SHORT COMMUNICATION

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Does clot composition impact the First Pass Effect in Mechanical Thrombectomy – preliminary results of a single-center study study

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Abstract

Introduction. Mechanical thrombectomy is an established therapeutic method for acute ischemic stroke and first pass effect (FPE) constitutes the ultimate goal of endovascular treatment.

Aim. To investigate the relationship between the clot composition in acute ischemic stroke (AIS) in patients with large-vessel occlusion and first pass effect of mechanical thrombectomy (MT).

Materials and Methods. Clots from AIS patients who underwent MT were examined histologically and the area occupied by red blood cells (RBCs), white blood cells (WBCs) and fibrin was quantified. The clinical outcome of the procedure was evaluated using modified Rankin Scale (mRS).

Results. Seventy consecutive patients were included in this prospective study. Demographics, occlusion site, procedural details and clinical outcomes were evaluated. Full recanalization was observed in 54 patients (77.1%) and from this group FPE was achieved in 28 patients. Statistical analysis did not show significant correlation between clot composition and FPE but low RBC clot area was close to significance (P=0.08).

Conclusion. Despite the lack of statistically significant correlation between clot composition and first pass effect in patients with acute ischemic stroke, we observed that red blood cell rich clots were associated with increased number of thrombectomy passes which supports the notion that clot histology influences recanalization outcomes and shows the need for further studies on this topic.

Keywords

acute ischemic stroke, thrombus, mechanical thrombectomy, first pass effect

INTRODUCTION

Ischemic stroke is a multifactorial neurological disorder and one of the most common causes of death and disability worldwide [1]. It occurs as a result sudden interruption of blood supply to brain tissues due to blockage of cerebral artery by blood clots, thrombus or vessel dissection [2]. Decreased brain perfusion leads to formation of infarct core and penumbra – surrounding area which maintains some blood supply through collateral circulation [3]. Acute ischemic stroke requires prompt diagnosis and treatment. Both computed tomography (CT) and magnetic resonance imaging (MRI) are excellent imaging modalities in stroke evaluation, with CT being more frequently used due to its availability and lower costs [4]. As far as the treatment is concerned, the main goal is to restore the blood flow in shortest possible time ("time is brain" paradigm). Currently available therapeutic approaches include medical (intravenous thrombolysis) and endovascular (thrombectomy) treatments [5]. Nonetheless, there are several promising novel strategies that are being implemented in the treatment of ischemic stroke patients [6, 7].

Mechanical thrombectomy (MT) became an established therapeutic method for acute ischemic stroke (AIS) caused by large vessel occlusion [8]. Current evidence suggests that achieving complete recanalization after single use of thrombectomy device (first pass effect – FPE) has a positive impact on clinical outcome and should therefore be the ultimate goal of endovascular treatment [9, 10]. That is why, factors associated with increased chance of achieving FPE became a topic of clinical and scientific research [11, 12]. Clot composition, especially different ratio of areas occupied by red blood cell (RBC), fibrin/platelets and white blood cell (WBC), is reported to be associated not only with number of recanalization maneuvers, but also rate of successful recanalization and procedural time [13, 14]. Although the

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initial studies on impact of clot histology on FPE failed to show statistically significant correlations, further prospective studies are required on this topic [15].

The aim of this study was to evaluate the correlation between histological clot composition and first pass effect in patients with acute ischemic stroke treated with mechanical thrombectomy.

MATERIALS AND METHODS

Study protocol

In this monocentric study, we retrospectively analyzed data of 70 prospectively enrolled patients admitted with AIS due to large vessel occlusion, who were treated with MT from March 2023 to November 2023. The inclusion criteria were as follows: (1) ischemic stroke due to M1 segment of middle cerebral artery (MCA) occlusion, internal carotid artery (ICA) occlusion, basilar artery (BA) occlusion or tandem occlusion (ICA and MCA) confirmed according to imaging examination (CT angio and/or MRI angio); (2) time from symptom onset to puncture < 6 h; (3) a National Institute of Health Stroke Scale (NIHSS) score ≥ 6; (4) a prestroke Rankin Scale (mRS) score ≤ 2. The CT brain with an Alberta Stroke Program Early CT Score (ASPECTS) ≥6. Exclusion criteria included (1) occlusion other than M1segment of MCA and occlusion of posterior cerebral artery; (2) the presence of intracranial hemorrhage (ICH) on a baseline CT; (3) a lack of integral laboratory data; (4) no follow-up. The demographic, clinical and laboratory results on admission as well as time metrics were collected and evaluated. In accordance with the current guidelines of European Stroke Organization for the management of patients with ischemic stroke, intravenous thrombolysis (rt-PA) was administered if patients arrived in a time window < 4.5 h in the case of no contraindication [16]. An institutional review committee (IRB) approved this study—approval number KE-0254/76/03/2023. All procedures were conducted in accordance with the Declaration of Helsinki.

ENDOVASCULAR PROCEDURE

Mechanical thrombectomies were performed by experienced neuroradiologists who used reperfusion strategy (aspiration/stent retriever alone or aspiration catheter + stent retriever) at his discretion. Modified treatment in cerebral infarction (mTICI) score was used to evaluate the angiographic outcome, and the procedure was considered successful if mTICI was 2b or 3. After the procedure, all patients were transferred to intensive neurological care unit. A non-contrast head CT was performed within first 24 hours after the intervention in order to evaluate brain infarction and assess the occurrence of hemorrhagic complications (ICH). The patients were also assessed for neurological status using the NIHSS.

Histopathological analysis

Thrombotic material retrieved during the procedure was immediately placed in formalin solution, and sectioned and prepared for histology afterwards. Martius Scarlet Blue, hematoxylin-eosin, CD61 and van Gieson staining were used to identify the three main clot components – red blood cells (RBCs) – RBC rich clots, white blood cells (WBCs) – WBC rich clots and fibrin, platelet and collagen – Fibrin-rich clot.

Follow-up

The clinical outcome was assessed based on the mRS score 3 months after the procedure. Favorable result was defined as mRS ≤ 2. Overall mortality rate was noted as well.

Statistical analysis

The patients were classified into two groups: patients with FPE and patients with no-FPE. Comparisons between the groups were made on the demographic data, initial NIHSS, risk factors, use of IVT, procedural details, clinical outcome and clot main composition (RBC rich clots, WBC rich clots and Fibrin rich clot). Student's *t*-test, the Mann–Whitney test and Chi-squared Pearson's tests were used when appropriate. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Seventy patients (mean age 70.9±13.3, range 38–95 years, 50% of females) were included in this study. Demographic data, pre-stroke mRS, cardiovascular risk factors, comorbidities and baseline medication are presented in Table 1.

Table 1. Demographic data, pre-stroke mRS, risk factors, comorbidities and baseline medication

Demographic data	
Sex (n,%)	
Female	35 (50%)
Male	35 (50%)
Age (mean ± SD, range)	70.9 ± 13.3 (38–95)
Pre-stroke mRS (n,%)	
0	39 (55.7%)
1	17 (24.3%)
2	14 (20%)
Risk factors and comorbidities (n,%)	
Smoking	26 (37.1%)
History of cardiologic disease	44 (62.9%)
Hypertension	59 (84.3%)
Atrial fibrillation	23 (32.0%)
History of stroke/TIA	11 (15.7%)
Hyperlipidemia	26 (37.1%)
Diabetes	29 (41.4%)
Baseline medication (n,%)	
Antihypertensives	56 (80%)
Beta-blockers	16 (22.3%)
Calcium channel blockers	34 (48.6%)
ACE inhibitors	19 (27.1%)
Angiotensis receptor blockers	10 (14.3%)
Diuretics	32 (45.7%)
Antiplatelets	28 (40%)
Acetylosalicylic acid (ASA)	49 (70%)
Clopidogrel	15 (21.4%)
Dual antiplatelet treatment (ASA + clopidogrel)	7 (10%)
NOAC	20 (28.6%)
Statins	25 (35.7%)

Majority of the patients (n=40, 57.1%) were admitted with a "mothership" paradigm and 17.7 ± 6 (6–34) NIHSS score on admission indicated moderate to severe neurological deficit. Most common site of occlusion was left MCA and mean time from onset to recanalization was 218.3 ± 73.5 minutes. Baseline clinical and laboratory results, occlusion sites and endovascular procedural times are shown in Table 2.

In terms of procedural details, in our center ADAPT (A Direct Aspiration First Pass Technique) is usually implemented as a primary revascularization strategy. Aspiration was used

Table 2. Baseline clinical and laboratory results, occlusion sites and times

Baseline clinical and laboratory results	
Admission model (n,%)	
Mothership	40 (57.1%)
Drip-and-Ship	30 (42.9%)
NIHSS (mean ± SD, range)	17.7 ± 6 (6–34)
Blood pressure in mmHg (mean ± SD)	152.5 ± 17/89.2 ± 8.8
Blood glucose in mg/dL (mean ± SD, range)	131.4 ± 37.2 (84–280)
I.v. tissue plasminogen activator (n, %)	29 (41.4%)
Occluded vessel (n, %)	
Middle cerebral artery (MCA)	
Left	30 (42.9%)
Right	15 (21.4%)
Internal carotid artery (ICA)	
Right	0 (0.0%)
Left	1(1.4%)
Basilar artery (BA)	6 (8.6%)
Tandem Occlusion (TO)	
With stent	10 (14.3%)
Without stent	8 (11.4%)
Procedural times in minutes (mean ± SD, range)	
Onset to arrival	97.3 ± 46.9 (20–240)
Door to groin	57.9 ± 72.7 (83.2–250)
Onset to groin	183.7 ± 67.5 (50–330)
Onset to recanalization	218.3 ± 73.5 (72.4–360)

as a primary method in 69/70 cases (98.6%). In 50% of patients (35/70) stent retriever was used if ADAPT technique was not effective. First pass effect was observed in 28 patients (40%). Overall, successful recanalization (mTICI 2b-3) was achieved in 60 patients (85.7%). Procedural details are described in Table 3.

Table 3. Procedural details

Procedural details (n, %)	
Revascularization strategy	
ADAPT	69 (98.6%)
Stent retriever	1 (1.4%)
Combined	35 (50%)
First pass effect	28 (40%)
Number of passages (mean, ±, SD, range)	2.8 ± 2.3 (1–12)
mTICI	
0	1 (1.4%)
1	1 (1.4%)
2a	8 (11.4%)
2b	6 (8.6%)
2c	4 (5.7%)
3	50 (71.4%)
Procedural time in min (mean ± SD, range)	41.1 ± 22.9 (10–120)

Median NIHSS score 24 hours after the endovascular treatment and at discharge was 10.8±7.8 (0–30) and 7.2±7.3 (0–25), respectively. Favorable 3-month clinical outcome (mRs ≤ 2) was achieved in 41.4% of patients. Controlled head CT performed within 24 after MT revealed radiological features of ICH in 13 patients (18.6%). Overall mortality at 3 months was 22.6% (16 patients) and mRS >2 was noted in 58.6% of patients.

Favorable clinical outcome was strictly correlated with lower baseline NIHSS score (p = 0.04), lower glucose level at admission (p = 0.0002), shorter onset to arrival time (p = 0.02) and lack of ICH in post-procedural head CT scan (p = 0.046). Contrary, mortality was correlated with longer time from onset to arrival (p = 0.0009), lack of successful recanalization (p=0.04) and occurrence of ICH (p = 0.006).

Histopathological analysis of the thrombi showed RBC-rich clots in 65.7%, WBC-rich in 11.4% and fibrin-rich in 22.9%. Statistical analysis did not show significant correlation between thrombus composition and FPE (Table 4a). Interestingly, only 32.6% of RBC-rich clots were removed with a first pass and FPE was achieved. Clinical and histopathological results are presented in Table 4b.

Table 4a. Relation between the clot composition and FPE

	RBC-rich clots [RRC] (n = 46)	WBC-rich clots [WRC] (n = 8)	Fibrin-rich clots [FRC] (n = 16)	*p* Value
FPE/non-FPE	15/31	5/3	8/8	0.13 RBC vs WBC 0.24 RBC vs FRC 0.68 WRC vs FRC

FPE – first pass effect, non-FPE – non first pass effect. Chi-squared Fisher exact test

Table 4b. Clinical and histopathological results

Clinical outcome (n,%)	
NIHSS (mean, ±, SD, range)	
at 24h	10.8 ± 7.8 (0–30)
at discharge	7.2 ± 7.3 (0–25)
Complications	
ICH	13 (18.6%)
Groin hematoma	3 (4.3%)
Outcome at 90 days	
Favorable (mRs ≤ 2)	29 (41.4%)
Unfavorable (mRs ≥ 3)	41 (58.6%)
Mortality	16 (22.9%)
Statistical results	
Favorable outcome vs unfavorable outcome	
NIHSS at admission (mean, range)	14 (6–27) vs 19 (9–34) p=0.04
Glucose level at admission (mg/dL) (mean, range)	107 (84–164) vs 135 (92–230) p=0.0002
Onset-to-arrival in minutes (mean, range)	80 (20–240) vs 95 (30–230) p=0.02
ICH in survival group (n,%)	0/29 (0%) vs 6/25 (24%) p=0.46
Death vs survival group	
Onset-to-arrival in minutes (mean, range)	120 (67–200) vs 86.5 (20–240) p=0.0009
Complete recanalization (n,%)	11/16 (69%) vs 43/54 (80%) p=0.04
ICH (n,%)	7/16 (53.8%) vs 6/54 (11.1%) p=0.006
Clot histopathloogical analysis (n, %)	
RBC-rich	46 (65.7%)
WBC-rich	8 (11.4%)
Fibrin-rich	16 (22.9%)
Clot composition and FPE (n, %)	
First pass effect	
RBC-rich clots	15/46 (32.6%)
WBC-rich clots	5/8 (62.5%)
Fibrin-rich clots	8/16 (50%)

DISCUSSION

Despite the fact that understanding of the histology of embolic material in patients with acute ischemic stroke might positively impact clinical and procedural decision-making, the data on this topic is currently lacking. Our prospective analysis of clots retrieved from 70 consecutive patients undergoing endovascular treatment demonstrated that red blood cells rich clots were less likely to be retrieved successfully on the first pass. These findings stay in line with the observation made by Johnson et al. [17]. On the

other hand, several authors reported an increased rate of FPE in clots with higher percentage of RBC as opposed to fibrin-rich and platelet-rich clots [13, 15, 18]. Similar findings were made by Karimian-Jazi et al. who assessed the clot composition using MR microscopy in addition to histopathology [19]. These findings were further confirmed in laboratory environment where fibrin-rich clots demonstrated both higher coefficient of friction and stronger interactions with the vessel wall compared with RBC-rich clots and were therefore more difficult to remove from the vessel wall [20, 21]. Our contradictory results emphasize the need for further prospective studies in this area. One possible explanation to this, might be the fact that although the fibrin-rich clots have higher friction, they are also more elastic and therefore easier to retrieve in one piece, whereas RBC-clots are more prone to cause distal emboli during mechanical removal [21]. In addition to this, this discrepancies with the other studies may be associated with restrictions in the number patients with fibrin rich clots (16) while comparing with RBC-rich clots (46).

Our study has several limitations which should be considered when interpreting the results. First and foremost, relatively small sample group which may impact generalizability. Secondly, very high percentage of aspiration used as a primary technique in our center might affect clot composition compared to stent retriever technique [22]. It also should be assumed, that the age of the patients can potentially affect the clot composition. Unfortunately, due to the quantitative limitation of the study group, we were not able to perform a statistical analysis in different age groups. Finally, there is a potential selection bias due to the fact that patients who underwent MT where no clots were retrieved were not included in the study.

In conclusion, despite the lack of statistically significant correlation between clot composition and first pass effect in patients with acute ischemic stroke, our results suggest that red blood cell rich clots might be associated with increased number of thrombectomy passes which supports the notion that clot histology influences recanalization outcomes.

CLINICAL IMPLICATIONS

Our study suggests that clot composition might be associated with the number of thrombectomy passes in patients undergoing endovascular recanalization due to large vessel occlusion. The understanding of this correlation might be important factor which could improve the rate of first pass effect which is crucial in the treatment of acute ischemic patients with large vessel occlusion. Recent studies on clot composition in mechanical thrombectomy investigate clot composition as it might be used as complementary diagnostic tools to determine stroke etiology, adapt the most efficient interventional strategy and predict clinical outcome and our paper adds to the on-going debate. Perhaps further studies could correlate the pre-operative imaging results with post-operative clot composition and develop a protocol for the most beneficial and personalized reperfusion strategy.

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