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Original Article

Heparin during endovascular stroke treatment seems safe

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ABSTRACT

Background and purpose. – the effect of intravenous heparin during mechanical thrombectomy for acute ischemic stroke is not clear. We aimed to study efficacy and safety of heparin use during endovascular stroke treatment in a real-world setting.
Materials and methods. – patients with anterior circulation stroke were divided, based on the use of intraprocedural heparin, in those treated and those untreated. Main outcomes were successful reperfusion defined as a TICI Score ≥ 2b, 3-month functional independence defined as a modified Rankin Scale ≤ 2, symptomatic intracranial hemorrhage (sICH) and mortality.
Results. – 361 patients were eligible for analysis; 200 were (H+) and 161 (H-). The (H-) group showed higher age and ASPECTS (74 ± 14 vs. 68.9 ± 12.2; $P = 0.001$; 8 ± 1.6 vs. 7.4 ± 2.1; $P = 0.009$) without differences in vascular risk factors. Heparin untreated patients showed a shorter onset-to-reperfusion time (271 ± 57.6 min vs. 309 ± 102.2 min; $P < 0.001$). No differences were found in 3-month functional independence, sICH and mortality whereas the rate of successful reperfusion was higher in the (H-) group. After logistic regression analysis successful reperfusion was independently associated with CT ASPECTS (OR: 1.16; 95%CI 1.01–1.35; $P = 0.040$) but inversely associated with the use of heparin (OR: 0.48; 95% CI 0.24–0.98; $P = 0.045$).
Conclusions. – Heparin use during mechanical thrombectomy for anterior circulation acute ischemic stroke in a real world setting is safe.

Introduction

The effect of intravenous (IV) heparin during endovascular procedures for acute ischemic stroke has been barely investigated and no definite recommendations exist regarding management of anticoagulation during mechanical thrombectomy. Avoiding IV thrombolysis after recent use of heparin as well as avoiding any antithrombotic treatment in the first 24 hours after IV thrombolysis is a well-known guideline for stroke physicians [1]. Urgent anticoagulation for prevention of early recurrent stroke is not recommended due to the risk of serious intracranial hemorrhage (ICH) (class III, level A) [1]. While patients without target occlusion for MT are less severe and have a lower risk of poor outcome, pooled analyses of IVT studies have shown a symptomatic ICH rate varying from 3.25 to 7.61% [2,3]. Therefore, currently no role is recognised for heparin in the first 24 hours of ischemic stroke nor as a periprocedural therapy in IV thrombolysis and mechanical thrombectomy treated patients. It is already established that percutaneous coronary interventions for acute coronary syndromes require effective anticoagulation to prevent adverse events such as stroke, catheter thrombosis and ischemic recurrences [4]. With the recent evidence of endovascular stroke treatment benefit, the need for thromboprophylaxis with systemic anticoagulation during arterial catheterization has been claimed and actually largely employed [5–9]. However due to the lack of evidence,peri-procedural use and doses of IV heparin during mechanical thrombectomy have been mainly at interventionist discretion [10,11].

The aim of our study was to compare efficacy and safety of heparin during mechanical thrombectomy for acute ischemic stroke in a real-world setting.

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sICH	symptomatic intracranial hemorrhage
ASPECT	Alberta stroke program early CT score
NIHSS	National institute of health stroke scale

Material and methods

This was a single-center study. Acute ischemic stroke patients from our prospective stroke registry were retrospectively analysed. Inclusion criteria were: 1. anterior circulation stroke; 2. MT procedure started within 6 hours of symptom onset; 3. available 3-month follow-up; 4. available heparin use data. IV heparin sodium use during endovascular procedure was not restricted and administered at discretion of operator. Total amount of IV heparin was calculated based on speed of infusion, use of bolus and time from first infusion to the end of the procedure. Patients were divided in two groups based on intra-procedural use of heparin: heparin treated and heparin untreated. The main variables were compared between groups.

Baseline characteristics included in the analysis were: age, gender, prior use of anti-platelets, NIHSS, site of occlusion, history of hypertension, diabetes, smoking, atrial fibrillation, ASPECTS on NCCT [12], collaterals adequacy on pretreatment CTA as evaluated in a previous study [13]. Procedural characteristics compared between groups were: IV thrombolysis, general anesthesia, type of device for thrombectomy, procedural times.

IV thrombolysis was administered within 4,5 hours after stroke onset at a full dose (recombinant tissue plasminogen activator 0.9 mg/kg, 10% as a bolus and the remaining in 1 hour infusion) [1] and continued during endovascular procedure [14].

Outcome measures compared between groups were: successful reperfusion defined, according to the TICI grading, as a Score $\geq$ 2b [15], hemorrhagic complications defined according to the European Cooperative Acute Stroke Study criteria (no hemorrhage, hemorrhagic infarction-1, hemorrhagic infarction-2, parenchymal hematoma-1, parenchymal hematoma-2) [16], sICH defined as an hemorrhage associated with an increase of at least 4 points in the NIHSS. We further evaluated the effect of heparin bolus on main safety and efficacy outcomes.

The study was approved by the local ethics committee.

Statistical analysis

All data were initially entered into an EXCEL database (Microsoft, Redmond, Washington – United States) and the analysis was performed using the Stata/IC version 13 (StataCorp 2013, College Station, TX, USA). Descriptive statistics consisted of means $\pm$ standard deviation (SD) or medians with range for parameters with gaussian distributions (after confirmation with histograms and the Kolmogorov-Smirnov test) or frequencies (%) as appropriate. Comparison of continuous variables was performed by means of Student's *t*-test or Mann–Whitney U test. Comparison of categorical variables was performed by means of Fisher's exact test. A *P*-value of < 0.05 was considered statistically significant for all analyses. To weigh for potentially confounding factors, alogistic regression analysis was finally performed to determine the independent predictors of outcome, including all significant variables in univariate analysis and also non-significant factors that could have contributed to the outcome. Odds ratios with standard errors and 95% confidence intervals were provided. A *P*-value $< .05$ was considered statistically significant.

Results

Out of 443 patients collected since august 2013 through august 2017 361 fulfilled inclusion criteria and were eligible for analysis as shown in Fig. 1. Heparin treated patients were 200 (55.4%), heparin untreated patients were 161. The median IV heparin dose used during endovascular procedure was 2500 U.I. (IQR:640–5000 U.I.) and bolus was used in 112 patients (56%) (median dose 4000 U.I.; IQR: 2500–5000 U.I.). The heparin untreated group showed higher age and ASPECTS (74 ± 14 vs. 68.9 ± 12.2; $P < 0.01$; 8 ± 1.6 vs.

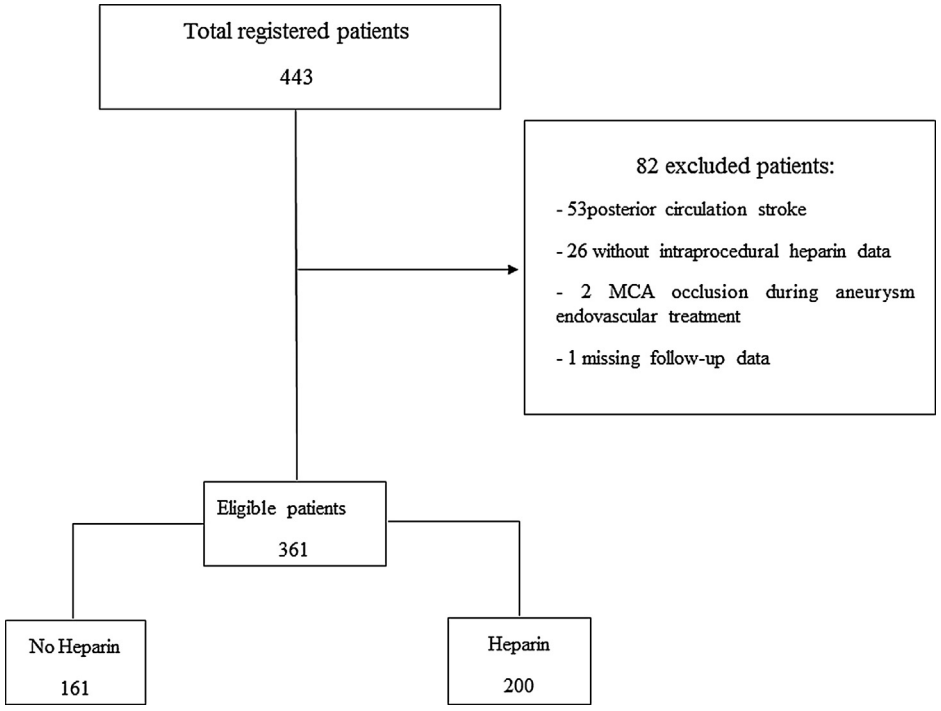

Fig. 1. Flow-chart of the analysed sample.

Table 1
Demographics, baseline and procedural characteristics.

	No Heparin ($n=161$)	Heparin ($n=200$)	P
Age, years (mean ± SD)	74 ± 14	68.9 ± 12.2	<0.01
Gender (male) (%)	62(38.5)	85(42.5)	0.45
Pre-stroke mRS 0–2 (%)	156(96.8)	198(99)	0.24
Prior antiplatelet therapy	70(43.4)	83(41.5)	0.74
Hypertension (%)	115(71.4)	147(73.5)	0.72
Diabetes (%)	24(14.9)	39(19.5)	0.26
Atrial Fibrillation (%)	72(44.7)	95(47.5)	0.67
Current Smoking (%)	25(15.5)	32(16)	1.00
Glycemia (mean ± SD)	128.2 ± 42.8	134.1 ± 50.7	0.36
NIHSS (mean ± SD)	17.1 ± 5.01	18.1 ± 4.1	
NIHSS (median/range)	18(2-26)	19(3-25)	0.17
SBP (mean ± SD)	144.9 ± 26.4	148.3 ± 26.8	0.47
DBP (mean ± SD)	79 ± 16.8	82.3 ± 14.8	0.07
ASPECTS (mean ± SD)	8 ± 1.6	7.4 ± 2.1	
ASPECTS(median/range)	8(2-10)	8(2-10)	<0.01
MCA occlusion (%)	102(63.3)	123(61.5)	0.74
Terminal ICA (%)	4(2.4)	2(1)	0.41
T occlusion (%)	9(5.5)	7(3.5)	0.44
Tandem occlusion (%)	46(28.5)	68(34)	0.3
Cervical ICA stenting (%)	1(0.6)	34(17)	<0.01
Good collaterals (%)	99(61.4)	128(64)	0.66
I.V. Thrombolysis (%)	112(69.5)	106(53)	<0.01
General Anesthesia (%)	25(15.5)	97(48.5)	<0.01
Clot Burden Score (median/range)	6(2-8)	6(2-9)	0.06
Onset-groin puncture[a] (min, mean ± SD)	224 ± 60.9	236.2 ± 96.8	0.08
Onset-reperfusion[a] (min, mean ± SD)	271 ± 57.6	309 ± 102.2	<0.01
Groin-reperfusion (min, mean ± SD)	46.3 ± 30.4	73.7 ± 41	<0.01
Device attempts[a] (mean ± SD)	2.6 ± 2.1	2.6 ± 1.6	0.9

NIHSS: National institute of health stroke scale; SBP: systolic blood pressure; DBP: diastolic blood pressure; ASPECTS: Alberta stroke program early CT score; MCA: middle cerebral artery; ICA: internal carotid artery; T occlusion: combined occlusion of terminal ICA, MCA and ACA.
Heparin group: 195 patients because of 5 wake-up stroke (without known last time seen well).
[a] Calculated on: No Heparin group: 152 patients because of 9 wake-up stroke (without known last time seen well).

7.4 ± 2.1; $P<0.01$) without differences in vascular risk factors as shown in Table 1. Heparin untreated patients showed higher use of IV thrombolysis (69.5% vs. 53%; $P<0.01$) and thromboaspiration devices (98.6% vs. 70.2%; $P<0.01$), a shorter onset-to-reperfusion time (271 ± 57.6 min vs 309 ± 102.2 min; $P<0.01$) and a lower rate of cervical internal carotid artery stenting (0.6% vs. 17%; $P<0.01$ (Table 1).

The analysis of safety and efficacy showed no difference at all in 3-month functional independence, sICH and mortality whereas the rate of successful reperfusion was higher in the (H-) group (82.6% vs. 69.5%; $P<0.01$) (Table 2). These findings were confirmed in the direct thrombectomy group (83.6% vs. 64.8%; $P=0.02$) but not in the combined treatment group (IV thrombolysis plus mechanical thrombectomy) in which the untreated and the treated groups did not show significant difference in successful reperfusion (82.1% vs. 73.5%; $P=0.14$) (Table 2).

As a secondary outcome, 24 hours ASPECTS was higher (indicating smaller infarction size) in the heparin untreated group [6(0–10) vs. 4(0–10); $P\leq0.01$] and these findings were confirmed after analyzing separately the direct thrombectomy and the combined treatment group. When we analysed the effect of heparin bolus on main outcomes no differences were detected in 3-month functional independence, sICH, successful reperfusion and mortality between patients treated and those untreated with bolus (Table 3).

After logistic regression analysis successful reperfusion was independently associated with CT ASPECTS (OR: 1.16; 95% CI 1.01 to 1.35; $P=0.040$) but inversely associated with the use of stentrievers (OR: 0.42; 95% CI 0.21 to 0.85; $P=0.025$) (i.e. directly associated to the use of thromboaspiration devices) and heparin (OR: 0.48; 95% CI 0.24 to 0.98; $P=0.045$). (Table 4)

Table 3
Comparison of treatment with and without bolus on main outcomes in the heparin group.

	Heparin bolus ($n=112$)	No Heparin bolus ($n=88$)	P
Any ICH (%)	39(34.8)	34(38.6)	0.65
Symptomatic ICH (%)	14(12.5)	12(13.6)	0.83
Successful reperfusion (%)	79(70)	60(68)	0.75
3-month mRS 0–2	43(38.3)	29(33)	0.4
Mortality	33(29.4)	30(34)	0.54

ICH: intracranial haemorrhage; mRS: modified Rankin scale.

Table 4
Multivariable regression model: predictors of successful reperfusion (TICI ≥ 2b).

	OR	SE	95% CI	P
Age	1.01	0.01	0.98–1.02	0.615
Onset NIHSS	0.96	0.03	0.89–1.03	0.313
ASPECTS	1.16	0.08	1.01–1.35	0.040
I.V. Thrombolysis	0.92	0.29	0.49–1.71	0.793
General Anesthesia	1.15	0.39	0.29–0.78	0.669
Heparin	0.48	0.17	0.24–0.98	0.045
Onset-reperfusion time	0.99	0.01	0.99–1.00	0.513
Good collaterals	1.44	0.47	0.76–2.72	0.261
Cervical ICA stenting	0.59	0.34	0.19–1.85	0.366
Stent retriever use	0.42	0.15	0.21–0.85	0.025

TICI: thrombolysis in cerebral infarction score; NIHSS: National institutes of health stroke scale; ASPECTS: Alberta stroke program early CT score; ICA: internal carotid artery; OR: odds ratio; SE: standard error; CI: confidence intervals.

Table 2
Univariate analysis of safety and efficacy outcomes.

	Overall			Direct MT			IVMT		
	No Heparin ($n=161$)	Heparin ($n=200$)	P	No Heparin ($n=49$)	Heparin ($n=94$)	P	No Heparin ($n=112$)	Heparin ($n=106$)	P
Successful reperfusion (%)	133(82.6)	139(69.5)	0.004	41(83.6)	61(64.8)	0.02	92(82.1)	78(73.5)	0.14
24 hs follow-up ASPECTS (median;range)	6(0-10)	4(0–10)	<0.001	6(0-10)	5(0–10)	0.03	6(0–0)	5(0–10)	<0.01
Any ICH (%)	58(36)	74(37)	0.9	19(38.7)	34(36.1)	0.85	39(34.8)	40(37.7)	0.67
SAH	3(1.8)	2(1)	0.66	1(2)	1(1)	1.00	2(1.7)	2(1.8)	1.00
HI-1	3(1.8)	7(3.5)	0.52	2(4)	3(3.1)	1.00	1(0.8)	4(3.7)	0.2
HI-2	12(7.4)	10(5)	0.37	7(14.2)	5(5.3)	0.1	5(4.4)	5(4.7)	1.00
PH-1	15(9.3)	23(11.5)	0.6	2(4)	9(9.5)	0.33	13(11.6)	12(11.3)	1.00
PH-2	25(15.5)	32(16)	1.00	7(14.2)	14(14.8)	1.00	18(16)	14(13.2)	057
Symptomatic ICH (%)	16(9.9)	19(9.5)	1.00	3(6.1)	12(12.7)	0.26	7(6.2)	14(13.2)	0.1
3-month mRS ≤ 2 (%)	66(40.9)	73(36.5)	0.38	13(26.5)	31(32.9)	0.45	53(47.3)	41(38.6)	0.21
3-month mRS ≤ 3 (%)	74(45.9)	91(45.5)	1.00	14(28.5)	41(43.6)	0.1	60(53.5)	49(46.2)	0.34
All-cause mortality (%)	49(30.4)	63(31.5)	0.9	18(36.7)	35(37.2)	1.00	31(27.6)	26(24.5)	0.64

MT: mechanical thrombectomy; IVMT: intravenous thrombolysis plus mechanical thrombectomy; ASPECTS: Alberta stroke program early CT score; ICH: intracranial haemorrhage; SAH: subarachnoid haemorrhage; HI: hemorrhagic infarction; PH: parenchymal haematoma; mRS: modified Rankin scale.

Discussion

Anticoagulation during endovascular stroke treatment is controversial and, even though widely used, has been insufficiently evaluated. In this retrospective study the use of IV heparin during endovascular treatment of acute ischemic stroke patients did not translate in better outcomes such as mortality, sICH and 3-month functional independence. However we found that heparin was associated with a lower rate of successful reperfusion. This finding was not affected by IV thrombolysis as shown by subgroup analysis and multivariable logistic regression. Our results are in contrast with those by Winningham et al. [10] who found, in a post-hoc analysis of TREVO 2 trial, periprocedural heparin to be associated with 90-day good clinical outcome. In line with this study our results demonstrated that heparin has a good safety profile since no differences in sICH nor in mortality were detected compared to patients not treated with heparin. These findings occurred despite heparin treated patients had a lower baseline ASPECTS indicating a larger stroke size at onset.

Another relevant finding from our analysis was that the heparin untreated group was associated with quicker times needed for reperfusion. This finding is in line with the higher reperfusion rate and unlikely to be affected by local protocols since no differences were found in onset to groin puncture between groups. These findings are similar to those from a post-hoc analysis of the Multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial which found a trend toward higher rate and faster reperfusion in the no heparin use group [11]. As a matter of fact heparin produces its anticoagulant effect by binding to antithrombin III but also binds to a number of acute phase reactant proteins, competing with antithrombin III, thereby impairing its anticoagulant effect [17,18]. In this regard low-molecular weighted heparins offer less nonspecific binding to plasma proteins [19] and may therefore contribute to a more predictable dose response [20]. However since heparin administration was at discretion of interventionist, some confounding variables, which we could not measure or adjust for, may have affect differences in angiographic outcomes. One above all, the time needed for reperfusion during the procedure or an hostile anatomy could have led operator to use heparin. In this view heparin was administered irrespective of pre-treatment imaging and clinical investigated variables, with the aim to avoid arterial thromboembolism and to increase operator's confidence. As a matter of fact in some cases decision concerning heparin use was taken after detection of catheter thrombosis soon after groin puncture. The higher 24-hours ASPECTS found in the heparin untreated patients is likely to be the consequence of higher rate of reperfusion and quicker reperfusion in this group.

Our study showed that the use of heparin bolus did not affect at all main outcomes. These findings are in contrast with those by Winningham et al. [10] who found heparin bolus to be an independent predictor of 3-month good outcome despite a lower mean dose compared to what reported in our study. It cannot be excluded that different protocols could have affect different findings.

This study has several limitations. First, it is retrospective and data are derived from a single-center thus limiting the generalizability of its findings. Second, no predefined dose of heparin per kilogram of body weight was established but rather decided by the interventionist on a case-by-case basis. Therefore no activating clotting time was used before or during treatment. Third, data on procedural complications rate such as distal embolization or arterial reocclusion were incomplete and therefore could not be reported. Despite this, in the above mentioned study from the TREVO 2 trial no differences in procedural complications were found [10].

Compared to previous studies evaluating this issue [10,11], our analysis included a higher number of patients, focused on anterior circulation stroke patients, excluding vertebro-basilar occlusions and to our knowledge, is the first report of a real-world experience.

Conclusions

Our study revealed that heparin use during endovascular treatment of anterior circulation acute ischemic stroke in a real world setting is safe and is associated with lower chance of reperfusion. Further investigation of this finding is warranted.

The authors declare that they have no conflict of interest.

Disclosure of interest

Fabrizio Sallustio: conceptualization, methodology, validation, writing-original draft preparation, funding acquisition.

Caterina Motta: methodology, software, formal analysis, writing- review and editing.

Stefano Merolla: investigation, resources, writing- review and editing.

Giacomo Koch: investigation, writing- review and editing, supervision, funding acquisition.

Francesco Mori: investigation, data curation, writing- review and editing, visualization.

Fana Alemseged: data curation, writing- review and editing, project administration.

Daniele Morosetti: investigation, resources.

Valerio Da Ros: investigation, resources, project administration.

Roberto Gandini: investigation, resources, writing- review and editing.

Marina Diomedi: conceptualization, formal analysis, resources, writing- review and editing, supervision.

The other authors declare that they have no competing interest.

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