patients on oral anticoagulation (OAC) and those not on OAC.

MATERIALS AND METHODS: The present retrospective study comprised 285 consecutive patients (115 males; mean age 74±13 years). The following data were collected: baseline characteristics, occurrence of risk factors, pre-event treatment with OAC, neurological deficit at the time of treatment, time to therapy, recanalisation rate (successful recanalisation defined as Thrombolysis in Cerebral Infarction score ≥2b), post-treatment imaging findings. The 90-day clinical outcome was assessed using modified Rankin scale (good outcome defined as 0–2).

RESULTS: The following statistically insignificant differences were found in 26 patients on OAC versus 259 patients without OAC: occurrence of symptomatic intracerebral haemorrhage 7.7% versus 8.1%, achievement of successful recanalisation 69.2% versus 82.6%, good 90-day clinical outcome 34.6% versus 56.8%, 90-day mortality 26.9% versus 20.8% ($p>0.05$ in all cases). Age and neurological deficit at the time of treatment were identified as independent negative predictors of good 90-day clinical outcome (odds ratio [OR]=0.90, 95% confidence interval [CI]: 0.88–0.94 and OR=0.83, 95% CI: 0.77–0.90, respectively) and as independent positive predictors of mortality (OR=1.12, 95% CI: 1.06–1.18 and, OR=1.17, 95% CI: 1.07–1.27, respectively; $p<0.05$ in all cases).

CONCLUSIONS: MT with stent-retrievers is safe and effective in ACS patients on OAC.

Introduction

Few results of mechanical thrombectomy (MT) procedures in anticoagulated patients can be found in the literature; the reported results differ, and moreover, the patient

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groups analysed are inconsistent in most cases regarding the retrievers used.[1–9] The studies of 2015 that did confirm the efficacy of MT using stent-retrievers either did not include any patients taking oral anticoagulation (OAC; EXTEND IA, SWIFT PRIME)[10,11] or included only very few of such patients (MR CLEAN: 18 patients in the intervention arm; REVASCAT: 23 patients in the intervention arm).[12,13]

The purpose of the present study was to evaluate the safety and efficacy of MT using stent-retrievers in patients with acute ischaemic stroke (AIS) in the anterior circulation due to cerebral artery occlusion and in patients on OAC compared to patients without OAC.

Materials and methods

Study population

The present observational cohort study comprised 285 consecutive patients (115 males; mean age 71.6±13.3 years) with AIS in the anterior circulation due to the occlusion of a large cerebral artery treated with MT using stent-retrievers with or without intravenous thrombolysis (IVT) at the Department of Neurology, Comprehensive Stroke Center (CSC), Hradec Králové, Czech Republic between April 2009 and May 2017. Basic routine investigations included neurological, physical, and laboratory examinations, and assessment of the neurological deficit using the National Institutes of Health Stroke Scale (NIHSS)[14] performed by a certified neurologist.

The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and was approved by the Ethics Committee of University Hospital Hradec Králové, Czech Republic (no. 201708 S13P). All procedures were performed in accordance with institutional guidelines. Informed consent for the eligible and available treatment was obtained from all conscious patients. Independent witnesses verified the signatures for cases in which there were technical problems.

Computed tomography imaging and digital subtraction angiography

All patients underwent unenhanced brain computed tomography (CT) imaging with assessment of the Alberta Stroke Programme Early CT Score (ASPECTS) and CT angiography (CTA) of the cervical and intracranial arteries with the intravenous administration of non-ionic contrast medium (iomeprol; Iomeron 400, Bracco, Torviscosa, Italy; total volume of 60 ml, speed 4 ml/s). Patients treated within 6–8 hours or with an unknown time of onset underwent also perfusion CT (PCT) using 40 ml of the same contrast medium infused intravenously (speed 5 ml/s). The time to maximum (Tmax) delay >6 seconds was used for the display of ischaemic penumbra and, the relative cerebral blood flow <30% of that in normal tissue for a diagnosis of ischaemic core (irreversibly injured brain tissue).[15] A follow-up CT examination was performed 24 hours after MT. Somatom Definition AS+ (Siemens, Forchheim, Germany) apparatus was used for CT examination.

During digital subtraction angiography, non-ionic contrast medium (iodixanol; Visipaque 320, GE Healthcare AS, Oslo, Norway) was administered intra-arterially using a Seldinger technique (total volume of 6 ml, speed 5 ml/s). A biplane angio machine (Philips Allura FD 20/20, Best, the Netherlands) was used for DSA examination.

Recanalisation treatment

Recanalisation treatment was performed in patients fulfilling the inclusion and exclusion criteria according to the valid guidelines.[16–19] Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA; Actilyse, Boehringer Ingelheim, Ingelheim am Rhein, Germany) was applied within 4.5 hours from stroke onset. Ten percent of the rtPA dose (0.9 mg/kg, maximum 90 mg) was administered as an intravenous bolus, followed by a 60-min infusion of the remaining 90% of the dose.[16,19]

MT was performed as soon as possible, without waiting for the effects of the IVT, if applied, and within a standard 6-hour time window.[17,18] According to the valid local protocol, patients between 6 and 8 hours since the onset of symptoms and patients with unknown stroke onset time were indicated for MT only in the case of a small proven ischaemic deficit (defined as ASPECTS[20] ≥6) or in the case of the finding of a small ischaemic core (volume threshold ≤70 ml[21]) and the presence of ischaemic penumbra on PCT.[10] The choice of the particular stent-retriever(s) used for clot extraction was at the discretion of the treating neuroradiologist. In the majority of procedures, the balloon guiding catheter (Merci 8 F, Concentric Medical, Mountain View, CA, USA) was placed within the internal carotid artery (ICA); in the case of the presence of a loop, the catheter was placed below it. Subsequently, a microcatheter (0.021 inch) with stent-retriever was introduced. The stent-retriever was deployed across the occlusion and after 4 minutes the stent was slowly retrieved, while flow arrest in the accessing artery was applied by balloon inflation. Manual aspiration was applied through the guiding catheter via a sidearm using a 20 ml syringe. General anaesthesia was avoided whenever possible. Systolic blood pressure was kept >140 mmHg.[22]

Parameters observed

The following parameters were observed: patient age and sex, presence of vascular risk factors (arterial hypertension, diabetes mellitus, dyslipidaemia, previous stroke, or transient ischaemic attack [TIA], ischaemic heart disease, atrial fibrillation), pre-event treatment with OAC (including the international normalised ratio [INR] value in patients treated with warfarin), neurological deficit (assessed using the NIHSS), localisation of arterial occlusion, the use of IVT and of particular stent retrievers, and onset-to-groin puncture time.

The efficacy of the recanalisation was assessed by a certified radiologist using the Thrombolysis in Cerebral

Infarction (TICI) score[23] with successful recanalisation defined as TICI 2b/3. The occurrence of any intracerebral haemorrhage (ICH) on follow-up CT was evaluated by a certified radiologist. Symptomatic ICH (SICH) was defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria.[24] The 90-day clinical outcome was assessed during follow-up clinical visit by a certified neurologist (not blinded for the result of the MT) using the modified Rankin scale (mRS).[25] The rates of a good clinical outcome (self-sufficiency; mRS 0–2) and of mortality (mRS 6) were observed. A telephone interview with another treating physician or the family members was used in patients, who were unable to attend a follow-up visit at the CSC.

Statistical analysis

The success rate of treatment with stent-retrievers was compared in patients with and without OAC. Fisher's exact test was used to compare the risk factors and demographic data in both groups. A multivariate linear logistic regression model was used for the prediction of successful recanalisation (TICI ≥2b), self-sufficiency (mRS ≤2), and mortality (mRS 6). The entire patient population (285 patients) was evaluated in the first model (successful recanalisation); 222 patients fulfilled the conditions for inclusion in the second model (self-sufficiency and mortality). When the onset-to-groin puncture time parameter was used, patients with an unknown stroke onset time had to be excluded. Adjustment variables (age and baseline NIHSS value) not subjected to optimisation were included in the models. The optimal model was estimated using backward manual stepwise logistic regression based on the *p*-value. The MATLAB Statistical Toolbox (MathWorks, Natick, MA, USA) was used for statistical analysis.

Results

For MT, the Solitaire (Covidien, Dublin, Ireland) stent-retriever was used 130 times (45.6%) and the Trevo ProVue (Concentric Medical, Mountain View, CA, USA) was used 153 times (53.7%); in the remaining cases, the ERIC 4 Retrieval Device (MicroVention Terumo, Saint-Germain-en-Laye, France) was used four times, the pREset (Phenox GmbH, Bochum, Germany) two times, and the Catch Device (Balt Extrusion, Montmorency, France) once.

Baseline characteristics of the study population are presented in Table 1. Out of the 26 patients who were on OAC before MT, 21 patients were on warfarin and five patients were on direct oral anticoagulants (DOAC): two on dabigatran 110 mg twice a day, one on dabigatran 150 mg twice a day, one on rivaroxaban 20 mg once a day and one on apixaban 2.5 mg twice a day. Five of these patients (with ineffective anticoagulation) also received IVT. The mean INR value of patients on warfarin was 1.81 (median 1.78). No statistically significant differences were found between the

Table 1
Baseline and outcome characteristics.

	All	OAC	Without OAC	*p*-Value
n	285 (100)	26 (9.1) (warfarin 21, DOAC 5)	259 (90.1)	N/A
Age (years)	71.6±13.3 (18–93)	75±8.0 (57–88)	71.1±13.8 (18–93)	0.15
Male sex	115 (40.4)	10 (38.5)	105 (40.5)	0.83
Vascular risk factors				
Arterial hypertension	209 (73.3)	22 (84.6)	187 (72.2)	0.65
Diabetes mellitus	73 (25.6)	12 (46.2)	61 (23.6)	0.09
Dyslipidaemia	110 (38.6)	16 (61.5)	94 (36.3)	0.14
Previous stroke/TIA	49 (17.2)	10 (38.5)	39 (15.1)	0.03
Ischaemic heart disease	63 (22.1)	11 (42.3)	52 (20)	0.07
Atrial fibrillation	140 (49.1)	26 (100)	114 (44)	0.01
INR value		1.78 (1.37–2.79)		
NIHSS baseline	14 (0–40)	15 (1–28)	14 (0–40)	0.41
Occlusion localisation				
MCA – M1	163 (57.2)	18 (69.2)	145 (56)	0.51
MCA – M2	36 (12.6)	3 (11.5)	33 (12.7)	1.00
Distal ICA + M1/A1	43 (15.1)	5 (19.2)	38 (14.7)	0.58
Tandem pathology	43 (15.1)	0	43 (16.6)	0.03
Onset-to-groin puncture time (min)	195 (15–765)	204 (55–464)	191 (15–765)	0.82
IVT	173 (60.7)	5 (19.2)	168 (64.9)	0.01
Outcome parameters				
Recanalisation (TICI ≥2b)	232 (81.4)	18 (69.2)	214 (82.6)	0.64
SICH	23 (8.1)	2 (7.7)	21 (8.1)	1.00
Other ICH	32 (11.2)	2 (7.7)	30 (11.6)	1.00
Good 90-day clinical outcome (mRS ≤2)	156 (54.7)	9 (34.6)	147 (56.8)	0.27
90-day mortality (mRS 6)	61 (21.4)	7 (26.9)	54 (20.8)	0.47

Data are mean ± SD (range), median (range) or *n* (%).
A1, proximal segment of anterior cerebral artery; DOAC, direct oral anticoagulant; ICA, internal carotid artery; INR, international normalised ratio; IVT, intravenous thrombolysis; MCA, middle cerebral artery; mRS, modified Rankin Scale; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulation; SICH, symptomatic intracerebral haemorrhage; TIA, transient ischaemic attack; TICI, Thrombolysis in Cerebral Infarction.

patient groups with and without OAC in terms of their age, sex, and severity of their neurological deficit. With the exception of tandem pathologies (ICA cervical segment stenosis/occlusion + M1/M2 segment occlusion), which was not present in any patient with OAC and present in 16.6% of patients without OAC (p=0.03), no statistically significant differences were found in the localisations of artery occlusions between both groups. The anticoagulated group showed a significantly more frequent occurrence of atrial fibrillation (100% versus 44.0%; p=0.01) and of previous stroke or TIA (38.5% versus 15.1%; p=0.03).

The achievement rate of successful recanalisation (TICI ≥2b) did not show a significant difference (69.2% of patients with OAC and 82.6% of patients without OAC; Table 1) and no statistically significant predictor of its achievement was identified (Table 2). In 25 OAC patients treated with warfarin, successful recanalisation was achieved in 75% of patients with therapeutic INR values (INR ≥2) and in 71.4% patients with sub-therapeutic INR values (INR <2; p=1). No statistically significant differences were found between the patients with and without OAC in terms of the occurrence of SICH (Fig 1) according to the SITS-MOST definition (7.7% versus 8.1%) and of other types of intracranial bleeding (7.7% versus 11.6%), and also as regards the achievement of a good 90-day clinical outcome (34.6% versus 56.8%) and in 90-day mortality (26.9% versus 20.8%; Table 1, Fig 2). In the OAC group, both patients suffering from SICH were treated with warfarin with sub-therapeutic INR values. The age and the neurological deficit at the time of the treatment were identified as independent negative predictors of the achievement of a good 90-day clinical outcome (odds ratio [OR]=0.90, 95% confidence interval [CI]: 0.88–0.94; p=0.0000002, and OR=0.83, 95% CI: 0.77–0.90; p=0.00001, respectively) and as independent positive predictors of mortality (OR=1.12, 95% CI: 1.07–1.18; p=0.00001, and OR=1.17, 95% CI: 1.07–1.27; p=0.0005, respectively; Table 2).

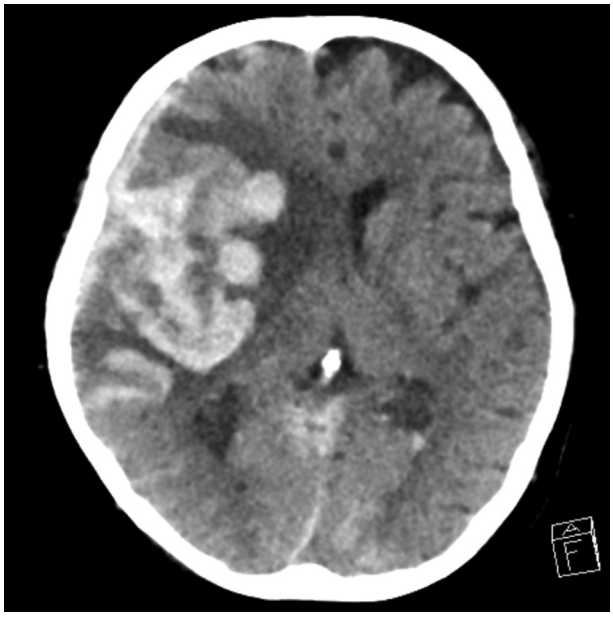

Figure 1 Axial CT image of parenchymal haematoma type 2, accompanied by subdural haematoma and subarachnoid haemorrhage developed on the second day in an 80-year-old woman treated by MT for the occlusion of the M1 segment of the right middle cerebral artery with TICI 3 result. The patient was on warfarin with an INR value of 1.8 at the time of stroke.

Discussion

The use of OAC before MT with stent-retrievers in the anterior circulation AIS was associated with a higher incidence of neither SICH nor any other intracranial bleeding in the present population. Other studies have reached similar conclusions to the present study, although their patients were not treated solely with stent-retrievers or some of them had additional occlusions in the posterior circulation. In the set of 28 patients with OAC, with median INR 1.79, undergoing endovascular treatment (out of the total set of 714 patients treated between December 1992 and October 2010), De Marchis *et al.*[3] determined SICH frequency of 7.1%, which is similar to what was found in the present study (7.7%). Purrucker *et al.*[4] published results for 28 patients with OAC treated between February 2012 and February 2015 using stent-retrievers. Basilar artery occlusion was present in three cases, and IVT was also applied in five patients as in the present study. Successful recanalisation (TICI ≥2b) was achieved in this group in 59% of patients (69% in the present study), mRS ≤2 at 3 months was found in 19% of patients (35% in the present study), and the mortality rate (26%) was similar to the present study (27%). The frequency

Table 2
Independent predictors of recanalisation, good 90-day clinical outcome and 90-day mortality.

Predictor	Recanalisation (TICI ≥2b)		Good 90-day clinical outcome (mRS ≤2)		90-day mortality (mRS 6)	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age	0.97 (0.94–1.01)	0.13	0.90 (0.88–0.94)	0.0000002	1.12 (1.07–1.18)	0.00001
Previous stroke/TIA	0.78 (0.32–1.90)	0.59	0.64 (0.28–1.46)	0.29	0.54 (0.19–1.60)	0.27
Atrial fibrillation	1.20 (0.52–2.75)	0.67	1.19 (0.58–2.44)	0.63	1.12 (0.46–2.69)	0.81
OAC	0.55 (0.18–1.68)	0.30	1.14 (0.39–3.33)	0.23	1.57 (0.45–5.44)	0.47
NIHSS baseline	0.93 (0.87–1.01)	0.07	0.83 (0.77–0.90)	0.00001	1.17 (1.07–1.27)	0.0005
Onset-to-groin puncture time	1.00 (1.00–1.00)	0.90	1.00 (0.99–1.00)	0.31	1.00 (0.99–1.00)	0.34
Other ICH	2.26 (0.58–8.71)	0.24	0.51 (0.18–1.49)	0.22	0.72 (0.22–2.42)	0.60

ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulation; TIA, transient ischaemic attack; TICI, Thrombolysis in Cerebral Infarction.

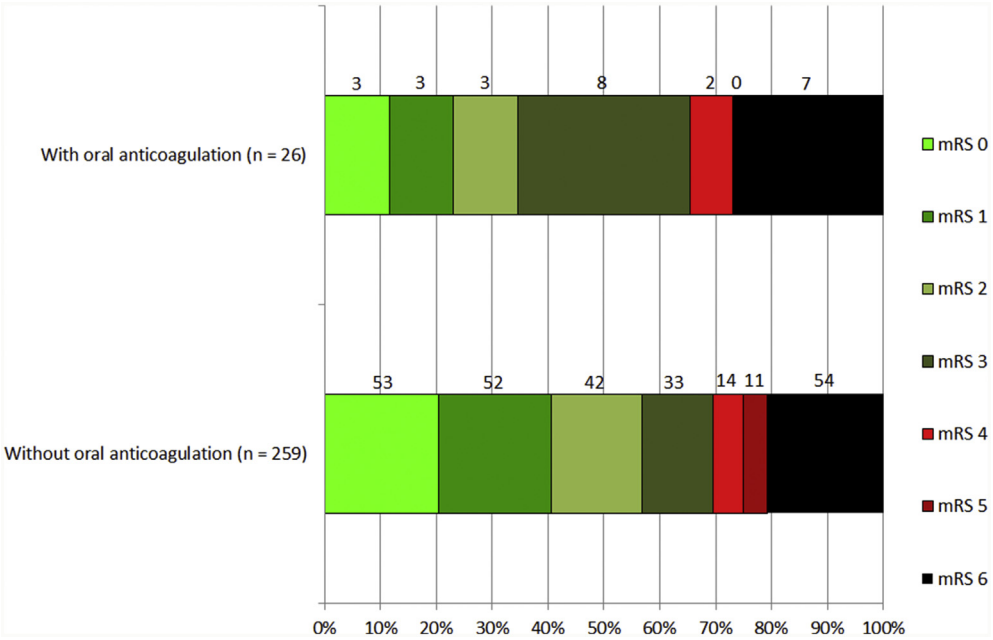

Figure 2 The 90-day clinical outcome assessed using mRS.

of SICH was only 4% (7.7% in the present study), but 50% of the patients showed other types of intracranial bleeding including two cases of subarachnoid haemorrhage (other intracranial bleeding was noted in 7.7% of patients in the present study). A similarly high frequency (53%) of other types of intracranial bleeding after endovascular treatment, this time in association with DOAC therapy, was reported by Rebello *et al.*[5] Although the frequency of SICH (8.1%) in the present cohort was higher than the 4–5% frequency reported in clinical trials,[26] this frequency is in better accordance with common clinical practice and with registry data. For example, SICH occurrence of 9.9% was found in the North American Solitaire Acute Stroke registry[27] and SICH incidence of up to 16% was reported in the set of 632 acute MT procedures performed using stent-retrievers at 21 sites in China.[28] This unusually high number may be related to the need for a higher number of passages due to the higher rate of intracranial atherosclerotic stenoses typical for the Asian population.

Good 90-day clinical outcome (mRS $\leq$2) was achieved more frequently in the present cohort without OAC (56.8%) than in those with OAC (34.6%). This statistically insignificant difference may be caused by several factors: the present cohort with OAC was older (75 versus 71.1 years), with more comorbidities (more frequent occurrence of arterial hypertension, diabetes mellitus, dyslipidaemia, ischaemic heart disease, atrial fibrillation, and history of previous stroke/TIA) and, none of them suffered from tandem pathology. Less frequent achievement of good clinical outcome in patients with OAC versus those without OAC was also reported by other authors, e.g., 30% versus 40% (Rebello *et al.*[5]), 47% versus 55% (Benavente *et al.*[6]), and 36% versus 49% (Černík *et al.*[8]).

The mean INR value of patients on warfarin was 1.81 (median 1.78) in the present study. Other authors reported mean values of 2.0 (Rebello *et al.*[5]) and 1.91 (Zapata-Wainberg *et al.*[9]) and, the median values of 1.79 (De Marchis *et al.*[3]) and 2.1 (Kurowski *et al.*[7]). The present group of 26 patients on OAC is too small to determine a possible dependency of SICH on a particular INR value; however, as found repeatedly in patients on warfarin with INR $\leq$1.7, treated with IVT, the INR value did not differ between patients with and without SICH,[29–31] and Benavente *et al.*[6] reported no difference in the occurrence of SICH also in patients with INR $<$1.7/$\geq$1.7 treated with MT.

In the present patient set, the age and the neurological deficit at the time of treatment were identified as independent negative predictors of the achievement of a good 90-day clinical outcome and as independent positive predictors for mortality. This finding fully corresponds to clinical practice.[32]

Several limitations of the present study should be mentioned. The two main limitations are its retrospective observational character and a relatively low number of patients treated with OAC. Third, the choice of treatment method was dependent on physician decision. Fourth, physicians assessing recanalisation success, the occurrence of SICH and 90-day clinical outcome were not blinded to the OAC treatment; however, the present study represents real-world data.

In conclusion, in the present cohort, the use of MT with stent-retrievers in AIS in the anterior circulation in anticoagulated patients seemed to be safe and efficient considering that this procedure was not associated with a higher risk of SICH and had no statistically significant impact on the 90-day clinical outcome. The general validity of these results should be confirmed in a larger, controlled, prospective study.

Conflict of interest

None declared.

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