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Clinical Study

Shorter time to intervention improves recanalization success and clinical outcome post intra-arterial intervention for basilar artery thrombosis

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ABSTRACT

Basilar artery thrombosis is associated with poor clinical outcomes and high mortality rate if untreated. Clinical outcome correlates with recanalization success. As arterial clot composition undergoes organization over time and may become more resistant to recanalization therapy, we postulate that recanalization success is time-dependent. We aim to investigate whether time to intervention predicts recanalization success leading to improved clinical outcomes. Forty-nine consecutive patients with basilar artery thrombosis treated with intra-arterial (IA) therapy between 1993 and 2011 were included. Patient demographics, clinical features, clot location, time to intervention and post-procedural thrombolysis in myocardial infarction (TIMI) scores were collected. Recanalization success was defined as a score of TIMI 2–3. Clinical outcome was measured using the 90-day modified Rankin Scale (mRS) score, with good neurological outcome defined as mRS 0–2. The mean patient age was 59.8 years ± 17.9 and 36.7% were females. IA therapy was commenced within 6 hours of stroke onset in 17/49 (34.7%) patients. Of this 6-hour onset group, 17/17 (100%) demonstrated recanalization success (TIMI 2–3) and 10/17 (58.8%) achieved good neurological outcome at 90-days. IA therapy was commenced after 6 hours of stroke onset in 32/49 (65.3%) patients, with 24/32 (75%) and 6/32 (18.75%) patients achieving recanalization success and good outcome, respectively. A shorter delay to IA therapy is significantly associated with recanalization success ($p = 0.038$) and good neurological outcome at 90 days ($p = 0.009$) in patients with acute basilar artery thrombosis. We recommend a systematic approach to minimize time delay to IA therapy for this condition.

1. Introduction

Acute basilar artery thrombosis represents from 1% to 4% of all ischaemic strokes.[1–3] It is a catastrophic subtype of posterior circulation ischaemic stroke which is associated with an 80% to 90% mortality rate in the absence of treatment.[4–6] Successful recanalization of an occluded artery is associated with better outcomes.[7,8] However, due to the low rates of successful recanalization of occluded basilar arteries by intravenous (IV) thrombolytics (30%),[9] intra-arterial (IA) interventions are justified.[4]

IA interventions have been shown to be efficacious in their ability to achieve high recanalization rates,[10,11] leading to lower mortality rates and better functional outcomes.[12,13] Only one multicentre randomized controlled trial has assessed the efficacy of IA therapy for acute basilar thrombosis. The Australian Urokinase Stroke Trial (AUST) recruited 16 patients over 7 years, randomised into either the treatment or placebo group.[14,15] Good neurological outcomes were more frequently observed in the treatment group (50%) than in the placebo group (12.5%).[15] Independent variables affecting survival were shown to include collateral state and age,[16] thrombus volume and pre-treatment morbidity,[17] and Glasgow Coma Scale (GCS) score.[18]

The recanalization rate for individual patients is not uniform. It may be that the longer the delay to intervention from stroke onset, the lower the chances of achieving successful recanalization. However, this has yet to be validated. A theory has been proposed that the clot composition changes with time. Fresh newly formed clots are more red blood cell dominant and less resistant to thrombolysis, while older clots are more fibrin-rich and well-organized and hence more resistant to thrombolysis.[19–22] Furthermore, shortening the delay to intervention is vital in ensuring the survival of penumbral tissue.[23] Successful intervention to attenuate the growth of the ischaemic core positively contributes to good clinical outcomes.[24–26] Survival of penumbra tissue relies on achieving

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successful recanalization of occluded arteries, which may be limited by delay to initiation of IA intervention.

In this study, we aim to determine if time to treatment is a predictor of recanalization success. We hypothesize that early intervention significantly improves recanalization success.

2. Methods

This is a retrospective single centre review of 49 consecutive patients with confirmed acute basilar artery thrombosis who received IA intervention between 1993 and 2011. Patients who presented within 24 hours of symptom onset were offered IA therapy following confirmation of basilar artery thrombosis by digital subtraction angiography (DSA). Exclusion criteria were: established extensive infarction on pre-operative CT scan, intracranial haemorrhage and patients presenting more than 24 hours post stroke. Study approval was granted by the local research and ethics committee.

Clinical parameters were identified through medical records review. Information on age, gender, vascular risk factors, clinical presentation and GCS score were collected. Time to intervention was defined as time from symptom onset or from when patient was last seen neurologically well to arterial puncture time. In the subgroup of patients presenting with a stuttering clinical course followed by sudden onset of decrease in conscious state, time of symptom onset was defined from the sudden deterioration in clinical state.

Angiograms were reviewed by three neuro-interventionists (BY, PJM, RJD), with consensus opinion reached on clot location, collateral supply, post procedural thrombolysis in myocardial infarction (TIMI) score and procedure time.

The TIMI grading system was used to grade recanalization success irrespective of vessel. TIMI grade 0 is defined as no recanalization, TIMI grade 1 as recanalization past the initial occlusion but no distal branch filling, TIMI grade 2 as recanalization with incomplete or slow distal branch filling and TIMI grade 3 as full recanalization with filling of all distal branches.[27] Successful recanalization was defined as TIMI grade 2 or 3.

Diagnostic angiography was performed to confirm location of thrombosis. A 6F femoral sheath was inserted into the common femoral artery, followed by selective catheterization of the vertebral arteries and subsequent confirmation of basilar artery thrombosis. Intra-arterial intervention required the placement of an Envoy 6F guide catheter (Codman and Shurtleff, Raynham, MA, USA) into the vertebral artery that allowed the passage of a Renegrade microcatheter (Boston Scientific, Natick, MA, USA). Once intra-thrombus placement of the micro-catheter was achieved, an initial 200,000 units of urokinase was injected, followed by pulsed hand injections of further urokinase (maximum 1000,000 units). Alternatively, IA tissue plasminogen activator (IA-tPA) was given (10 mg/hour; 20 mg total infused). Repeat selective angiography was conducted in 15-minute (min) intervals to assess for recanalization. If flow disruption or occlusion persisted at 30 min since the start of intervention, attempts to recanalize using a Penumbra Device (Penumbra, Alameda, CA, USA), Solitaire Device (ev3 Neurovascular, Irvine, CA, USA) or angioplasty were conducted. Mechanical thrombectomy with Concentric Merci (Concentric Medical, Mountain View, CA, USA) or the Solitaire Device was used at the discretion of the neurointerventionists. Heparin infusion was continued post-operatively for 24 hours, aiming for an activated partial thromboplastin time of 60–65, unless there was evidence of significant infarction or haemorrhage.

Patients underwent a standardized clinical neurological evaluation, with clinical outcome graded according to the 90-day mRS score. Good neurological outcome was defined as mRS $\leqslant$ 2.

Statistical analysis was performed by the Clinical Epidemiology and Health Services Evaluation Unit at the Royal Melbourne Hospital, using STATA10 (StataCorp, College Station, TX, USA). A p-value < 0.05 was considered to be statistically significant. Fisher's exact test was used to determine the correlation between categorical variables and outcome variables. Multivariate logistic regression was used to find predictors of good neurological outcome.

3. Results

Of the 49 patients, the mean age was 59.8 years ± 17.9, 36.7% were females and mean GCS score was 9.5 ± 4.4. Baseline characteristics, vascular risk factors, clinical presentation and key angiographic and clinical data are presented in Table 1.

3.1. Recanalization success

IA intervention included IA urokinase (89.8%), angioplasty (34.7%), stent insertion (24.5%), mechanical embolectomy with the Concentric MERCI device (8.2%), Solitaire device (4.1%), and IA-tPA (2.0%) (Table 2) The mean urokinase dose was 752,000 units. Successful recanalization (TIMI 2–3) was achieved in: 37/44 (84.1%) patients treated with IA Urokinase; 14/17 (82.4%) treated with angioplasty; 11/12 (91.7%) with stent insertion ; 2/4 (50%) with a MERCI device; and 2/2 (100%) with a Solitaire device. A total of 41/49 (83.7%) patients achieved successful recanalization. Of 49 patients, TIMI 3 was achieved in 34 (69.4%) patients, TIMI 2 in seven (14.3%) patients, TIMI 1 in three (6.1%) patients and TIMI 0 in five (10.2%) patients. The mean time to intervention was 10.81 hours ± 7.646. Patients were dichotomised into those treated $\leqslant$6 hours and >6 hours after symptom onset as similar to previous reports.[28,29] All 17 (100%) patients with treatment initiated within 6 hours from stroke onset achieved successful recanalization (TIMI 2–3). The association between time to intervention and

Table 1
Baseline characteristics, vascular risk factors, clinical presentation and key angiographic and clinical data of patients treated with intra-arterial intervention for basilar artery thrombosis

Variable	Total (n = 49)
Baseline characteristics	
Female	18 (36.7)
Age (years)	59.8 ± 17.9
Vascular risk factors	
Atrial fibrillation	13 (26.5)
Ischaemic heart disease	9 (18.4)
Diabetes	9 (18.4)
Chronic obstructive pulmonary disorder	2 (4.1)
Hypertension	27 (55.1)
Hypercholesterolaemia	16 (32.7)
Cardiac failure	5 (10.2)
Previous stroke	8 (16.3)
Clinical presentation	
GCS score	9.5 ± 4.4
Hemiparesis	21 (42.9)
Hemiplegia	11 (22.4)
Quadraparesis	4 (8.2)
Quadraplegia	4 (8.2)
Locked-in	2 (4.1)
Ocular motor dysfunction	31 (63.3)
Dysarthria	26 (53.1)
Seizure	6 (12.2)
Ataxia	10 (20.4)
Dysphasia	0 (0)
Time to intervention	
$\leqslant$6 hours	17 (34.7)
>6 hours	32 (65.3)

Data are mean ± standard deviation or number (%).
GCS = Glasgow Coma Scale score.

Table 2
Intra-arterial (IA) intervention with time to intervention

IA intervention	Time to intervention		
	⩽6 hours (n = 17)	>6 hours (n = 32)	p-value
Urokinase	15 (88.2)	29 (90.6)	1.000
Angioplasty	5 (29.4)	12 (37.5)	.754
Stent	6 (35.3)	6 (18.8)	.296
MERCI	0 (0)	4 (12.5)	.284
Solitaire	2 (11.8)	0 (0)	.116
tPA	0 (0)	1 (3.1)	1.000

Data are number (%).
tPA = tissue plasminogen activator, MERCI = Concentric Merci Device (Concentric Medical, Mountain View, CA, USA), Solitaire = Solitaire Device (ev3, Irvine, CA, USA).

Table 3
Key angiographic data for patients treated with intra-arterial intervention for basilar artery thrombosis and clinical outcome with TIMI scores

Variable	TIMI 0–1 (n = 8)	TIMI 2–3 (n = 41)	p-value
Time to intervention			
⩽6 hours	0 (0)	17 (100)	0.038
>6 hours	8 (25)	24 (75)	
Clinical outcome			
mRS 0–2	1 (6.3)	15 (93.8)	0.245
mRS 3–6	7 (21.2)	26 (78.8)	
90-day mortality	5 (31.3)	11 (68.8)	0.094

Data is number (%).
TIMI = thrombolysis in myocardial infarction, mRS = modified Rankin Scale.

recanalization success (TIMI 2–3) was statistically significant (p = 0.038). Key angiographic data and clinical outcome with TIMI scores is presented in Table 3.

3.2. Time to clinical outcome

Of 49 patients, 16 (32.7%) achieved a good neurological recovery (mRS 0–2), while 17 (34.7%) patients had moderate to severe disability (mRS 3–5). The 90-day mortality rate (mRS = 6) was 32.7%. Of 16 patients who died, eight (50%) were due to basilar artery thrombosis, two (12.5%) to vessel perforations as a result of an intra-operative complication and six (37.5%) due to intracranial haemorrhagic conversion. Dichotomisation of patients using a cut-off point of 6 hours post-stroke onset revealed that of 17 patients, 10 (58.8%) and seven (41.2%) patients who received IA intervention ⩽6 hours post stroke onset achieved good (mRS 0–2) and poor (mRS 3–6) neurological recovery at 90 days post-stroke respectively. Fisher's exact test revealed statistically significant association between time to intervention and the 90-day mRS scores (p = 0.009). Key angiographic and clinical data and treatment outcome information with 90-day mRS scores are presented in Table 4.

Table 4
Key angiographic and clinical data and treatment outcome information with 90-day mRS scores for patients treated with intra-arterial intervention for basilar artery thrombosis

Variable	mRS 0–2 (n = 16)	mRS 3–6 (n = 33)	p-value
Time to intervention			
⩽6 hours	10 (58.8)	7 (41.2)	.009
>6 hours	6 (18.8)	26 (81.2)	
Time to successful recanalization			
⩽6 hours	10 (58.8)	7 (41.2)	.021
>6 hours	5 (20.8)	19 (79.2)	
Post-procedural complications			
Haemorrhagic conversion	1 (6.3)	8 (24.2)	.238

Data are number (%).
mRS = modified Rankin Scale.

Table 5
Multivariate logistic regression of association between time to intervention and good neurological outcome (mRS 0–2) for patients treated with intra-arterial Intervention for basilar artery thrombosis

Good neurological outcome (mRS 0–2)	Odds ratio	95% confidence interval	p-value
Time to intervention > 6 hours	0.159	0.042–0.599	0.007
Age	1.003	0.967–1.041	0.872

mRS scores = modified Rankin Scale.

There were six intra-operative complications – three vessel perforations, two groin complications and one arterial dissection. Of three vessel perforations, two (66.7%) were guide wire perforations, while one (33.3%) was a MERCI device related perforation. The arterial dissection was caused by the placement of a guiding catheter into the parent artery. Nine of 49 patients (18.4%) had complicating intracranial haemorrhagic conversion, and six (66.7%) of these patients died within 90 days.

Multivariate logistic regression of the association between mRS and time to intervention demonstrated that time to intervention is a significant predictor (p = 0.007) for good neurological outcome with an odds ratio of 0.159 (95% confidence interval: 0.042–0.599), adjusting for age (Table 5).

4. Discussion

The natural history of acute basilar artery thrombosis managed with antiplatelet and/or anticoagulant therapy is poor.[9,30] Hacke et al. reported a mortality rate of 86% in a cohort of 22 patients who received antiplatelet or anticoagulant therapy,[9] while Schonewille et al. reported a mortality rate of 40% in a cohort of 82 patients and a dependency rate (mRS 4–5) of 65% in a similar subgroup of patients.[30] Coupled with the low spontaneous recanalization rate in patients with acute basilar thrombosis, a more aggressive approach of IA intervention is justified.[4] IA interventions such as IA urokinase, mechanical thrombectomy with Concentric Merci, Penumbra or Solitaire Devices, angioplasty and stent placement may provide high recanalization rates, which are significantly associated with a greater than 50% decrease in mortality rate.[8] The preferred method is mechanical recanalization, with the Solitaire Device shown to achieve a recanalization rate of 89%,[31] and the Penumbra Device a 100% recanalization rate.[32]

However, failed recanalization with IA intervention is not uncommon.[9,10] Our study suggests time to intervention, defined with a relatively strict time window of 6-hours, is a predictor of recanalization success in basilar artery thrombosis. It is possible that the changes in clot composition over time result in older fibrin-rich clots to be more organized and hence more resistant to thrombolysis, decreasing the likelihood for the occluded arteries to be recanalized.[19–22]

Recanalization is associated with a significant survival benefit.[7,8] Our study showed that 30/41 (73.2%) patients who were recanalized survived at 90 days, compared to 3/8 (37.5%) non-recanalized patients (p = 0.094). This compares to findings from Eckert et al that showed a reduction in mortality rate from 72% to 54% with recanalization (p = 0.118).[28] In our study, 15/41 (36.6%) recanalized patients achieved a good neurological outcome (mRS 0-2), compared to 1/8 (12.5%) if recanalization did not occur (p = 0.245). Furthermore, our study found that early time to successful recanalization (TIMI 2-3) is significantly associated with good clinical outcome. Thus, 10/17 (58.8%) patients who achieved successful recanalization within 6-hours from stroke onset developed favourable clinical outcomes, while 5/24 (20.8%) patients successfully recanalized beyond 6-hours from stroke onset developed poor clinical outcomes (mRS 3-6) (p = 0.021). Eckert et al found similar

findings, reporting that 16/54 (30%) successfully recanalized patients achieved a favourable outcome at 90-days (Barthel index > 90), while 3/30 (10%) non-recanalizated patients survived with a favourable outcome.[28] They also showed no association between recanalization success and favourable outcome at 90 days ($p = 0.125$).[28] However, despite similar results in both studies, classification systems used to define recanalization success and favourable clinical outcome differs, with Eckert et al defining recanalization success as a fully visible basilar artery with filling of the posterior cerebral artery (PCA) and failure of recanalization as no changes or only little improvement of basilar artery opacification without filling of the basilar tip.[28] Eckert et al also used the Barthel index to investigate clinical outcome, instead of the mRS scoring system used in this study.[28]

We found a significant correlation between earlier treatment and good neurological recovery (58.8% if treated $\leqslant$6 hours compared to 18.8% if treated >6 hours; $p = 0.009$). Eckert et al also reported a significant improvement in neurological outcome (Barthel index > 90) if treatment could be initiated within 6-hours (36% if treated $\leqslant$6 hours compared to 7% if treated >6 hours; $p = 0.005$), concluding that early treatment is the most important factor for successful endovascular therapy in acute vertebrobasilar occlusion.[28] There are several limitations to our study. This is a retrospective single-centre study of consecutive patients that, however, may lead to selection bias. The number of patients reviewed is also small. However, despite these limitations, findings from this study highlight the need for system implementations, with the aim of increasing patient awareness to stroke symptoms,[33] and introducing protocols aimed at minimizing door to needle time.[34] These protocols can be in the form of a "Code Stroke" protocol that expressly avoids some elements of clinical evaluation that is believed to contribute little to the management of stroke patients, thereby preventing any time delays in treatment.[34]

5. Conclusion

Our study suggests that early intervention improves the likelihood of achieving recanalization success and good clinical outcome post IA intervention in basilar artery thrombosis. We propose a need for hospital system implementations to minimize the delay to treatment.

Conflict of interest/disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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