

Mechanical thrombectomy in patients with M1 occlusion and NIHSS score ≤ 5 : a single-centre experience

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To cite: Bhogal P, Bücke P, Ganslandt O, *et al.* Mechanical thrombectomy in patients with M1 occlusion and NIHSS score ≤ 5 : a single-centre experience. *Stroke and Vascular Neurology* 2016;0:e000052. doi:10.1136/svn-2016-000052

Received 25 October 2016
Accepted 28 October 2016



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ABSTRACT

Background: The recent success of several mechanical thrombectomy trials has resulted in a significant change in management for patients presenting with stroke. However, it is still unclear how to manage patients that present with stroke and low National Institutes of Health Stroke Scale (NIHSS) ≤ 5 . We sought to review our experience of mechanical thrombectomy in patients with low NIHSS and confirmed M1 occlusion.

Methods: We retrospectively analysed our prospectively maintained database of all patients undergoing mechanical thrombectomy between January 2008 and August 2016. We identified 41 patients with confirmed M1 occlusion and low NIHSS (≤ 5) on admission to our hospital. We collected demographic, radiological, procedural and outcome data.

Results: The mean age of patients was 72 ± 14 , with 20 male patients. Associated medical conditions were common with hypertension seen in $\sim 80\%$. Just over 50% presented with NIHSS 4 or 5. The average ASPECTS score on admission was 8.8 (range 6–10), and the average clot length 10 mm. Angiographically Thrombolysis in Cerebral Infarction (TICI) $\geq 2b$ was obtained in 87.8% of patients. 7 patients had haemorrhage on follow-up, 2 of which were symptomatic. Of 40 patients with 90-day follow-up, 75% had modified Rankin Scale (mRS) score 0–2. There were 3 deaths at 90 days.

Conclusions: Mechanical thrombectomy in patients with low NIHSS and proximal large vessel occlusion is technically possible and carries a high degree of success with good safety profile. Patients with low NIHSS and confirmed occlusion should be considered for mechanical thrombectomy.

INTRODUCTION

Mechanical thrombectomy in selected patients has become the gold standard treatment for patients presenting with acute thromboembolic infarction. The publication of multiple trials documenting a significant benefit represents a major step forward in the management of patients with acute ischaemia. These trials, with the exception of the Multicentre Randomised Clinical Trial of Endovascular Treatment for

Acute Ischaemic Stroke in the Netherlands (MR CLEAN)¹ and Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTAND-IA),² focused on patients with moderate-to-severe neurological deficits with a score of at least 6–8 on the National Institutes of Health Stroke Scale (NIHSS). Even though, the inclusion criteria for MR CLEAN included people with low NIHSS (≥ 2) the median NIHSS score of patients across all the trials ~ 15 –17.

The complex interplay between large vessel proximal occlusion, blood pressure, collateral status and clinical symptomatology can result in some patients with large vessel thrombus presenting with low NIHSS scores³ and it has been suggested that all patients with an NIHSS score of 2 or above should undergo angiographic imaging in order to detect at least 90% of proximal occlusions.³ Furthermore, it is known that patients with proximal occlusion can deteriorate rapidly.⁴ Therefore, it is important to recognise that patients with a proximal large vessel occlusion do not necessarily have a high NIHSS score.

We sought to determine the outcome of patients with acute ischaemic stroke with minor symptomatology and NIHSS score ≤ 5 with confirmed occlusions in the M1 segment of the middle cerebral artery (MCA). We present our data on the clot length, initial imaging findings, collateral status, recanalisation rate, complications rate and clinical outcome.

MATERIALS AND METHODS

From our prospectively maintained database, we retrospectively selected patients with admission NIHSS scores of ≤ 5 and confirmed thrombus in the M1 segment of the MCA on preoperative imaging (CT or MRI) and in whom a mechanical thrombectomy procedure was performed at our institution. All consecutive patients entered into the

database between January 2008 and August 2016 who met the inclusion criteria were included in the analysis.

We chose an upper limit of 5 points on the NIHSS scale because patients with low scores are under-represented in the current literature. We selected only those patients with clot in the M1 segment as these patients represented a significant proportion of the patients included in the recent stroke trials.

A neurologist examined all the patients at admission and this included the NIHSS score. Patients with suspected acute ischaemic stroke underwent dedicated imaging, either CT or MRI. Those who underwent CT imaging had an unenhanced CT scan as well as CT angiogram. Those patients who underwent MRI had axial diffusion weighted imaging (DWI), Fluid Attenuated Inversion Recovery (FLAIR), susceptibility weighted imaging (SWI) and time of flight magnetic resonance angiogram (TOF-MRA) sequences to evaluate for further treatment with either thrombolysis and/or mechanical thrombectomy. Imaging was performed from the aortic arch to the vertex.

Stroke therapy

The use of intravenous (IV) thrombolysis followed national and international guidelines and was performed only if the patients presented with 4.5 hours of symptom onset.

The patients were determined to be candidates for mechanical thrombectomy after discussion between the treating neurologist and the neurointerventionist. Mechanical thrombectomy was only offered if an acute occlusion could be demonstrated on the preoperative imaging and if salvageable brain tissue was present. An upper age limit for performing mechanical thrombectomy is not used in our institution, rather the premorbid status of the patient is taken into consideration along with comorbidities and the will of the patient or family members.

All patients underwent mechanical thrombectomy under general anaesthesia. All patients underwent thrombectomy with stent retrievers and either a balloon guide catheter or distal aspiration catheter.

Postinterventional management

All patients were admitted to the neurointensive care or stroke unit after mechanical thrombectomy. All patients had routine follow-up imaging with either CT or MRI 24–36 hours postintervention. Follow-up assessment, including modified Rankin Scale (mRS) score, was obtained at 90 days by an inpatient hospital visit or telephone interview with a neurologist.

Data collection

Data collection included baseline demographics (age, sex), medical history (including history of diabetes mellitus, hypercholesterolaemia, hypertension, atrial fibrillation), smoking history, and time of symptom onset and NIHSS to assess severity. The ASPECTS score was

calculated for all patients on axial CT or DWI MRI sequences. The location of the occlusion and the thrombus length were assessed on axial images and correlated with catheter angiography. The collateral supply was graded according to the proposal by Higashida *et al*⁵ (grade 0—no collaterals visible to the ischaemic site, grade 1—slow collaterals to the periphery of the ischaemic site with the persistence of some of the defect, grade 2—rapid collateral to the periphery of the ischaemic site with persistence of some of the defect to only a portion of the ischaemic territory, grade 3—collaterals with slow but complete angiographic blood flow of the ischaemic bed by the late venous phase, grade 4—complete and rapid collateral blood flow to the vascular bed in the entire ischaemic territory by retrograde perfusion). The number of passes to obtain the final result was recorded. The final angiographic outcome was recorded using the Thrombolysis in Cerebral Infarction (TICI) scale.⁶ Post-treatment repeat imaging, at 24 hours, was performed and the ASPECTS score noted. The presence of haemorrhage was also recorded.

RESULTS

Demographics

Between January 2008 and August 2016, we identified 41 patients who underwent mechanical thrombectomy for M1 occlusion and NIHSS ≤ 5 . The baseline characteristics are outlined in table 1. The mean age of the patients was 72 years old (± 12 years) and 20 patients were male. Associated conditions were common among our cohort with over 80% of patients having a medical history of hypertension and 43.9% of patients having atrial fibrillation. The main suspected cause of the stroke was cardiac embolism with extracranial atherosclerosis being the second most common cause.

Admission status

All patients had an admission NIHSS of ≤ 5 but ~50% of these patients had an NIHSS of 4 or 5. Preoperative MRI was performed in ~70% of patients and just over half of patients had a left-sided thromboembolic occlusion. In our cohort, the average clot length was 10 mm (range 4.6–23.1 mm). The average preoperative ASPECTS score was 8.8 (range 6–10). Six patients received IV alteplase prior to mechanical thrombectomy (mean average dose 67 mg).

Angiographic and procedural details

All patients underwent mechanical thrombectomy. In all patients, the procedure was performed via a standard right common femoral approach. Just over 70% of the patients in our cohort had a collateral status of 3 or 4 on catheter angiography performed prior to the thrombectomy. In patients with occlusion of the internal carotid artery, this was determined via angiographic runs of the contralateral ICA and vertebral arteries.

Table 1 Baseline and outcome characteristics of patients with low NIHSS stroke and M1 thromboembolic occlusion that underwent mechanical thrombectomy

Characteristic	Results
Age (mean±SD)	72±14
Male	20 (48.7%)
Associated conditions	
Atrial fibrillation	18 (43.9%)
Diabetes mellitus	7 (17.1%)
Hypertension	33 (80.5%)
Hypercholesterolaemia	15 (36.6%)
Smoker	6 (14.6%)
Suspected cause	
Cardiac embolism	16 (39%)
Extracranial atherosclerosis	11 (26.9%)
Intracranial atherosclerosis	2 (4.9%)
Dissection	2 (4.9%)
Unknown	10 (24.3%)
NIHSS on admission	
0	3 (7.3%)
1	3 (7.3%)
2	7 (17.1%)
3	7 (17.1%)
4	13 (31.7%)
5	8 (19.5%)
Preoperative MRI	28 (68.3%)
Preoperative CT imaging	13 (31.7%)
ASPECTS score preoperative	8.8 (6–10)
Side	
Left	22 (53.6%)
Right	19 (46.4%)
Clot length (mm)	10 (4.6–23.1 mm)
Mean duration of procedure (min)	119±3 (range 36–294)
Mean number of thrombectomy attempts	1.8
Time from stroke onset to recanalisation (min) (n=33)	385±57 (235–727)
Postoperative ASPECTS (24 hours)	8.1 (5–10)
Haemorrhage postoperative	7 (2 symptomatic haemorrhage)
Collateral status	
0	0
1	3 (7.3%)
2	9 (21.9%)
3	23 (56.1%)
4	6 (14.6%)
TICI≥2b	36 (87.8%)
TICI 3	26 (63.4%)
90-day Mrs	
0	20 (50%)
1	7 (17.5%)
2	3 (7.5%)
3	3 (7.5%)
4	3 (7.5%)
5	1 (2.5%)
6	3 (7.5%)
NA	1 (2.5%)

mRS, modified Rankin Scale; NA, not available; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction.

In 5 cases, a proximal balloon guide catheter was used, and in 37 cases, a distal aspiration catheter was used. A distal aspiration catheter was used in all cases that did not use a proximal balloon guide catheter. In 39 cases, stent retrievers were used with aspiration used

in the two remaining cases. The pREset (phenox, Bochum, Germany) stent retriever was used in 34 cases⁷ and a variety of other stents used in the remaining cases. The mean number of thrombectomy attempts was 1.8 (range 1–8 attempts). Thirteen patients (31.7%)

required extracranial stenting with 2 patients requiring stenting for acute dissections and 11 patients requiring carotid stents for severe (>70%) stenosis or complete occlusion of the internal carotid artery. Carotid stenting was always performed prior to the thrombectomy. The mean duration of the procedure was 119 min and the mean time from stroke onset to recanalisation was 407 min (n=34). In seven patients the time of stroke onset was unknown. A TICI 2b result or better was achieved in 87.8% of patients with TICI 3 achieved in 63.4% of patients.

There were no intraprocedural complications.

Postprocedural clinical and angiographic

All patients had follow-up imaging. The average ASPECTS score on the 24-hour scan was 8.1 (5–10). Seven patients showed signs of haemorrhage, five of which had localised clinically asymptomatic subarachnoid haemorrhage (SAH). Two patients had symptomatic haemorrhage, both of which were SAH.

At 90-day follow-up (n=40), 75% of patients had a good outcome with mRS≤2 and a moderate outcome with mRS≤3 in 82.5% of patients. There were three deaths in our cohort, one of which was secondary to a severe lower respiratory tract infection and the other secondary to the stroke.

DISCUSSION

The recent meta-analysis conducted by the HERMES collaborators confirmed the beneficial effect of mechanical thrombectomy in patients with acute large vessels thromboembolic stroke.⁸ This meta-analysis grouped patients from the five major trials, (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA) carried out between 2012 and 2014 with data from 1287 patients being analysed. They concluded that endovascular thrombectomy led to significantly reduced disability compared with control at 90 days (mRS 0–2 46% for the interventional arm, and 26.5% for control population).^{1 2 9–11} The number needed to treat via mechanical thrombectomy to reduce disability by at least one point on the mRS for one patient was 2.6 and subgroup analysis showed persistent benefits in patients aged over 80, those with symptom onset over 300 min prior to randomisation and in those patients not receiving alteplase. It was also seen that a similar effect on disability was seen across the entire NIHSS severity range and despite the relative paucity of patients with mild strokes (≤10, n=177) included in the studies there was a trend to favour intervention. This was contrary to previous studies that have identified patients with the most severe strokes (baseline NIHSS>19) as deriving most benefit from mechanical thrombectomy.¹² However, there is evidence that a significant number of patients with large vessel occlusion can present with relatively mild neurological symptoms. In the study by Maas *et al*,³ they demonstrated that a large number of patients with low

baseline NIHSS scores (55% of patients with NIHSS scores <11) had large vessel occlusion on non-invasive imaging. Furthermore, Smith *et al*¹³ showed that 31.2% of patients (29 200 of 93 517) with acute ischaemic stroke did not receive IV thrombolysis because of mild or improving symptoms and that of this group 28.3% could not be discharged home and 1.1% died. The study by Nedeltchev *et al*¹⁴ showed similar findings. In this study of 90-day postdischarge outcomes in patients were not given recombinant tissue plasminogen activator (rtPA) because of mild or rapid stroke symptoms, 24.7% showed mRS≥2. In the study by Mokin *et al*¹⁵ the authors noted the variability seen in the outcomes of patients admitted with low baseline NIHSS scores (range 0–7). Within this range, the authors demonstrated that an increase in NIHSS score by each point demonstrated a trend towards progressively higher numbers of patients being unable to ambulate at discharge. Interestingly, there appeared to be a rapid drop in the ability to ambulate independently at discharge (mean duration of stay 6 days) for patients with NIHSS 0–2 (NIHSS=0–86%, 1–73%, 2–52%) with a second drop occurring for patient with NIHSS 5–7 (NIHSS=5–52%, 6–44%, 7–28%). There is also some evidence to suggest that right-sided infarcts may present with falsely mild symptoms and poor outcomes without thrombolytic treatment.¹⁶ Taken together, this information strongly suggests that a low admission NIHSS score is not necessarily predictive of a good functional outcome and that these patients should undergo investigation to exclude large vessel occlusion as has been suggested.^{15 17}

The limited symptomatology of some patients presenting with proximal large vessel occlusion is likely due to their leptomeningeal collateral status. Numerous studies have shown a correlation between collateral status and clinical outcome. For example, Miteff *et al*¹⁸ graded collaterals into good, moderate and poor based on the filling of the MCA branches distal to the obstruction on CT angiography. They found good collaterals in 55% of patients, moderate collaterals in 26% and poor collaterals in 18%. They found that good collateral status was associated with reduced infarction expansion as well as good outcome at 3 months (mRS≤2) in addition to the acute NIHSS, which was lower in patients with good collaterals. Interestingly of those patients with poor collaterals, none had a good outcome at 3 months. Similarly, Maas *et al*¹⁹ studied 134 patients with acute MCA occlusion and graded the collateral circulation on a five-point scale. They showed that patients with poor collaterals were four times more likely to clinically deteriorate in hospital as those with normal or exuberant collaterals. Other groups have also shown a relationship between collateral status and functional outcome^{20–22} with the recent post hoc analysis of the MR CLEAN data showing a significant modification of treatment effect by collateral status with the strongest benefit seen in patients with good collaterals (grade 3) and no effect seen in patients with absent collaterals (grade 0).²³ Our findings

are consistent with previous reports with ~70% of patients having good leptomeningeal collaterals.

Miteff *et al.*¹⁸ identified further interesting information in their study. They showed that those patients with good collaterals and reperfusion all achieved a good outcome. However, they also showed that in those with good collateral status but no major reperfusion, only 38% had a favourable outcome. Therefore, the presence of good collaterals alone will not prevent a poor outcome and reperfusion is still key. Furthermore, the status of the collaterals is not static and a decrease in their ability to supply the demands of the brain will result in expansion of the infarction. Campbell *et al.*²⁴ have previously shown that collateral circulation is not static, and in patients with good collaterals at baseline but without successful reperfusion, there was a strong correlation between collateral deterioration and infarct growth. Therefore, the question then arises as to why collaterals fail and if there is anything that can be done to prevent this? At the moment, conclusive answers to these questions remain elusive. Blood pressure appears to play an important role in cerebral collaterals with a post hoc analysis of data from the MR CLEAN trial demonstrating that the use of general anaesthesia negated the beneficial effects of thrombectomy. This was also confirmed by Ouyang *et al.*²⁵ and Brinjikji *et al.*²⁶ although it has been noted that confounding factors are difficult to eradicate from the current data. The exact nature of this deterioration in outcome is unknown; however, the drop in blood pressure commonly seen during the induction of anaesthesia is thought by many to be a contributory cause and in two small clinical trials norepinephrine- α -phenylephrine-induced hypertension improved the outcome in patients with stroke^{27, 28} which gives some credence to this theory. Other authors have suggested that a rise in intracranial pressure (ICP) can cause a collapse in the collateral circulation²⁹ and in animal models ICP rise of even 5 mm Hg can cause significantly retarded flow via collateral pathways. This change in the flow seems to be related to as of yet unidentified cellular processes within the ischaemic penumbra as they are oedema-independent.³⁰ Other proposed mechanisms are cerebral venous steal,³¹ reversed Robin Hood syndrome³² and blood pressure fluctuations secondary to autonomic dysfunction³³ as well as others.³⁴ Interestingly, with regard to the latter, a recent study by Xiong *et al.*³⁵ showed that 76.5% of patients with relatively mild strokes (mean NIHSS score 4.4) had severe autonomic dysfunction and that those with more severe autonomic dysfunction had poorer outcomes at 2 months. In all likelihood, it is probable that multiple processes interact to cause the deterioration and the over-riding aim should be to restore normal or near normal flow as soon as possible through whichever means is most suitable. Pfaff *et al.*³⁶ recently published the results from their series of 33 patients with low NIHSS (≤ 8) treated by mechanical thrombectomy. The median NIHSS score was 5 (IQR 4–7) and presenting

median ASPECTS score 10 (IQR 9–10). Just over half of the patients had a confirmed M1 occlusion and 72.7% had grade 3 collaterals (93.9% had grade 2 or 3 collaterals). In this study, 63.6% of patients had a favourable outcome (mRS ≤ 2) at 90 days with 90.9% having moderate clinical outcome (mRS ≤ 3) with 9.1% mortality, one of which was caused by SAH secondary to wire perforation. While the results of this study do not differ significantly from those of Strbian *et al.*³⁷ one very important finding was that the median thrombus length was 12 mm (IQR 10–12 mm) and it is known that the chance of recanalisation with thrombus lengths over 8 mm is extremely low.^{38, 39} Our results are similar and interestingly we also showed the presence of long clots with the mean average clot length in our cohort measuring 10 mm. It is also perhaps worth considering clot length in a slightly different way. On average, ~75% of patients in the five major mechanical thrombectomy trials achieved TICI $\geq 2b$ reperfusion status. A similar probability of reperfusion after IV-tPA is seen if the clot is below 4 mm. Therefore, one should actually consider mechanical thrombectomy in all patients in whom the clot is 4 mm or longer since at this length the probability of achieving reperfusion favours mechanical thrombectomy. In our data, all the clots were longer than 4 mm with the shortest clot measuring 4.6 mm.

Recently Haussen *et al.*⁴⁰ published their intention-to-treat study. In this study, patients with a low NIHSS ≤ 5 and confirmed large vessel occlusion were assigned to either medical treatment with thrombolysis (69% of patients at admission) or thrombectomy (31% at admission). Of those assigned to medical treatment, 41% deteriorated and required mechanical thrombectomy despite the fact that the median NIHSS for patients in the medical treatment group was only 2 meaning that the collateral status in these patients was likely to be very good (median NIHSS=4 in the group treated immediately with mechanical thrombectomy). Unfortunately, the collateral status for each patient was not documented. Furthermore, the median time to deterioration of 5.2 hours (range 2–25 hours) which adds credence to the stance that the collateral pathways that preserve brain tissue are exhaustible and when these systems collapse propagation of the infarct will ensue. This finding is consistent with Campbell *et al.*²⁴ as mentioned earlier. It is also noteworthy to mention that in those patients who went on to require mechanical thrombectomy, the average time from deterioration to reperfusion was 2.7 hours. This is important since at the time of arrival in hospital, the collateral pathway is able to sustain hypoxic brain tissue. However, once the patient begins to deteriorate, the implication is that the collaterals have failed and therefore the rate of expansion of infarction is likely to be greater at this time point than earlier in the clinical course. If correct, this should warrant early intervention when the time pressure is not as acute. This group also demonstrated a mRS phase shift of -2.5 points in favour of mechanical

thrombectomy even though the median NIHSS score in both groups was ≤ 2 . There were three deaths in the medically treated group and none in the thrombectomy group.

Although randomised controlled trial data do not currently exist, there is a growing body of evidence to suggest patients presenting with low NIHSS scores should be considered for mechanical thrombectomy, and that if this is considered feasible, it should be performed early.

This study has several limitations. First it is retrospective in nature and we have no control group of patients with low NIHSS scores and confirmed M1 occlusions who did not receive mechanical thrombectomy to compare with. We have focused on patients with low NIHSS and anterior circulation thromboembolic stroke and therefore the study is not applicable to those patients with low NIHSS score and posterior circulation stroke. Furthermore, we excluded those patients with terminal carotid and internal carotid artery terminus (ICA-T) occlusions in this analysis and therefore the results may not be applicable to this group of patients.

CONCLUSION

Thrombectomy in patients presenting with low NIHSS scores is safe and carries a high rate of technical success and good safety profile. Although data from randomised controlled trial data is lacking, we would advocate a policy of early intervention if the presence of an occlusive thrombus is identified.

Contributors PB was involved in data collection, analysis and overall study design. HB and OG were involved in review and editing. HH was involved in data collection, study design, review and editing. MAP is the guarantor.

Competing interests MAP and PB serve as proctors and consultants for Phenox GmbH, with moderate financial compensation. HH is a co-founder and shareholder of Phenox GmbH.

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement No additional data are available.

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