ORIGINAL RESEARCH

Periprocedural heparin use in acute ischemic stroke endovascular therapy: the TREVO 2 trial

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ABSTRACT

Background The use of periprocedural heparin has previously been reported to be safe and potentially beneficial during thrombectomy with older generation devices. We aimed to evaluate the safety and clinical outcomes of heparin use in the stent retriever era.

Methods A post hoc analysis of the TREVO 2 trial was performed comparing baseline characteristics and clinical outcomes between patients who received (HEP+) and those who did not receive periprocedural heparin (HEP–) while undergoing MERCI or TREVO clot retrieval.

Results Of 173 patients, 58 (34%) received periprocedural heparin including 40 who received one preprocedural bolus (median 3000 units). Baseline characteristics among HEP+ and HEP– patients were similar except HEP+ patients had a lower NIH Stroke Scale (NIHSS) score (17 vs 19; p=0.04), lower IV tissue plasminogen activator use (38% vs 64%; p<0.01), and a higher median ASPECTS score (8.0 vs 7.0; p=0.02). HEP+ patients were more likely to have vertebrobasilar and middle cerebral artery (MCA)-M1 occlusions but less likely to have internal carotid artery and MCA-M2 occlusions (p=0.04). Time from symptom onset to puncture was similar in the two groups while procedure duration was longer in HEP+ patients (99 vs 83 min; p<0.01). Thrombolysis In Cerebral Infarction (TICI) 2b–3 reperfusion rates, embolization to unaffected territories, access site complications, and intracranial hemorrhages were similar between the groups. In multivariable logistic regression, a good outcome (90-day modified Rankin Scale score 0–2) was independently associated with heparin bolus use (OR 5.30; 95% CI 1.70 to 16.48), TICI 2b–3 reperfusion (OR 6.56; 95% CI 2.29 to 18.83), stent retriever use (OR 3.54; 95% CI 1.38 to 9.03) and inversely associated with intubation (OR 0.10; 95% CI 0.03 to 0.33), diabetes (OR 0.11; 95% CI 0.03 to 0.39), NIHSS (OR 0.84; 95% CI 0.75 to 0.93), time from symptom onset to puncture (OR 0.64; 95% CI 0.45 to 0.89), and heart failure (OR 0.23; 95% CI 0.06 to 0.83).

Conclusions The use of periprocedural heparin in stent retriever thrombectomy is associated with a good clinical outcome at 90 days and similar rates of symptomatic intracranial hemorrhage. Further studies are warranted.

Clinical trial registration URL:http://www.clinicaltrials.gov. Unique identifier: NCT01270867;Post-results.

INTRODUCTION

Multiple randomized clinical trials have demonstrated no benefit with the use of intravenous heparin in acute ischemic stroke (AIS), summarized by the recommendation against early heparin use in the American Heart Association/American Stroke Association guidelines for the early management of AIS.[1] Its benefit in the setting of AIS endovascular therapy, however, is less clear. A post hoc analysis of the Multi MERCI trial previously demonstrated in a multivariable analysis that use of periprocedural heparin was associated with improved outcomes at 90 days after thrombectomy (OR 5.89; 95% CI 1.34 to 25.92; p=0.02) with no significant increase in symptomatic intracranial hemorrhage (sICH) or rates of all-cause mortality.[2] Considering the superior performance of stent retrievers over Merci, the potential risks and benefits of periprocedural heparin use in AIS endovascular therapy with contemporary technology are not known.

Protocols from 13 randomized clinical trials evaluating AIS endovascular treatment show marked variability in recommendations on periprocedural heparin use.[3–15] Earlier endovascular trials evaluating the efficacy of intra-arterial (IA) thrombolytics protocolized the administration of heparin along a spectrum, with bolus doses ranging from 2000 IU to 100 IU/kg and continuous infusion doses ranging from none to 500 IU/hour for 4 hours. Symptomatic hemorrhage rates in these trials ranged from 5% to 27.3%, with higher rates associated with higher heparin doses.[3–5] Later endovascular trials evaluating mechanical thrombectomy devices (aspiration devices, coil retrievers, and stent retrievers) administered heparin periprocedurally with bolus doses ranging from 2000 IU to 5000 IU and infusion rates ranging from 450 to 500 IU/hour; rates of symptomatic hemorrhage ranged from 0% to 6% in these studies.[8–10 15] In some trials no recommendations on the use of heparin were provided in the study protocol.[6 7 11–14]

Given the limited data on periprocedural heparin use in AIS endovascular treatment, the objective of our study was to evaluate the periprocedural complication rates and clinical outcomes of periprocedural heparin use in the TREVO 2 trial.

MATERIALS AND METHODS

TREVO 2 was a randomized, prospective, controlled multicenter, open-label, adaptive, non-inferiority trial designed to evaluate the comparative efficacy and safety of the Merci coil retriever and the Trevo stent retriever for mechanical thrombectomy in AIS due to large vessel occlusion. Adults aged 18–85 years presenting with acute stroke and significantly disabling symptoms in the setting of

an angiographically-proven occlusion of a proximal intracranial artery (internal carotid, M1 or M2 segments of the middle cerebral, basilar, or vertebral arteries) who underwent endovascular therapy within 8 hours from the time last assessed at baseline were included. Eligible patients were required to have baseline National Institutes of Health Stroke Scale (NIHSS) scores between 8 and 29, failure of treatment with intravenous recombinant tissue plasminogen activator (r-tPA), defined as absence of recanalization on baseline conventional cerebral angiography or ineligibility for intravenous r-tPA, no significant pre-stroke disability with modified Rankin Scale (mRS) score ≤1, and life expectancy of at least 6 months. Complete trial methods have been described previously.[7] Eligible patients were randomly allocated (in a 1:1 ratio) to mechanical thrombectomy with Trevo or Merci devices. The trial did not restrict periprocedural heparin use and was administered at the discretion of the operator. Appropriate institutional review board and regulatory approvals were obtained by participating centers in TREVO-2. The study is registered with ClinicalTrials.gov, number NCT01270867.

CT or MRI scans performed prior to thrombectomy, CT or MRI scans at 24 hours after the procedure (with a tolerance of 18–36 hours), and the complete set of angiographic images were sent to core imaging laboratories for an independent assessment of post-procedural hemorrhagic complications (by criteria established in ECASS trials) and evaluation of the degree of recanalization, as defined by the Thrombolysis in Cerebral Infarction (TICI) score (0–3). The investigating sites were asked to provide clinical outcome assessments from masked investigators (certified on NIHSS and mRS grading but not part of the treating team). Patients were followed up for 90 days after the procedure.

The primary efficacy endpoint was revascularization success, defined as TICI ≥2 flow in the territory of the occlusion and the primary safety endpoint was a composite of procedure-related adverse events 24 (18–36) hours after the procedure defined as the following events: any vascular perforation or intramural dissection, sICH, embolization to a previously uninvolved territory, access site complications requiring surgical repair or blood transfusion, periprocedural mortality, device failure (in vivo breakage), or any other complications regarded by the clinical events committee to be related to the procedure. Prespecified secondary endpoints were time to revascularization (mean time from initial guide catheter placement to achievement of TICI ≥2 reperfusion or end of procedure in non-reperfused patients), good clinical outcomes at 90 days (defined as an mRS score of ≤2), all-cause mortality at 90 days, incidence of any sICH within 24 (18–36) hours of the procedure, and neurologic deterioration (≥4 point increase in NIHSS score) at 24 hours.

Statistical analysis

Since the trial did not specify heparin use in the protocol, a post hoc analysis was performed to compare baseline characteristics and clinical outcomes between patients who received any periprocedural heparin (HEP+) and those who received no heparin (HEP−) from standardized case report form questions. Patients who had been receiving low molecular weight heparin (LMWH) prior to the procedure were excluded from this analysis. A total of 178 patients were treated in the trial and, after excluding five patients who were receiving LMWH prior to endovascular treatment, the analysis cohort included 173 patients. Baseline characteristics and patient demographics were compared between the HEP+ and HEP− groups using the Wilcoxon rank sum test, unequal variance t-test, and Fisher's exact test. Predictors of a good outcome at 90 days (mRS 0–2) were evaluated using multivariable logistic regression modeling. The model was created using a backward elimination method. Variables were eligible for inclusion into the multivariable model building process if the variable had a univariate p value ≤0.2. All p values obtained in the multivariable analysis are from the Wald χ^2 statistic in the final model and a p value ≤0.05 was considered significant.

RESULTS

Of 173 patients included in this analysis, 58 (34%) received any periprocedural heparin (total mean dose 4016 units), including 40 patients who only received a preprocedural bolus (mean 2950 units, median 3000 units). Baseline characteristics were similar among HEP+ and HEP− patients, except that HEP+ patients had lower NIHSS (17±5 vs 19±5; p=0.04), less IV rt-PA use (38% vs 64%; p<0.01), and higher baseline ASPECTS (7.6±1.3 vs 7.1±1.7; p=0.02; . Site of occlusion varied, with HEP+ patients having more vertebrobasilar (10 vs 5%) and MCA-M1 (71% vs 55%) occlusions and fewer ICA (9% vs 22%) and MCA-M2 (10% vs 17%) occlusions than HEP− patients (p=0.04). Time from symptom onset to puncture was similar between the two groups; however, procedure duration was longer in HEP+ patients (99±48 vs 83±42 min; p<0.01) table 1.

CLINICAL OUTCOMES WITH HEPARIN USE

There were similar rates of TICI 2b–3 reperfusion between HEP+ and HEP− patients (65.5% vs 62.6%; p=0.74) and a trend toward higher numbers of HEP+ patients with good functional outcome (mRS 0–2) compared with HEP− patients at 90 days (40.0% vs 25.7%; p=0.07); 90-day mortality rates were similar between the groups (29.3% vs 27.8%; p=0.85).

In multivariable logistic regression, a good outcome (90-day mRS 0–2) was independently associated with heparin bolus use (with or without continuous infusion) (OR 5.30; 95% CI 1.70 to 16.48), TICI 2b–3 reperfusion (OR 6.56; 95% CI 2.29 to 18.83), stent retriever use (OR 3.54; 95% CI 1.38 to 9.03) and inversely associated with intubation (OR 0.10; 95% CI 0.03 to 0.33), diabetes (OR 0.11; 95% CI 0.03 to 0.39), NIHSS (OR 0.84; 95% CI 0.75 to 0.93), time from symptom onset to puncture (OR 0.64; 95% CI 0.45 to 0.89), and heart failure (OR 0.23; 95% CI 0.06 to 0.83) (table 2). Clinical outcomes at 90 days and safety outcomes were also evaluated in patients who received any heparin use versus no heparin use after stratifying patients by baseline CT ASPECTS score (table 3). No significant differences in were found between HEP+ and HEP− patients in 90-day mRS in low ASPECTS (0–7) and high ASPECTS (8–10) groups.

Of 58 patients who received any heparin, 22 (38%) had received IV thrombolysis prior to thrombectomy; demographics and baseline characteristics including age, baseline NIHSS, and clot location were similar between patients who received and those who did not receive IV thrombolysis. Patients who received IV thrombolysis followed by any heparin use during thrombectomy trended toward higher rates of 90-day mRS 0–2 than those who did not receive IV thrombolysis (IV lytic+ 57.1% vs IV lytic− 29.4%, p=0.052).

SAFETY OUTCOMES WITH HEPARIN USE

Rates of embolization to the unaffected territory (5.2% vs 6.1%; p=1.00) and access site complications (1.7% vs 1.7%; p=1.00) were similar between the groups. sICH rates were also similar

Table 1 Demographics, patient baseline characteristics, reperfusion grade and access site complications of any heparin use versus no heparin use

	All patients (n=173)	Heparin (+) (n=58)	Heparin (–) (n=115)	p Value
Age				
Mean±SD, years	67.5±13.9	66.6±13.9	67.9±14.0	0.47
Sex				
Male*	43.40%	41.40%	44.30%	0.75
Systolic blood pressure				
Mean±SD, mm Hg	149.8±28.0	153.3±28.5	148.1±27.7	0.22
Diastolic blood pressure				
Mean±SD, mm Hg	80.6±16.3	82.4±17.2	79.7±15.8	0.23
Suspected stroke etiology				
Large artery atherosclerosis	9.2%	12.1%	7.8%	0.18
Cardioembolic	69.4%	62.1%	73.0%	
Small vessel disease	0.0%	0.0%	0.0%	
Unknown	15.6%	22.4%	12.2%	
Other	5.8%	3.4%	7.0%)	
Baseline NIHSS score				
Mean±SD	18.3±5.0	17.2±5.4	18.9±4.6	0.043
Median (Q1, Q3)	19.0 (15.0, 21.0)	17.0 (13.0, 21.0)	19.0 (16.0, 22.0)	
Score ranges				
8–15	27.7%	39.7%	21.7%	
16–23	56.1%	46.6%	60.9%	
24–29	16.2%	13.8%	17.4%	
Baseline modified Rankin score				
0	75.7%	69.0%	79.1%	0.17
1	23.7%	31.0%	20.0%	
≥2	0.6%	0.0%	0.9%	
Clot location				
Vertebrobasilar	6.9%	10.3%	5.2%	0.043
ICA	17.3%	8.6%	21.7%	
MCA-M1	60.7%	70.7%	55.7%	
MCA-M2	15.0%	10.3%	17.4%	
Anterior circulation hemisphere				
Left	50.3%	55.8%	47.7%	0.40
Post-procedure (final) TICI				
0	8.7%	3.4%	11.3%	0.56
1	6.4%	3.4%	7.8%	
2a	21.4%	27.6%	18.3%	
2b	53.2%	56.9%	51.3%	
3	10.4%	8.6%	11.3%	
Access site complications requiring surgical repair or blood transfusion	1.7%	1.7%	1.7%	1.00

p Values are from Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables.
ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction.

Table 2 Multivariable logistic regression modeling of 90-day good outcome (modified Rankin score 0–2)

Variable	OR (95% CI)	p Value*
Intubation during procedure	0.1 (0.03 to 0.33)	0.0001
Post-device TICI 2b+	6.56 (2.29 to 18.83)	0.0005
Diabetes mellitus	0.11 (0.03 to 0.39)	0.0006
Baseline NIHSS score	0.84 (0.75 to 0.93)	0.0007
Heparin bolus	5.3 (1.70 to 16.48)	0.004
Study device (Trevo vs Merci)	3.54 (1.38 to 9.03)	0.0083
†Time from symptom onset to arterial puncture (hours)	0.64 (0.45 to 0.89)	0.0089
CHF	0.23 (0.06 to 0.83)	0.0251

*p Values are from the Wald χ^2 statistic.
†Continuous variable. All other variables are binary.
CHF, congestive heart failure; NIHSS, National Institutes of Heart Stroke Scale; TICI, Thrombolysis in Cerebral Infarction.

between the groups (ECASS HI1/HI2 27.6% vs 24.3%, p=0.71; PH1/PH2 22.4% vs 25.2%, p=0.85). No significant differences were found in 90-day mortality between HEP+ and HEP− patients, although a non-significant increased trend in sICH rates was seen in groups with low ASPECTS (0–7) (HEP+ 16.7%, HEP− 7.1%; p=0.23) and high ASPECTS (8–10) (HEP+ 10.7%, HEP− 1.9%; p=0.12). Patients who received IV thrombolysis followed by any heparin use during thrombectomy had lower sICH rates (IV lytic+ 0% vs IV lytic− 19.4%; p=0.04) and similar rates of access site complications (IV lytic+ 0% vs IV lytic− 2.8%; p=1.00) as those who received no IV thrombolysis.

DISCUSSION

Our post hoc analysis of the TREVO 2 data demonstrates that the use of periprocedural heparin in AIS endovascular therapy is safe with no associated increase in the risk of sICH or access site complications. Additionally, the use of a heparin bolus was independently associated with good functional outcomes at 90 days. These findings are similar to a post hoc analysis of the Multi Merci trial which also found that heparin use in AIS endovascular therapy was an independent predictor of good outcome at 90 days.[2] Our results are also consistent with a retrospective analysis of AIS patients who underwent endovascular therapy in which patients who received intraprocedural heparin had no increase in ICH compared with patients not receiving heparin.[16]

Heparin use in AIS endovascular therapy may in theory be beneficial for reducing rates of arterial reocclusion during and after thrombectomy, which have been reported to occur in 18–22% of cases, may help limit distal embolization intraprocedurally, which can affect up to 16% of acute stroke patients who undergo endovascular therapy, or limit clot extension.[17–21] Reductions in these complications could potentially reduce final infarct volume, improving the overall outcome. Our current study, however, did not identify significant reductions in reocclusion rates or distal embolization.

These potential benefits with periprocedural heparin use must be considered along with the potential risk of hemorrhagic complications which may be dose-dependent. In the PROACT I trial evaluating the efficacy of IA thrombolytics, heparin administration was stratified into a higher and lower dosing regimen: the first 16 patients received the higher dose including a 100 IU/kg bolus followed by an infusion of 1000 IU/hour for 4 hours achieving an 81% recanalization rate; however, sICH was

Table 3 Clinical outcomes and safety endpoints of any heparin use versus no heparin use stratified by ASPECTS score

	ASPECTS 0–7			ASPECTS 8–10		
	Heparin (+) n=24 %	Heparin (–) n=56 %	p Value	Heparin (+) n=28 %	Heparin (–) n=53 %	p Value
90-day modified Rankin score			0.38			0.78
0	4.3	0		23.1	17.0	
1	13.0	5.6		15.4	13.2	
2	17.4	11.1		11.5	5.7	
3	4.3	16.6		7.7	17.0	
4	17.4	24.1		15.4	24.5	
5	4.3	7.4		3.8	3.8	
6	39.1	35.2		23.1	18.9	
90-day good outcome (mRS 0–2) (95% CI)	34.8 (16.4 to 57.3)	16.7% (7.9 to 29.3)	0.13	50.0 (29.9 to 70.1)	35.8 (23.1 to 50.2)	0.33
90-day mortality (95% CI)	37.5 (18.8 to 59.4)	33.9 (21.8 to 47.8)	0.8	21.4 (8.3 to 41.0)	18.9 (9.4 to 32.05)	0.78
Symptomatic ICH (95% CI)	16.7 (4.7 to 37.4)	7.1 (2.0 to 17.3)	0.23	10.7 (2.3 to 28.2)	1.9 (0.0 to 10.1)	0.12

ICH, intracranial hemorrhage.

reported in 27.3% of patients (recanalization was defined as a Thrombolysis in Myocardial Infarction (TIMI) score of 2 or 3 on a final angiogram within 120 min of infusion initiation). The remaining patients received a lower dose of heparin (2000 IU bolus followed by an infusion of 500 IU/hour) resulting in a lower recanalization rate of 40% and a lower sICH rate of 6.7%. This lower dose regimen has since been used in two recent endovascular trials, but no standardized regimen has been established due to limited data.[4 8] The lack of an increased risk of hemorrhage with heparin use may be related to the relatively limited extent of early ischemic changes seen on baseline imaging prior to thrombectomy in our study (mean baseline ASPECTS score 7.2) and should not be extrapolated to the risk in patients with more extensive early ischemic changes.

Limitations of our study include the post hoc nature of these analyses. Additionally, a relatively small number of study patients received periprocedural heparin in this study without a prespecified dosage and timing recommended in the study protocol. No activated clotting times were collected to evaluate the effects of heparin among those who received it. Our analysis included patients treated with stent retriever or the Merci clot retriever, which has been shown to be inferior in 90-day outcomes, although we found no significant difference in the frequency of heparin use between the devices used. Because our analysis only included patients with AIS treated with thrombectomy within 8 hours of their last seen well time, it remains unclear whether periprocedural heparin is safe beyond the 8-hour treatment window. Given the lack of randomized treatment among these patients and the fact that more than one-third of patients received periprocedural heparin, future randomized trials evaluating heparin use in AIS endovascular therapy are warranted.

CONCLUSION

The use of periprocedural heparin in stent retriever thrombectomy is associated with a good clinical outcome at 90 days and similar rates of sICH. Further prospective randomized studies are warranted.

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