Pathological changes in non-contrast CT scans, safety, and outcome differences in patients with elevated INR compared to patients with normal INR after acute ischemic stroke treatment with mechanical thrombectomy

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ABSTRACT

Background and aim: Stroke is the second main reason for death worldwide [1]. Patients with atrial fibrillation have an increased ischemic stroke risk. Therefore, they are anticoagulated to reduce thromboembolic event chance [2]. Although anticoagulation is associated with haemorrhage complications, there is little information about the safety and the outcomes of treating acute ischemic stroke with mechanical thrombectomy in patients with elevated international normalised ratio (INR) [3]. This trial aimed to find out if there are differences in safety and outcomes in patients with elevated INR when treating acute ischemic stroke with mechanical thrombectomy.

Materials and methods: 183 cases were divided into two groups: patients with INR < 1.2 and patients with INR ≥ 1.2. Age and gender distribution were evaluated. Intracranial haemorrhage and mortality rates were analysed. Four pathological changes (signs of acute ischemia, haemorrhage transformations, deformations in the ventricular system, and the midline shift) in non-contrast CT scans before the mechanical thrombectomy and 24 hours after the thrombectomy were analysed.

Results: Results revealed that there was no statistical significance between the groups in intracranial haemorrhage ($p = 0.292$) or morality ($p = 0.345$) rates. Several pathological changes before the mechanical thrombectomy ($p = 0.631$) and 24 hours after mechanical thrombectomy ($p = 0.398$) were not statistically significantly different. In 24 hours, the study group did not develop ($p = 0.548$) a statistically significant number of new pathological changes when comparing to the control group.

Conclusion: Mechanical thrombectomy safety and outcomes when treating acute ischemic stroke in patients with elevated INR did not differ from patients who had regular INR.

Keywords: Acute ischemic stroke, non-contrast CT, mechanical thrombectomy, safety, elevated INR.

1. INTRODUCTION

Each year stroke is the second main reason for death worldwide [1]. According to the latest available statistics in Europe (2016), the number of noncommunicable diseases is increasing [4]. Mainly, stroke and ischemic heart disease caused around 15.2 million deaths worldwide in 2016 [4]. Although the absolute mortality from stroke has a downtrend due to improvements in diagnostics and therapy, the absolute number of people who have a stroke every year is increasing [5,6].

There are two main types of stroke – ischemic and haemorrhagic. Only about 13% of all strokes are haemorrhagic [7]. They occur when there is extravasation due to a defect in the vessel wall. When comparing mortality, haemorrhagic stroke (68%) has a higher death rate than ischemic stroke (57%) [8]. Ischemic stroke accounts for 87% of all strokes, and this type is usually caused by atherosclerosis and thromboembolic events when the middle cerebral artery is occluded with thrombi [9]. Even though ischemic stroke is responsible for fewer deaths than haemorrhagic stroke, according to other sources, it is the leading long term disability causing disease [10,11]. It is thought that by the year 2035, there will be 34% more cases of ischemic stroke worldwide when compared to the 2015 year data. This

means that the number of people who require permanent nursing will also increase [12,13].

Symptoms of ischemic stroke are usually associated with dysfunction of the brain region, in which the occluded artery is proving blood to [14]. A quick neurological deficit is one of the main ischemic stroke symptoms. Patients complain of sudden numbness or weakness in the face, arm, or leg, especially on one side of the body, speech disorder is also frequently observed.
When it comes to diagnostics, the modality of choice is a non-contrast computed tomography (CT) scan because of its full availability and speed. It is also sensitive in detecting intracerebral haemorrhage, which can be found when a haemorrhagic stroke occurs [15]. This is very important because of entirely different treatment tactics. The main objective of ischemic stroke treatment is the administration of intravenous thrombolysis and mechanical thrombectomy, while in the case of haemorrhagic stroke, the main treatment aspects are systolic blood pressure control and discontinuation of anticoagulants [16,17].

In the early stages of ischemic stroke, pathological findings in non-contrast CT can be minor and difficult to detect. According to other authors, we can see these pathological findings in the scans: hypodense ischemic area, hyperdense middle cerebral artery, loss of grey-white differentiation, cortical swelling, and loss of sulcation [18]. Midline shift, which can occur due to cerebral oedema, cerebral ventricle deformation, and haemorrhagic transformation, is associated with worse patient outcomes [19,20].
When an acute ischemic stroke is suspected, the main objective is to restore blood flow as quickly as possible. All the necessary diagnostic procedures: non-contrast CT scan, blood oxygenation, glucose levels, international normalised ratio (INR), and an electrocardiogram – must be performed within 60 minutes of the patient reaching the hospital [17,21]. Intravenous thrombolysis must be performed within 4,5 hours from the first symptom onset time because studies have shown that after this therapeutic window, intravenous Alteplase becomes ineffective [17]. If occlusion of a large vessel causes the stroke, there is little chance that thrombolysis will be useful, in this case, mechanical thrombectomy becomes the primary treatment choice. This endovascular procedure is accomplished by aspirating thrombus with stent retrievers [22]. According to the newest recommendations, mechanical thrombectomy should be performed within 6 hours from the first symptom onset [17].

When we talk about ischemic stroke, a significant factor is an atrial fibrillation [22]. Our society is getting older, and atrial fibrillation numbers are increasing [4,23]. According to other sources, patients with atrial fibrillation have five times increased risk of developing an ischemic stroke while comparing to the rest of the population in the same age group [2]. This is because people with atrial fibrillation have an increased risk of thromboembolic complications due to the pathological formation of thrombus in the atriums [2]. To reduce the risk of these complications, patients are getting anticoagulated [2]. It is known that anticoagulation increases the risk of intracranial haemorrhage, which is also one of the mechanical thrombectomy complications associated with worse patient prognosis [3,24].

Many studies have proven that mechanical thrombectomy is a safe and effective method for treating acute ischemic stroke [25–28]. On the other hand, previously mentioned studies have not involved anticoagulated patients in their study groups. Does this pose a question, is mechanical thrombectomy safe to these patients? Also, there is little information about the safety and outcomes of performing mechanical thrombectomy on patients with elevated INR. Therefore, this research aimed to investigate if there is a significant difference in safety, outcomes, and non-contrast CT scan pathological changes between patients with elevated INR and patients with regular INR.

2. MATERIALS AND METHODS

We performed a retrospective study of 183 patients based on the data from the Lithuanian University of Health Sciences Hospital (LUHSH)

Kauno Klinikos electronic registry. Case-reports in 2014 January and 2018 January were analysed. Data about patient age, gender, INR, intracranial haemorrhage rate, mortality was recorded. Also, non-contrast CT scans before mechanical thrombectomy and 24 hours after mechanical thrombectomy were analysed. The study was approved by the Bioethics Committee of the LUHS (No. BEC-MF-210).

Firstly, the research was performed in these databases: PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Wiley Online Library (https://onlinelibrary.wiley.com), Science Direct (https://www.sciencedirect.com). Keywords were used: acute ischemic stroke, stroke diagnostics, ischemic stroke CT signs, mechanical thrombectomy safety, patients with elevated INR, acute ischemic stroke treatment.

The study group included 55 patients who met these inclusion criteria:
• Patients who had an acute ischemic stroke and were treated with mechanical thrombectomy at LUHSH Kauno Klinikos Interventional Radiology unit.
• Patient INR was ≥ 1.2.
• Non-contrast CT scans were performed at the LUHSH Kauno Klinikos Radiology department.
• The patient had a non-contrast CT scan performed before mechanical thrombectomy and 24 hours after the treatment.
• No cerebral anomalies were found in non-contrast CT scans.

The control group included 128 patient who met these inclusion criteria:
• Patients who had an acute ischemic stroke and were treated with mechanical thrombectomy at LUHSH Kauno Klinikos Interventional Radiology unit.
• Patient INR was < 1.2.
• Non-contrast CT scans were performed at the LUHSH Kauno Klinikos Radiology department.
• The patient had a non-contrast CT scan performed before mechanical thrombectomy and 24 hours after the treatment.
• No cerebral anomalies were found in non-contrast CT scans.

Study and control group patient distribution by age and gender was compared. We analysed if patients with elevated INR have a higher intracranial haemorrhage and mortality rate.

Non-contrast CT scans were performed in the study and control group patients. We looked for four pathological findings: signs of acute ischemia, haemorrhage transformations, deformations in the ventricular system, and the midline shift ≥ 0.5 cm. These pathological findings were associated with further patient prognosis. Each finding was equivalent to a score of "1: if it was present. "0" was given if the pathological finding was absent. Non-contrast CT scan findings before mechanical thrombectomy were analysed to see if both groups had similar pathological changes when they arrived at the hospital. We analysed changes 24 hours after the procedure to predict the outcome of the patient. Bucker et al. supported this idea., who stated that both the 24-hour and 1-week ischemic lesions were similarly significantly associated with functional outcome (both $p < 0.001$) [29]. We also looked at how many new changes were developed by the patients in a period of 24 hours. This was accomplished by subtracting the number of changes before the procedure out of the number of changes 24 hours after the procedure. All the non-contrast CT scans were analysed with a radiologist ensuring the quality of the final results.

Statistical analysis was performed with "SPSS (Statistical Package for the Social Sciences) program 23.0" ("IBM," Armonk, New York, USA) and "Microsoft Excel 2019" ("Microsoft Corporation," Redmond, Washington, USA") programs. To calculate statistical significance, an analysis of covariance (ANCOVA) with age as a covariate was performed. Levene's test was used to test if the groups were homogenous. Pearson chi-square ($\chi 2$) tests were used to calculate the frequency of categorical variables. Summarised statistics were used for: value means, standard deviation, maximum and minimum values. The observed differences were considered statistically significant when the calculated significance level (p-value) was lower than the selected significance level ($\alpha = 0.05$).

3. RESULTS

In the study, we observed 183 cases of patients aged 40-85 diagnosed with acute ischemic stroke and treated with mechanical thrombectomy. The study group consisted of 55 patients: 33 (60%) males and 22 (40%) females. The age means of males in the study group was 72.41 (SD = 5.55) years, females – 73.42 (SD = 6.43) years. The age mean by gender did not differ statistically significantly (p = 0.372) in the study group. The control group consisted of 128 patients, 60 (46.88%) males, and 68 (53.12%) females. The age means of males was 71.32 (SD = 6.64) years; the age mean of females was 73.45 (SD = 6.08) years. The age mean by gender did not differ statistically significantly (p = 0.442) in the control group. While comparing both groups, the age means of the study group 72.91 (SD = 6.48) years was not statically significantly higher (p = 0.232) than the age means of the control group 72.02 (SD = 7.46) years. The data is presented in Table 1.

Table 1. Study and control group patient distribution by age and gender

	Study group (N=55)	Control group (N=128)
Age		
Male, age mean (SD)	72.41 (5.55)	71.32 (6.64)
Female, age mean (SD)	73.42 (6,43)	73.45 (6.08)
Total, age mean (SD)	72.91 (6.48)	72.02 (7.46)
Gender		
Male, N (%)	33 (60)	60 (46.88)
Female, N (%)	22 (40)	68 (53.12)

The incidence of intracranial haemorrhage was not statistically significantly higher in the study group (p = 0.292) than in the control group. When comparing mortality rate, death occurred to 8 (14.54%) patients in the study group and to 23 (17.96%) patients in the control group, but this difference was not statically significant (p = 0.345). The data is summarised in Table 2.

Table 2. Study and control group intracranial haemorrhage and mortality rates

	Study group (N = 55)	Control group (N = 128)
Intracranial haemorrhage		
Present, N (%)	31 (56.36)	62 (48.44)
Absent, N (%)	24 (43.64)	66 (51.56)
Mortality		
Died, N (%)	8 (14.54)	23 (17.96)
Survived, N (%)	47 (85.46)	105 (80.04)

First, we calculated that there was no statistical significance in non-contrast CT scans before thrombectomy between anticoagulated patients and patients with normal INR (p = 0.631). Patient group with normal INR non-contrast CT scan sum mean was 0.54 (SD = 0.614) compared to anticoagulated group 0.49 (SD = 0.635). From this, we can say that both groups had roughly the same number of pathological changes before mechanical thrombectomy treatment.

Next, we did not find statistically significant differences between the groups in non-contrast CT scans 24 hours after mechanical thrombectomy (p = 0.398). The patient group with normal INR had an average number of 2.05 (SD = 1.260) pathological changes, while the elevated INR group patients had an average number of 1.97 (SD = 1.177) pathological changes.

Also, the study group did not show significant pathological changes score difference in developing new pathological changes over 24 hours between the two CT scans (p = 0.548). The study patient group developed around 1.75 (SD = 1.324) new pathological changes in 24 hours, while the control group around 1.82 (SD = 1.139) new pathological changes. The data is presented in Fig. 1.

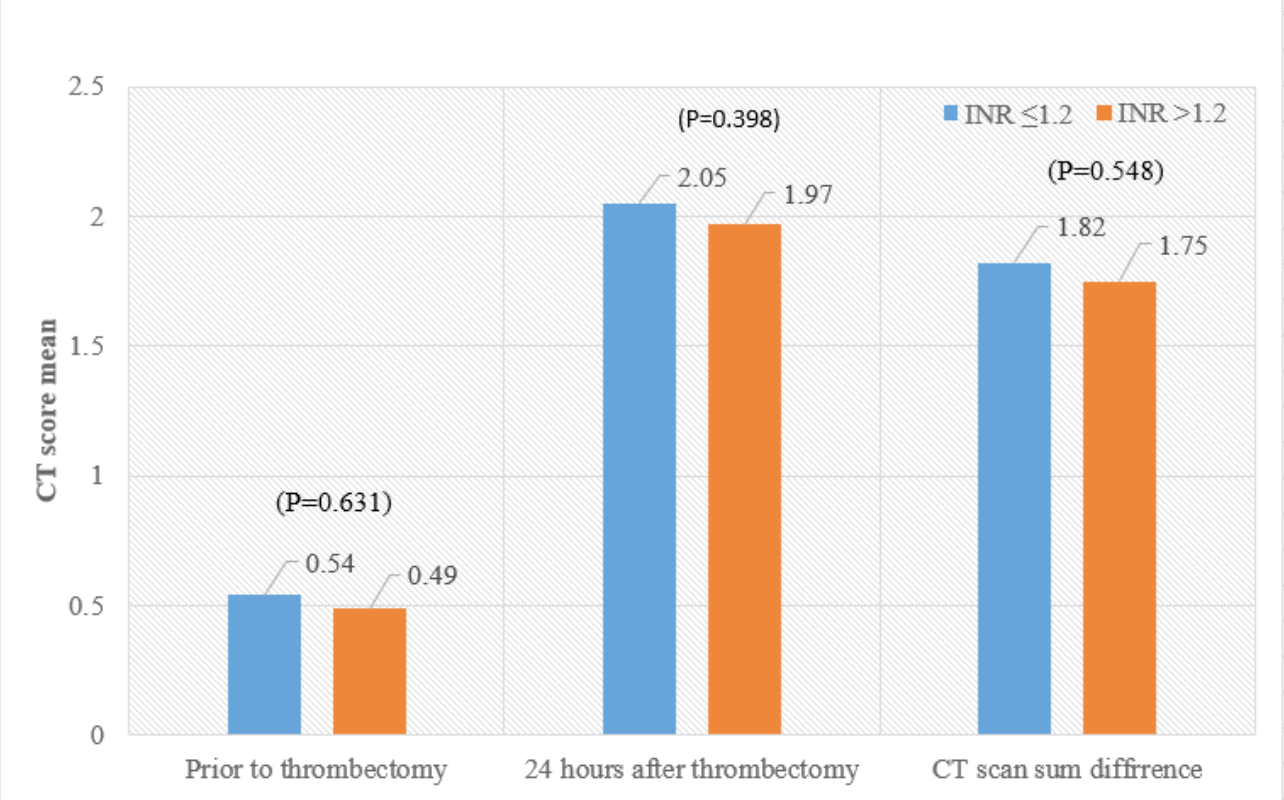

Fig. 1. Non-contrast CT score mean diversity before the thrombectomy, 24 hours after the thrombectomy and new changes over 24 hours

4. DISCUSSION

This study showed that the safety of acute ischemic stroke treated with mechanical thrombectomy statistically significantly different between patients with normal blood clotting and anticoagulated patients. The number of pathological changes in non-contrast CT scans, the frequency of intracranial is no haemorrhage, and mortality did not differ between the two groups. This result supports the safety of mechanical thrombectomy independent of the patient's blood clotting.

Some authors have been investigating whether antiplatelet agents may increase the risk of haemorrhagic stroke. Garcia-Rodriguez et al. [24] studied patients who were taking aspirin or warfarin. This study found that aspirin use was not associated with an increased risk of intracranial haemorrhage. Patients who took aspirin daily for over three years even had a reduced risk of subarachnoid haemorrhage. In contrast to aspirin, warfarin users had a significantly higher risk of intracranial haemorrhage and a moderately increased risk of subarachnoid haemorrhage. Our study did not analyse which antiplatelet agent or anticoagulant the patient was taking, but, in contrast to the Garcia-Rodriguez [24] study, our group of anticoagulated patients did not have a significantly higher incidence of intracranial

haemorrhage. Our sample size was significantly smaller, only 183 patients, compared to the 3131 cases analysed in the recently mentioned work [24], which could have led to different results.

In 2016, a study was conducted to analyse the safety of mechanical thrombectomy when treating acute ischemic stroke in patients who were taking vitamin K antagonists. Uphaus et al. [30] collected data from 815 patients and concluded from the results that the use of vitamin K antagonists was not associated with worse clinical outcomes or an increased risk of intracranial haemorrhage. Although this contradicts to the results obtained by Garcia-Rodriguez et al. [24], we have to keep in mind that Garcia-Rodriguez investigated the association of intracranial haemorrhage risk with the use of vitamin K antagonists in the general population, rather than among patients who received endovascular treatment after an ischemic stroke. Our results support the results obtained by Uphaus et al., that mechanical thrombectomy safety and outcomes are not associated with patient INR.

Rebello et al. [31] conducted a prospective study in patients with ischemic stroke who were treated endovascularly. After collecting 297 cases of patients with INR 1.7–2.0 between 2010 and 2015, they analysed petechial haematomas, procedure success, and 90-day functional outcomes. This study is similar to ours because it did not track, which anticoagulant the patient was taking. Study calculations showed that neither demographics, safety, or efficacy differed between the groups. No statistically significant changes were observed when comparing mortality, which also supports our findings.

Seiffge et al. [32] searched about the relation between patient blood coagulation and outcomes after acute ischemic stroke. Their study was about the impact of prior treatment with novel oral anticoagulants on bleeding complications and outcomes. They stated that the safety of intravenous thrombolysis or endovascular treatment is the same in patients receiving subtherapeutic vitamin K antagonist treatment or novel oral anticoagulants when comparing with those without prior anticoagulation. Although in our study, we did not track what anticoagulant patients were taking, Seiffge et al., conclusions support our ones.

There were some limitations in our study. First, the results might be controversial because of the small sample size. Also, both groups were not equal in the number of patients. Furthermore, types of anticoagulants were not taken into perspective as well as the type of anaesthesia during the mechanical thrombectomy. Studies have shown that general anesthesia could be associated with worse outcomes after endovascular treatment [33]. Lastly, this is a retrospective study in a single-centre, therefore our results need to be further validated in a large scale, multi-centre study.

Based on these analysed studies, we can say that decreased blood clotting is not a contraindication to treat ischemic stroke with mechanical thrombectomy. Our work was mainly based on the changes seen in the non-contrast CT scan images; this type of analysis method is not described in either Lithuanian or foreign literature. However, the results we obtained were similar to those of other authors, so this method can be considered correct and further proves that endovascular treatment is a safe, minimally invasive approach for treating ischemic stroke regardless of the patient's INR.

5. CONCLUSIONS

After analysing results, we could say that mechanical thrombectomy safety and outcomes when treating acute ischemic stroke in patients with elevated INR did not differ from patients who had regular INR. Intracranial haemorrhage, mortality rate, and several pathological changes in non-contrast CT scans were not statistically significantly different between patient groups with different INR.

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