Cardiovasc Intervent Radiol (2021) 44:750–755
https://doi.org/10.1007/s00270-020-02726-9

CLINICAL INVESTIGATION STROKE/NEUROINTERVENTIONS

Effect of Heparinized Flush Concentration on Safety and Efficacy During Endovascular Thrombectomy for Acute Ischemic Stroke: Results from the MR CLEAN Registry

Faysal Benali[1] · Wouter H. Hinsenveld[2] · Christiaan van der Leij[1] · Bob Roozenbeek[3,5] · Rob A. van de Graaf[3] · Julie Staals[2] · Hester F. Lingsma[4] · Aad van der Lugt[5] · Charles B. M. Majoie[6] · Wim H. van Zwam[1] · MR CLEAN REGISTRY investigators

Received: 24 August 2020 / Accepted: 22 November 2020 / Published online: 3 January 2021

Abstract

Background Currently, there are no recommendations regarding the use of heparinized flush during endovascular thrombectomy (EVT) for acute ischemic stroke. Periprocedural heparin could, however, affect functional outcome and symptomatic intracranial hemorrhage (sICH). We surveyed protocols on heparin flush concentrations in Dutch EVT centers and assessed its effect on safety and efficacy outcomes.

Methods Patients registered in the MR CLEAN Registry, from 2014 up to 2017 were included. We collected data on center protocols regarding heparin flush concentrations (IU/L) and grouped patients by their per protocol administered heparin flush concentration. We used a random effects model with random intercepts by EVT center and analyzed endpoints using regression models. Endpoints were sICH, mRS at 90 days, mortality and reperfusion rates.

Results A total of 3157 patients were included of which 45% (6 centers) received no heparin in the flush fluids, 1.8% (1 center) received flush fluids containing 2000 IU/L heparin, 26% (4 centers) received 5000 IU/L, 22% (4 centers) received 10.000 IU/L and 5.6% (1 center) received 25.000 IU/L. Higher heparin concentration was associated with increased sICH (aOR 1.15; 95% CI 1.02–1.29), but not with functional outcome, mortality or reperfusion rates.

Conclusion Effect of heparin in flush fluids should not be ignored by clinicians or researchers as higher concentrations may be associated with higher rates of ICH. The observed variation in protocols regarding heparin concentrations between EVT centers should encourage further studies, ideally in a controlled way, resulting in recommendations on heparin use in flush fluids in future guidelines.

Keywords Ischemic stroke · Endovascular thrombectomy · Heparin · Heparin flush · Flush fluids · Functional outcome

Faysal Benali and Wouter H. Hinsenveld: shared first author.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00270-020-02726-9.

✉ Faysal Benali
faysal.benali@mumc.nl

[1] Department of Radiology, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands

[2] Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute, Maastricht, The Netherlands

[3] Department of Neurology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

[4] Department of Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands

[5] Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

[6] Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Location AMC, Amsterdam, The Netherlands

Introduction

In order to prevent thrombus formation around devices and catheters during endovascular thrombectomy (EVT) for acute ischemic stroke (AIS), heparin is often administered either as a single bolus (intra-arterially or intravenously) or continuously in saline flush during the procedure. Periprocedural heparin could also play a role in restoring "incomplete microvascular reperfusion" (IMR) [1–3] after EVT for AIS and therefore could lead to better functional outcome. However, it could also lead to an increased risk of symptomatic intracranial hemorrhage (sICH) with subsequent increased mortality and morbidity [3, 4]. With a single heparin bolus, the amount administered to the patient is known. However, with heparinized flush, the total amount of administered heparin is mostly unknown and may be significant, especially in long procedures. Because no recommendations concerning heparin concentration in saline flush are given in current EVT-guidelines, concentrations may vary among different center protocols.

Therefore, the aim of this study was to survey the current policy of heparin flush concentrations in all Dutch EVT centers and to study its effects on safety and efficacy outcome in EVT for AIS.

Materials and Methods

Study Design and Patient Enrolment

We used data from the MR CLEAN Registry, a prospective observational study of all centers in the Netherlands that perform EVT in patients with AIS due to intracranial large vessel occlusion (LVO) from March 2014 up to October 2017. The central medical ethics committee of the Erasmus Medical Center Rotterdam, the Netherlands, evaluated the MR CLEAN Registry study protocol and granted permission to carry out the study as a registry (MEC-2014-235).

Therefore, the need for individual patient consent has been waived.

Details on the objectives and the full study design of the MR CLEAN Registry have previously been described [5]. Patients were enrolled from start of the registry on March 16, 2014. For the present study, we analyzed data of patients enrolled up to October, 2017. Included patients adhered to the following criteria: arterial puncture within 6.5 h of symptom onset, age $\geq$ 18 years, treatment in a center that participated in the MR CLEAN Registry and presence of a proximal intracranial LVO in the anterior circulation (internal carotid artery (ICA), internal carotid artery terminus (ICA-T), middle (*M*1/*M*2) cerebral artery, or anterior (*A*1/*A*2) cerebral artery) shown by CT angiography (CTA). We surveyed data from all 16 centers participating in the MR CLEAN Registry on protocols regarding periprocedural heparin use, protocol changes over time and individual interventionist deviations from these protocols. Clinical and imaging data were centrally collected and adjudicated by a core laboratory.

The data, analytic methods and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, but detailed analytic methods and study materials, including log files of statistical analyses, can be made available to other researchers on request to the first author.

Definitions and Endpoint Measures

Patients were analyzed on per protocol heparin flush concentrations (IU/L saline) of each individual center and in a second analysis on whether heparinized flush fluids were administered or not (see supplemental Table I). Primary clinical endpoint was probability of sICH, defined as any intracranial extravascular blood on the postprocedural ($<$ 24H) CT scan and symptomatic if patients died or deteriorated neurologically (a decline of the National Institutes of Health Stroke Scale (NIHSS) score of at least 4 points) due to the intracranial hemorrhage. Secondary clinical endpoints were the modified Rankin Scale (mRS) score at 90 days as measured by trained trial nurses of the local intervention center, functional independence (mRS $\leq$ 2) at 90 days, mortality and stroke progression. Radiological endpoints were reperfusion rate and rate of distal embolization. We considered successful reperfusion as achieving an extended treatment in cerebral infarction (eTICI) of 2B ($\geq$ 50% reperfusion) or greater [5]. If final two-directional digital subtraction angiography (DSA) images were missing, eTICI scores 2B or more could not be reliably determined. These patients were excluded from all reperfusion analyses; in all other analyses, these patients were included and given a maximal score of TICI 2A. Distal embolization was defined as any occlusion on final DSA in a distal branch of the initial occluded artery. Stroke progression was defined as neurological deterioration of 4 points or more on the NIHSS score or death that could not be explained by hemorrhage or other causes. Collaterals were defined according to a scoring system by Tan et al. [6] with a four point scale ranging from absent, less than 50%, 50–99% and 100% collaterals present in the affected hemisphere compared to the contralateral hemisphere.

Statistical Analysis

We used nonparametric trend testing. After imputing for missing data using multiple imputation with 20 chained equations, we used a random effects model with random

intercepts by treating center and analyzed endpoints using logistic regression models. All proportionality assumptions were met. For the mRS analysis, we inverted the mRS score and used ordinal logistic regression analysis to capture the ordinal nature of this outcome scale. In these models, heparin flush concentration was entered as an ordinal variable.

Since the aim was to study the effect of the heparin concentration in the flush fluids, we adjusted outcomes for single IV/IA heparin bolus and length of procedure (groin-to-reperfusion time). Further adjustments were made for age, NIHSS at baseline, systolic blood pressure, oral anticoagulation use (vitamin K antagonists or direct oral anticoagulants), intravenous thrombolysis (IVT), collaterals and segment of occlusion.

Clinical outcomes were additionally adjusted for mRS score at baseline. For the endpoint distal thrombi, we did not adjust for segment of occlusion due to fitting problems. Statistical analyses were performed using Stata/SE14.1 (StataCorp, TX).

Results

A total of 3157 patients were included (Fig. 1) of whom 45% (6 centers) received no heparin in flush fluids, 1.8% (1 center) received flush fluids containing 2000 IU/L heparin, 26% (4 centers) received 5000 IU/L, 22% (4 centers) received 10000 IU/L and 5.6% (1 center) received 25000 IU/L. All interventionists adhered to their center protocol. Baseline characteristics are described in Table 1.

Primary Endpoint

With increasing heparin flush concentrations, unadjusted complete-data analysis showed a gradual increase of sICH from 5% (0 IU/L) to 9.6% (25.000 IU/L) (Table 2). Regression analysis showed a significant rise in the rate of sICH with increasing heparin flush concentrations with an adjusted OR of 1.15 (95% CI of 1.02–1.29) (Table 3).

Secondary Endpoints

There was some variation in the rate of successful reperfusion, occurrence of distal embolization, functional outcome, mortality and stroke progression among the different groups (Table 2). However, in the adjusted regression analyses, no significant effect of heparin concentration on any of these outcomes was found (Table 3).

Supplemental Analyses

We performed supplemental analyses stratifying the study group in the use of any heparin in flush fluids versus no heparin in flush fluids (supplemental Table 1) and IVT administration versus no IVT administration (supplemental Table 3). No significant interactions were found between the different subgroups. Furthermore, we performed additional analyses excluding all groups where heparin bolus was administered and small sample groups, such as the groups receiving 2000 IU/L and 25,000 IU/L (supplemental Table 2), in which the increasing probability of having sICH remained.

Discussion

In this study, we surveyed heparinized flush fluid protocols of Dutch centers performing EVT and analyzed the effect on the rate of sICH and on functional outcome. We observed marked variation in protocols concerning heparin concentration in flush fluids among these centers; ranging from 0 to 25.000 IU/L. Half of the included patients were treated in centers that use 5000 IU/L or more (up to 25.000 IU/L), which is much higher than the concentrations described in the current literature on EVT in AIS (2000–5000 IU/L heparinized flush) [3]. Higher concentrations were mainly used in EVT centers that do not perform other neuro-interventions. It might be that those centers adopted protocols from peripheral interventions for EVT. For further minimizing bias, we performed additional

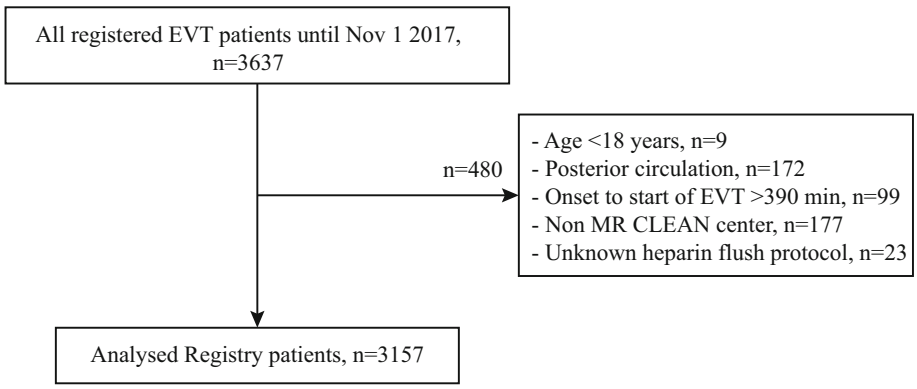

Fig. 1 Flowchart of included patients

Table 1 Baseline data (n = 3157 patients) grouped by heparin flush concentrations

	0 IU/L N = 1426 6 centers	2000 IU/L N = 58 1 center	5000 IU/L N = 814 4 centers	10,000 IU/L N = 681 4 centers	25,000 IU/L N = 178 1 center
Age (years, median, IQR)	71 (61–80)	72 (62–84)	71 (61–80)	75 (62–81)	73 (62–81)
Men (%)	761/1426 (53)	27/58 (47)	402/814 (49)	361/681 (53)	94/178 (53)
NIHSS at baseline (median, IQR)	15 (10–19)	17 (11–20)	16 (12–19)	17 (12–20)	15 (11–20)
Systolic blood pressure (mmHg, median, IQR)	150 (134–166)	155 (128–170)	147 (130–163)	150 (132 –167)	149 (130 –165)
Pre-mRS 3 or higher (%)	149/1387 (11)	15/58 (26)	78/787 (9.9)	92/675 (14)	23/178 (13)
History of:					
Atrial fibrillation (%)	306/1411 (22)	16/58 (28)	184/805 (23)	210/665 (32)	37/176 (21)
Hypertension (%)	708/1404 (50)	32/58 (55)	383/782 (49)	378/670 (56)	118/177 (67)
Previous stroke (%)	229/1415 (16)	14/58 (24)	131/811 (16)	138/670 (21)	19/176 (11)
Myocardial infarction (%)	186/1396 (13)	9/58 (16)	112/798 (14)	108/665 (16)	25/176 (14)
Oral Anticoagulation use (%)	199/1420 (14)	8/58 (14)	131/810 (16)	126/675 (19)	37/177 (21)
Antiplatelet use (%)	457/1415 (32)	28/58 (48)	238/800 (30)	205/666 (31)	46/177 (26)
IVT performed (%)	1083/1424 (76)	47/58 (81)	643/813 (79)	497/673 (74)	137/178 (77)
Onset to groin puncture (minutes, median, IQR)	197 (150–255)	168 (150–220)	195 (155–260)	186 (144 –240)	162 (120 –233)
Procedure length (minutes, median, IQR)	45 (29–72)	82 (45–115)	50 (30–74)	49 (32–72)	58 (37–77)
ASPECTS at baseline (median, IQR)	9 (7–10)	9 (8–10)	9 (7–10)	9 (8–10)	9 (8–10)
Occlusion site n/n (%)					
ICA	80/1348 (5.9)	2/57 (3.5)	32/772 (4.2)	32/654 (4.9)	9/170 (5.3)
ICA-T	277/1348 (21)	12/57 (21)	150/772 (19)	153/654 (23)	42/170 (25)
M1	759/1348 (56)	36/57 (63)	484/772 (63)	369/654 (56)	100/170 (59)
M2	220/1348 (16)	7/57 (12)	97/772 (13)	97/654 (15)	19/170 (11)
Other (M3, A1)	12/1348 (0.9)	0	9/772 (1.2)	3/654 (0.5)	0
First treatment option n/n (%)					
Stent retriever	840/1156 (73)	27/42 (64)	452/640 (71)	326/567 (58)	116/138 (84)
Aspiration	274/1156 (24)	15/42 (36)	164/640 (26)	205/567 (36)	21/138 (15)
IA Thrombolytics	10/1156 (0.9)	0	3/640 (0.5)	9/567 (1.6)	0
Other	32/1156 (2.8)	0	22/640 (3.4)	27/567 (4.8)	1/138 (0.7)

Numbers are counts/total (percentage) unless otherwise noted

IQR interquartile range, *ASPECTS* alberta stroke programme early CT score, *NIHSS* national institutes of health stroke scale, *mRS* modified Rankin scale, *IVT* intravenous thrombolysis, *ICA* intracranial carotid artery, *ICA-T* ICA top, *M1-2-3* first, second and third segment of the middle cerebral artery, *A1* first segment of the anterior cerebral artery, *IA* Intra-arterial

Table 2 Outcome grouped by heparin flush concentrations using unimputed and unadjusted data

	0 IU/L	2000 IU/L	5000 IU/L	10000 IU/L	25000 IU/L
sICH	72/1426 (5.1)	3/58 (5.2)	44/814 (5.4)	49/681 (7.2)	17/178 (9.6)
Successful reperfusion[a]	904/1173 (77)	12/29 (41)	427/620 (69)	343/475 (72)	69/102 (68)
Distal emboli on DSA	173/1247 (14)	7/47 (15)	114/709 (16)	96/609 (16)	24/152 (16)
Stroke progression	120/1426 (8.4)	10/58 (17)	79/814 (9.7)	61/681 (9.0)	16/178 (9.0)
Functional independence (mRS $\leq$ 2)	524/1280 (41)	18/57 (32)	312/773 (40)	276/667 (41)	61/168 (36)
Mortality	358/1280 (28)	17/57 (30)	201/773 (26)	222/667 (33)	57/168 (34)

Numbers are counts/total (percentages) unless otherwise noted

sICH symptomatic intracranial hemorrhage, *DSA* digital subtraction angiography, *mRS*: modified Rankin scale

[a]Only if two-directional DSA runs were available

Table 3 Regression analysis using imputed data with heparin flush concentrations as an independent ordinal variable

Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
sICH	1.15 (1.03–1.27)	1.15 (1.02–1.29)
Successful reperfusion	0.90 (0.80–1.01)	0.91 (0.81–1.01)
Distal emboli	1.06 (0.95–1.19)	1.06 (0.94–1.20)
Stroke progression	1.03 (0.91–1.18)	1.03 (0.89–1.20)
mRS[a]	0.97 (0.90–1.05)	1.02 (0.92–1.13)
Mortality	1.06 (0.99–1.14)	1.03 (0.95–1.13)

OR odds ratio, *CI* confidence interval, *sICH* symptomatic Intracranial Hemorrhage, *mRS* modified Rankin scale

[a]Common OR

analyses excluding all 'small sample'—centers (2000 IU/L and 25,000 IU/L) and all cases in which a heparin bolus was administered (supplemental Table 2). These results still revealed an increased probability of having sICH with an aOR of 1.23 (0.98–1.53), however, nearly significant. No other significant differences for functional and technical endpoint measures were observed. This shows that the effect of heparin in flush fluids is independent of the heparin bolus administered. Furthermore, we found no significant interaction between the groups when we stratify for IVT administration (see supplemental Table 3).

We observed an association between higher heparin concentrations and higher rates of sICH. This effect was not accompanied by a higher rate of mortality or worse functional outcome. This discrepancy could not be explained by a "compensating effect" of lower rate of distal embolization (as we did not find this association). A more probable hypothesis is the "restoration effect" on incomplete microvascular reperfusion (IMR) after EVT, as described by del Zoppo et al. and Tanvir et al. [1–3], that counterbalances the negative effect of increased sICH. Regarding heparinized flush during neuro-interventions, very scarce information is available in the literature. A strong anticoagulant effect of heparinized flush (without bolus), as measured by prolonged aPTT, during neuro-interventional procedures, has been confirmed [7].

Further literature from the last 10 years mainly provides information about heparinization during EVT, as bolus and/or continuous infusion. In a systematic review published in 2018, four studies were reported on systemic heparinization with an average dose ranging from 2000 to 5000 IU [3]. Two of the included studies (TREVO 2 trial and multi MERCI trial) [8, 9] estimated the effect of heparin bolus use on occurrence of sICH, functional independence and mortality. They found neutral effects on sICH and mortality, but a positive effect on functional outcome after adjustments for main prognostic factors. We, however, must take into consideration the small population sizes ($n = 173$ and $n = 51$, respectively) and post hoc design of these 2 studies.

Recently, a Chinese group (ANGEL collaborators) prospectively investigated the effect of heparinization during EVT (dose: IV heparin at 50–100 IU/Kg at first and additional 1000 IU bolus every hour during the procedure) [4]. They observed more frequent sICH and distal embolization in heparinized patients (9.3% vs. 5.1%, $p = 0.02$ and 7.1% vs. 3.1%, $p = 0.04$, respectively). Although we also observed a higher rate of sICH, our analysis did not show an effect on distal embolization rate. This difference could be due to plaque softening and fragmentation due to heparin, which may occur more often in Asian population in which intracranial atherosclerotic disease is more common [10].

Other recent studies show a great diversity in opinions and implications concerning the protective role of heparinization. The Titan investigators [11] for example investigated the effect of periprocedural heparin (bolus ranging from 1500 IU - 2500 IU or target activating clotting time of 250 s) in 122 patients with tandem occlusions. They found no association with functional, angiographic or safety outcome. Keep into consideration the low doses given, and the selected population of only tandem occlusions.

Another retrospective study performed in 2016 also investigated the effect of periprocedural heparin during EVT for AIS (dose: 2787 ± 1309 units (median 2475, IQR 2000–4000)) [12]. They found a lower rate of hemorrhage and a higher rate of reperfusion. They concluded their findings from univariate analyses only and a relatively small population group ($n = 76$).

The main message of the current study should be to alert interventionists to be aware that heparin concentrations in flush fluids during EVT could increase the rate of sICH, especially when procedures last longer. Ideally, a properly designed randomized trial should investigate the true effect of heparin (including the heparin in flush fluids) on outcome after EVT. Such a trial is currently underway in the Netherlands (MR CLEAN Registry, ISRCTN76741621). Nonetheless, for now, the role of heparinization during EVT is still controversial and in addition, most attention so far has been paid to fixed amounts mainly given as a bolus. The additional effect of heparin in flush fluids has largely been neglected and we feel responsible to warn for this as we see large variation and very high amounts in the Netherlands.

Limitations

Protocols regarding heparin in flush fluids differed per hospital; therefore, a hospital effect on our results cannot be avoided although we mitigated the possibility with a random effects model and all the patients included in the Registry were treated according to the same National Guidelines. Treatment was offered to all patients within 6.5 h with a large vessel occlusion stroke. Advanced age, low ASPECT score or large infarct core was not an exclusion criterium. Most intervention centers did not perform perfusion imaging. For those that did, core or penumbra size was no in -or exclusion criterium for treatment. Secondly, different interventionists with various experience levels possibly using different drip rates performed the procedures. However, the large dataset of more than 3000 patients in a multicenter design, the random effects model we used, and the adjustments we have made for procedure time (this could be a measure for interventionist‘ experience) probably averages these effects out. For other measurable confounders, further extensive adjustments were made. Also, we used a random effects model with random intercepts per center. Such a regression model can adjust for any unmeasured variation between centers.

Conclusion

Effect of heparin in flush fluids should not be ignored by clinicians or researchers as higher concentrations may be associated with higher rates of ICH. The observed variation in protocols regarding heparin concentrations between EVT centers should encourage further studies, ideally in a controlled way, resulting in recommendations on heparin use in flush fluids in future guidelines.

Funding This study was not supported by any funding.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent for Publication For this type of study, consent for publication is not required.

Ethical Approval For this type of study, formal consent is not required.

Informed Consent For this type of study, informed consent is not required.

References

1. Choudhri TF. Reduced microvascular thrombosis and improved outcome in acute murine stroke by inhibiting GP IIb/IIIa receptor-mediated platelet aggregation. J Clin Invest. 1998;102(7):1301–10.
2. Del Zoppo GJ, et al. Experimental acute thrombotic stroke in baboons. Stroke. 1986;17(6):1254–65.
3. van de Graaf RA, et al. Periprocedural antithrombotic treatment during acute mechanical thrombectomy for ischemic stroke: a systematic review. Front Neurol. 2018;9:238.
4. Yang M, et al. Safety and efficacy of heparinization during mechanical thrombectomy in acute ischemic stroke. Front Neurol. 2019;10:299.
5. Liebeskind DS, et al. eTICI reperfusion: defining success in endovascular stroke therapy. J Neurointerv Surg. 2019;11(5):433–8.
6. Tan JC, et al. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol. 2007;61(6):533–43.
7. Ramesh VJ. An audit of fluid and heparin administration during interventional neuroradiologic procedures. J Neurosurg Anesthesiol. 2006;18(4):251–5.
8. Nahab F, et al. Safety of periprocedural heparin in acute ischemic stroke endovascular therapy: the multi MERCI trial. J Stroke Cerebrovasc Dis. 2012;21(8):790–3.
9. Winningham MJ, et al. Periprocedural heparin use in acute ischemic stroke endovascular therapy: the TREVO 2 trial. J Neurointerv Surg. 2018;10(7):611–4.
10. Pu Y, et al. Geographic and sex difference in the distribution of intracranial atherosclerosis in China. Stroke. 2013;44(8):2109–14.
11. Zhu F, et al. Periprocedural heparin during endovascular treatment of tandem lesions in patients with acute ischemic stroke: a propensity score analysis from TITAN registry. Cardiovasc Intervent Radiol. 2019;42(8):1160–7.
12. Farook N, et al. Role of heparin during endovascular therapy for acute ischemic stroke. Clin Neurol Neurosurg. 2016;145:64–7.