

Transradial versus transfemoral access for anterior circulation mechanical thrombectomy: analysis of 375 consecutive cases

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ABSTRACT

Objective To compare transradial artery access (TRA) to the gold standard of transfemoral artery access (TFA) in mechanical thrombectomy (MT) for stroke caused by anterior circulation large vessel occlusion.

Methods The clinical outcomes, procedural speed, angiographic efficacy and safety of both techniques were analysed in 375 consecutive cases over an 18-month period in a high volume statewide neurointerventional service.

Results There was no significant difference in patient characteristics, stroke parameters, imaging techniques or intracranial techniques. The median time elapsed between CT scanning and reperfusion was 96.5 min (IQR 68–123) in the TFA group and 95 min (IQR 68–123) in the TRA group ($p=0.456$). Of 336 patients who were independent at presentation 58% (124/214) of the TFA group and 67% (82/122) of the TRA group had a modified Rankin score of 0–2 at 90-day follow-up ($p=0.093$). Cross-over from radial to femoral was 4.6% (4/130) compared with 1.6% cross-over from femoral to radial (4/245), but did not meet the predetermined level of statistical significance (OR 2.92, 95% CI 0.81 to 10.52), $p=0.088$ and did not impact median procedural speed. Adequate angiographic reperfusion, first pass reperfusion, embolisation to new territory and symptomatic intracranial haemorrhage were similar in both groups. There was a significant difference in major access site complications requiring an additional procedure. None of the TRA cases had a major access site complication but 6.5% (16/245) of the TFA cases did ($p=0.003$).

Conclusion This study suggests that using TRA for anterior circulation MT is fast, efficacious, safe and not inferior to the gold standard of TFA.

BACKGROUND

Transradial artery access (TRA) is used for neurointerventional procedures including cerebral angiography, intracranial aneurysm treatment, carotid stenting, vertebral artery stenting, dural arteriovenous fistula (dAVF)/arteriovenous malformation (AVM) embolisation, external carotid artery (ECA) embolisation and posterior circulation stroke intervention.^{1–5} Its use has been driven by

Summary box

What is already known about this subject?

- ▶ Mechanical thrombectomy via transfemoral access (TFA) is the gold-standard treatment for anterior circulation stroke secondary to large vessel occlusion.
- ▶ Transradial access (TRA) is an established technique in interventional cardiology and an emerging technique in the endovascular treatment of intracranial aneurysms.
- ▶ There are small series of mechanical thrombectomy via TRA but to date there is no large series directly comparing it to the established gold standard of TFA.

What are the new findings?

- ▶ Mechanical thrombectomy via TRA is as fast as it is via TFA.
- ▶ Mechanical thrombectomy via TRA is as efficacious as it is via TFA.
- ▶ Mechanical thrombectomy via TRA may be safer than it is via TFA.

How might it impact on clinical practice in the foreseeable future?

- ▶ Neurointerventional practitioners may increasingly switch to using a trans-radial approach as first line arterial access in mechanical thrombectomy for stroke.

the findings of large interventional cardiology RCTs proving that TRA is safer, cheaper and better tolerated than transfemoral artery access (TFA).⁶

Mechanical thrombectomy (MT) for anterior circulation stroke is the most efficacious neurointerventional procedure and also the most time critical.^{7,8} The efficacy and safety of MT via TFA has been proven in several RCTs and is the accepted gold standard.⁸ Despite small series with positive results in selected cases, ongoing reluctance to adopt TRA for anterior circulation MT is due to concerns that navigating a stable large-calibre guide

catheter to the cervical ICA from the radial artery may be slower than from the femoral artery.^{9–11}

OBJECTIVES

The objective of this study is to compare TRA to TFA in anterior circulation MT, by analysing the clinical outcomes, procedural speed, angiographic efficacy and safety of both techniques in 375 consecutive cases over an 18-month period in a high volume statewide neurointerventional service.

METHODS

Study design

TRA for neurointerventional procedures was introduced locally in July 2018 and in August 2018 the first anterior circulation MT via TRA was performed. Patient, disease, procedural and outcome data is routinely collected in a centralised database for all MT procedures in the state. Institutional ethics board approval was obtained for this retrospective review of prospectively collected data. In May 2020, the database was queried for all anterior circulation MT cases performed between 1 August 2018 and 31 January 2020; to capture the first TRA anterior circulation MT and to include a minimum of 90 days follow-up for all cases. The cases were divided into TFA and TRA groups. ‘Cross-over’ cases were grouped according to the first artery punctured. Patient details, stroke details, procedural techniques, time metrics, angiographic reperfusion, clinical complications and 90-day clinical outcomes were compared. All anterior circulation MT cases in the 18-month time period were included.

Group matching

To test if the TFA and TRA groups were otherwise matched; patient data (age, gender), stroke details (National Institutes of Health Stroke Scale (NIHSS), Rapid Arterial Occlusion Evaluation (RACE) score, arterial occlusion site, Alberta Stroke Program Early CT score (ASPECTS)), use of non-invasive imaging (Computed Tomography Angiography (CTA), Computed Tomography Perfusion (CTP)), pretreatment time metrics (onset time, last seen normal, emergency room (ER) presentation, CT, arteriotomy) and therapeutic techniques (intravenous TPA, general anaesthetic, aspiration only or stent-retriever use, permanent stenting) were compared.

Primary and secondary outcomes

To detect any differences in procedural speed and clinical outcome, the time elapsed between CT scan and first reperfusion, and the clinical outcome measured by modified Rankin score (mRS) 0–2 at 90 days or more, were chosen as coprimary outcomes. In this database, reperfusion is timestamped at the first DSA demonstrating expanded treatment in cerebral ischemia (eTICI) score 2B or greater, or final DSA if this is not achieved; following methods used in the landmark MT RCTs.⁸ Patients with a pretreatment mRS of 3 or higher before presentation

were excluded from the analysis of 90 day mRS 0–2 and their outcomes reported separately. To analyse procedural efficacy and arteriotomy safety, the frequencies of arteriotomy cross-over, adequate reperfusion (eTICI 2B–3), first pass reperfusion (FPR), embolisation to new territory (ENT), symptomatic intracranial haemorrhage (sICH), arteriotomy related clinical complications requiring an additional procedure, and 90-day mortality were chosen as secondary outcomes.

Radial artery occlusion on day one postprocedure is routinely audited for all TRA cases and is reported in this study. The rates of femoral artery complications not requiring additional procedures, such as retroperitoneal haemorrhages managed conservatively, large groin hematomas necessitating prolonged bed rest, anaemia, blood transfusions and silent femoral artery occlusions; were not systematically recorded.

Statistical analysis

Nominal categorical variables were compared using Pearson χ^2 , with ORs, 95% CIs and p values reported. Ordinal categorical variables were compared using Cochran-Mantel-Haenszel test and p values reported. Continuous and pseudocontinuous variables were tested for normality with Kolmogorov-Smirnov, reported as medians and IQRs, and Mann-Whitney U tests were used to generate p values. The level of significance was set at $p=0.05$. Logistical and linear regression were used to produce multivariable analyses assessing independent predictors of good clinical outcome. Statistical analysis was performed using SPSS V.1.20 (GNU FSF, 2019).

Operative technique

In this real-world consecutive cohort, the choice of arterial access site and the choice of intracranial MT technique were at the discretion of the neurointerventionist (the operator). All four operators are experienced and full-time neurointerventionists, certified by the Conjoint Committee for Recognition of Training in Interventional Neuroradiology.¹² The department is a high volume statewide neurointerventional service performing 213–287 intracranial aneurysm endovascular treatments, 255–304 intracranial MT procedures and greater than 1000 neurointervention procedures each year for the past 4 years.

Intracranial MT

In all cases regardless of arteriotomy site, standard techniques were used including aspiration-only thrombectomy using a 0.058–0.070 inch inner diameter (ID) suction catheter introduced through a 0.088 inch ID 90 cm sheath; combined stent-retriever and aspiration thrombectomy using a stent-retriever delivered through an appropriate 0.017–0.027 ‘ID microcatheter inside a suction catheter and long sheath; or a 0.084 inch ID balloon guide catheter and stent-retriever combination with or without an intermediate 0.058–0.060 inch ID suction catheter. Cervical carotid stenting was performed when required. Anticoagulation and antiplatelet therapy

was administered at the operators discretion on a case-by-case basis.

Transfemoral arterial access

The common femoral artery was accessed using either manual palpation or ultrasound guidance. The arteriotomy size ranged from 6-French for direct use of the 0.088 'ID device as a sheath, to a 9-French sheath used to introduce a 0.088 inch ID catheter and provide invasive arterial pressure side-arm monitoring. Guide catheter access to the carotid artery was obtained using a coaxial system with either angled tip or Simmons shaped catheters depending on the aortic arch anatomy. At the end of the procedure the arteriotomy was closed with either a Cordis Exoseal or Terumo Angioseal device.

Transradial access

The radial artery was accessed at the level of the wrist or the anatomical snuffbox under ultrasound guidance. A thin-walled radial specific 7-French sheath with 2.79 mm outer diameter and >2.34 mm ID (Glidesheath Slender, (Terumo, Japan) or Prelude Ideal (Merit Medical, USA)) was introduced. Spasmolytic drugs were injected into the sheath at the operator's discretion, to a maximum of 5 mg verapamil and 200 µg nitroglycerin, aiming to keep the systolic blood pressure above 140 mm Hg. Guide catheter access to the subclavian artery was obtained using one of; a 90 cm 0.088–0.091 'ID catheter (AXS Infinity LS (Stryker, USA), Neuron MAX (Penumbra, USA), or Fubuki 6Fr Dilator kit (Asahi Intecc, Japan)) introduced in exchange for the radial sheath, a 0.081 'ID 100 cm catheter (Fubuki 7Fr (Asahi Intecc, Japan)) introduced into the 7Fr radial sheath, or a 0.084 inch ID 95 cm balloon guide catheter (Flowgate2 (Stryker, USA)) introduced via an 8Fr 25 cm sheath (Radifocus Pinnacle (Terumo, Japan)). From the right subclavian artery the guide catheter was advanced into the carotid artery over a Simmons-2 shaped catheter (Select (Penumbra, USA), or Impress (Merit Medical, USA)). In three cases a 0.070 inch ID aspiration catheter (Sofia Plus (Microvention, USA)) was introduced directly into the radial sheath and navigated into the internal carotid artery (ICA) over a microcatheter. At the end of the procedure 200 µg of nitroglycerin was injected into the radial artery before sheath removal and an external balloon compression device (TR-Band (Terumo, Japan) or Prelude Sync (Merit Medical, USA)) was used to titrate the compression to patent hemostasis using published techniques.¹³

RESULTS

Between 1 August 2018 and 31 January 2020, 427 MT procedures were performed in the state and recorded in the database. Thirty-six posterior circulation intracranial occlusions and 16 cases with no retrievable intracranial occlusion were excluded from the study. A total of 375 consecutive anterior circulation MT cases were included. A total of 245 were performed via TFA and 130 via TRA. In 37 cases, the patients had an mRS of 3 or higher before

presentation and were therefore excluded from the analysis of 90-day mRS 0–2, but included in all other analyses.

Patient, stroke and procedural characteristics

The patient age, gender, prestroke disability, NIHSS, RACE score, CT ASPECT score, use of CTA, use of CTP and the anatomical site of intracranial large vessel occlusion were similar for TFA and TRA cases. There was no significant difference in the frequencies of patients receiving intravenous TPA prior to MT, general anaesthesia, MT using aspiration alone, cervical carotid stenting or permanent intracranial stenting. The median times elapsed between stroke onset (or last known normal) and presentation to the ER, and between presentation to the ER and first CT scan, were similar for TFA and TRA cases. These results are presented in table 1.

Operator preference for TRA

Ninety per cent (117/130) of the TRA cases were performed by one particular operator who had a significantly higher TRA:TFA ratio than the other four operators (89% vs 5%, OR 9.39, 95% CI 5.6 to 15.8, $p < 0.0001$). This operator was an early adopter of TRA for neurointerventional procedures. The other operators had a more gradual uptake of the technique during the study and chose TRA when they anticipated difficulty with TFA due to aorticiliac steno-occlusive disease or in the setting of aortic arch and branch anatomy anticipated to be easier to navigate from TRA than TFA.

Coprimary outcomes

The median time elapsed between CT scanning and reperfusion was 96.5 min (IQR 68–123) in the TFA group and 95 min (IQR 68–123) in the TRA group ($p = 0.456$).

Of the 375 anterior circulation MT cases studied, 37 had a prestroke mRS score of 3 or greater prior to presentation and were excluded from the 90-day mRS primary outcome analyses. Of the 338 cases with a prestroke mRS of 0–2 at presentation, 2 were lost to follow-up after moving interstate and 336 had available 90-day mRS data for analysis.

At the first clinical in-person or telephone follow-up at 90 days or greater, 58% (124/214) of the TFA group had a mRS of 0%–2% and 67% (82/122) of the TRA group had a mRS of 0–2 ($p = 0.093$). These results are presented in table 2.

Secondary outcomes

The frequency of adequate reperfusion (eTICI 2B-3), FPR and ENT; all of which in this study are self-assessed by the operator and not reviewed by a core laboratory, were similar for the TRA and TFA groups. In both groups the 90-day mortality was 15% in patients who had mRS scores of 0–2 at presentation (OR 1.02, 95% CI 0.54 to 1.92, $p = 0.947$) and there was no difference in sICH.

Cross-over from radial to femoral was more frequent 4.6% (6/130) than the rate of cross-over from femoral to radial (1.6%, 4/245), but did not meet the predetermined level of statistical significance (OR 2.92, 95% CI

Table 1 Patient, disease and treatment characteristics

Categorical and dichotomous variables	Whole cohort	Femoral	Radial	Pearson χ^2
Pre-stroke independence (mRS 0–2)	90.1% (338/375)	88.2% (216/245)	93.8% (122/130)	OR 2.05 (0.91–4.62) p=0.079
Operator three performing procedure	35.2% (132/375)	6.1% (15/245)	90.0% (117/130)	OR 138 (64–300) p=0.000
Wake-up stroke/onset unknown	31.5% (118/375)	29.8% (73/245)	34.6% (45/130)	OR 1.25 (0.79–1.96) p=0.339
Female	50.7% (190/375)	51.4% (126/245)	49.2% (64/130)	OR 0.92 (0.60–1.40) p=0.685
Use of CTA	95.7% (359/375)	96.3% (236/245)	94.6% (123/130)	OR 0.67 (0.24–1.84) p=0.435
Use of CTP	65.6% (246/375)	66.1% (162/245)	64.6% (84/130)	OR 0.94 (0.60–1.46) p=0.770
Intracranial large vessel occlusion site				
Internal Carotid Artery	24.3% (91/375)	22.4% (55/245)	27.7% (36/130)	
Middle Cerebral Artery M1 segment	52.0% (195/375)	51.0% (125/245)	53.8% (70/130)	
Middle Cerebral Artery M2 segment	23.5% (88/375)	26.1% (64/245)	18.5% (24/130)	
Anterior Cerebral Artery	0.3% (1/375)	0.4% (1/245)	0.0% (0/130)	P=0.290 *Cochran–Mantel
IV TPA prior to MT	9.9% (37/375)	11.8% (29/245)	6.2% (8/130)	OR 0.49 (0.22–1.10) p=0.079
GA	89.9% (337/375)	91.4% (224/245)	86.9% (113/130)	OR 0.62 (0.32–1.23) p=0.169
GA induction before arteriotomy	35.9% (121/337)	29.9% (67/224)	47.8% (54/113)	OR 2.14 (1.34–3.42) p=0.001
Aspiration only (no stent-retriever)	34.9% (131/375)	31.4% (77/245)	41.5% (54/130)	OR 0.65 (0.42–1.00) p=0.051
Carotid stenting	16.0% (60/375)	14.7% (36/245)	18.5% (24/130)	OR 1.31 (0.75–2.32) p=0.344
Intracranial stenting	5.6% (21/375)	4.9% (12/245)	6.9% (9/130)	OR 1.44 (0.59–3.52) p=0.417
Continuous variables—median (IQR)	Whole cohort	Femoral	Radial	Mann-Whitney U test
Age	75 (64–84)	76 (64–85)	74 (62–83)	P=0.375
NIHSS	14 (8.5–19)	14 (8–19)	15 (10–19)	P=0.231
RACE	6 (3.5–8)	6 (3–8)	6 (5–8)	P=0.140
ASPECTS	9 (8–10)	9 (8–10)	9 (8–10)	P=0.053
Onset/last known normal to ER presentation (mins)	120 (65–401)	110 (63.5–321)	150 (65.5–602)	P=0.103
ER presentation to CT (min)	17 (12–29)	17 (12–27)	18 (12–34)	P=0.515
CT to arteriotomy (min)	59.5 (37–84)	58.5 (35–85)	60 (40–84)	P=0.777
Arteriotomy to reperfusion (min)	29 (19–46.5)	30 (20–40)	25 (17–43)	P=0.036
CT to reperfusion (min)	95.5 (70–126.5)	96.5 (71–130)	95 (68–123)	P=0.456
Days in MT hospital	4 (2–8)	4 (2–8)	4 (2–7)	P=0.888

ER, emergency room; GA, general anaesthesia; ICA, internal carotid artery; IV, intravenous; mRS, modified Rankin score; MT, mechanical thrombectomy.

0.81 to 10.52, p=0.088). In each of the 10 cases the reason for changing access was an inability to access the cervical ICA from the initially selected route. In the six TRA to TFA cross-over cases, access was obtained to the subclavian artery but navigation of the large bore guide catheter to the cervical ICA was not possible. Anecdotally the operators felt this was due to a combination of radial artery

spasm and challenging common carotid artery origin angles.

6.5% of the TFA group suffered a femoral artery access site clinical complication requiring an additional procedure or operation, and none of the TRA did (p=0.003). The additional procedures included laparotomy for intra-abdominal haemorrhage, open endarterectomy to treat

Table 2 Primary outcomes

Primary outcomes	Whole cohort	Femoral	Radial	Pearson χ^2 /Mann-Whitney U test
mRS 0–2 at 90 days (in patients with prestroke mRS 0–2)	61.3% (206/336)	57.9% (124/214)	67.2% (82/122)	OR 1.49 (95% CI 0.93 to 2.37) p=0.092
CT to reperfusion (median (IQR) min)	95.5 (70–126.5)	96.5 (71–130)	95 (68–123)	P=0.456

Table 3 Secondary outcomes

Categorical and dichotomous variables	Whole cohort	Femoral	Radial	Pearson χ^2
Arteriotomy cross-over	2.7% (10/375)	1.6% (4/245)	4.6% (6/130)	OR 2.92 (0.81–10.52) p=0.088
First pass reperfusion	54.7% (205/375)	55.5% (136/245)	53.1% (69/130)	OR 0.91 (0.59–1.39) p=0.652
Final angiographic result=eTICI 2B-3	94.4% (354/375)	94.3% (231/245)	94.6% (123/130)	OR 1.06 (0.42–2.71) p=0.895
sICH	4.% (15/375)	4.9% (12/245)	2.3% (3/130)	OR 0.46 (0.13–1.66) p=0.223
Access site complication requiring additional procedure	4.3% (16/375)	6.5% (16/245)	0% (0/130)	p=0.003
mRS 0–2 at 90 days (in patients with pre-stroke mRS 0–2)	61.3% (206/336)	57.9% (124/214)	67.2% (82/122)	OR 1.49 (0.93–2.37) p=0.092
Continuous variables - medians (IQR)	Whole cohort	Femoral	Radial	Mann-Whitney U Test
CT to arteriotomy	59.5 (37–84)	58.5 (35–85)	60 (40–84)	P=0.777
Arteriotomy to reperfusion	29 (19–46.5)	30 (20–40)	25 (17–43)	P=0.036
CT to reperfusion	95.5 (70–126.5)	96.5 (71–130)	95 (68–123)	P=0.456
Days in MT hospital	4 (2–8)	4 (2–8)	4 (2–7)	P=0.888

mRS, modified Rankin score; MT, mechanical thrombectomy; sICH, symptomatic intracranial haemorrhage.

femoral artery occlusion, and percutaneous injection of thrombin to treat femoral artery pseudoaneurysm.

In four patients in the TRA group, an asymptomatic radial artery occlusion was detected on day 1 postoperatively and confirmed with ultrasound. In one of these cases, spontaneous recanalisation of the radial artery occurred on day 2, making the rate of radial artery occlusion at discharge 2.3% (3/130).

The median time elapsed between arteriotomy and reperfusion was 25 min (IQR 17–43) in the TRA group and 30 min (IQR 20–40) in the TFA group (p=0.036). However, of the 90% of cases performed under general anaesthesia, a significantly greater proportion of the TRA group had arteriotomy after induction of anaesthesia and intubation (48% vs 30% OR 2.14, 95% CI 1.34 to 3.42, p=0.001), which is likely to shorten the median arteriotomy to reperfusion times. For this reason, the median time elapsed between CT scanning and reperfusion was chosen as the primary outcome to measure the overall speed of reperfusion from the time point at which the neurointerventional team assumes control of the patient journey. These results are presented in [table 3](#).

Logistical regression analysis, using medians to dichotomise continuous variables, demonstrated age <75 (p<0.001), NIHSS <14 (p<0.001), ASPECTS >8 (p=0.02) and eTICI 2B-3 (p=0.001) were independently associated with good clinical outcome. TRA was not independently associated (B 1.71 95% CI 0.97 to 3.01, p=0.065). Linear regression analysis of the continuous variables demonstrated that decreasing age (p<0.001), NIHSS (p<0.001)

and CT to reperfusion time (p=0.001) were independently associated with good clinical outcome.

DISCUSSION

This real-world study used prospectively collected data in a statewide MT service to study whether TRA is inferior to the established gold standard of TFA for anterior circulation MT.

Due to the more time-sensitive disease process and the larger bore guide catheters, it is reasonable to assert that TRA for MT requires more TRA experience than TRA for intracranial aneurysm treatment. It has been our practice that operators first become proficient at rapid safe TRA for cerebral angiography, intracranial aneurysm treatment and carotid stenting; before attempting TRA for MT.

The time period was deliberately chosen to encompass the first TRA anterior circulation MT performed in the state and to have a minimum of 3 months follow-up for all cases. All intracranial anterior circulation MT cases performed in the state during that time period were captured and group according to the first artery (femoral or radial) accessed during the MT procedure.

Analysis of the TRA and TFA groups demonstrated no significant difference in patient characteristics, stroke parameters, imaging techniques or intracranial MT techniques; so the groups can be considered to be reasonably matched.

The procedural speed (time elapsed between CT and reperfusion) and the 90-day clinical outcomes (mRS 0–2

in patients independent prestroke) were not inferior in the TRA group when compared with the TFA group. The frequencies of adequate angiographic reperfusion, FPR, ENT and sICH, were also similar in both groups.

There was an increased frequency of arteriotomy cross-over in the TRA group (4.6% (6/130)) compared with the TFA group (1.6% (4/245)). The small numbers in both groups may indicate the dataset is underpowered to prove a significant difference (OR 2.92, 95% CI 0.81 to 10.52, $p=0.088$). Importantly however, despite this 2.98% absolute increase in cross-over there was no difference in procedural speed.

There was a significant difference in major access site complications, defined as a complication requiring another procedure. None of the TRA cases had a major access site complication but 6.5% (16/245) of the TFA cases did ($p=0.003$). This mirrors the findings of the large cardiology TRA RCTs.⁶ In this study, the rate of good clinical outcome was 40% and the mortality 27% in patients who suffered major access site complications, but there is insufficient data in this cohort to draw conclusions on the degree to which femoral arteriotomy complications negatively affect clinical outcomes in stroke patients (Pearson χ^2 OR 0.53, 95% CI 0.18 to 1.51, $p=0.226$; logistic regression analysis $B=0.73$, 95% CI 0.19 to 1.25). The rates of femoral artery complications not requiring additional procedures, such as retroperitoneal haemorrhages managed conservatively, large groin hematomas necessitating prolonged bed rest, anaemia, blood transfusions and silent femoral artery occlusions; were not systematically recorded.

The four clinically silent RAOs (3.1%) detected on day 1 post-MT, three of which persisted at discharge (2.3%) in the TRA cohort are within the ranges reported in cardiology RCTs.¹⁴

Limitations

Although the data are prospectively collected in a statewide database, the retrospective nature of this review is a limitation. Another limitation is the differing ratios of TRA: TFA between the operators performing the MT procedures, however, this is reflective of the differing real-world uptake of TRA in neurointerventional surgery. All operators are proficient in TRA and the majority of intracranial aneurysm treatments and cerebral angiograms are performed by TRA in our service.

CONCLUSION

This study suggests that using TRA for anterior circulation MT is fast, efficacious, safe and not inferior to the gold standard of TFA. The significantly lower frequency of major arterial access site complications in the TRA group is further evidence of its benefits to patients. A larger and randomised study of TRA versus TFA for anterior circulation MT will be useful to further investigate this.

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Contributors TJP planned the study, wrote the manuscript, and is responsible for the overall content. MTC and GDS contributed to data collection. RK, AHYC, TS, CP and WM provided critical review of the manuscript.

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Data availability statement Deidentified participant data may be available from the corresponding author on reasonable request, subject to permission from the local ethics board.

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