

Acute Anterior Circulation Stroke: Recanalization Using Clot Angioplasty

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ABSTRACT: Background and Purpose: Different strategies have been employed to recanalize acutely occluded middle cerebral and internal carotid arteries (ICA) in the setting of acute stroke including intravenous and intra-arterial tPA. However, pharmaceutical thrombolysis alone, may not be effective in patients with a large amount of clot volume (complete M1, terminal internal carotid artery). We report our initial experience with endovascular clot disruption using a soft silicone balloon in addition to intravenous or intra-arterial thrombolysis with tPA. **Methods:** This is a retrospective review of nine patients with symptoms of acute stroke from clot in the middle cerebral or internal carotid territories who were treated with intracranial balloon angioplasty. All patients presented with symptoms of acute anterior circulation stroke less than six hours from onset. Patients in whom computed tomography (CT) angiography confirmed the presence of large vessel clot (terminal ICA, M1 or proximal M2) were included in the study. A CT perfusion was performed providing maps of cerebral blood volume, flow and mean transit time. If the patient presented less than three hours from onset then intravenous tissue plasminogen activator (tPA) was also administered. Intra-arterial tPA was delivered into the clot. If the volume of clot was judged to be significant by the treating neurointerventionist, then a limited trial of tPA was administered intra-arterially followed by balloon angioplasty of persistent clot. The time from imaging to vessel recanalization was recorded. Clinical outcomes were assessed using the modified Rankin scale and Barthel Index. **Results:** Diagnostic CT perfusion studies were performed in 7 (78%), all of which showed a significant amount of salvageable tissue as judged by the treating neurointerventionist and neurologist. Recanalization (TIMI 2 or 3) was possible in 8 (89%). There were no cases of symptomatic intracranial hemorrhage and 2 (22%) asymptomatic hemorrhages. The average time from performance of the initial emergency CT to vessel recanalization was 2.1 hours with mean time from symptom onset to vessel recanalization of 4.1 hours. Five (56%) patients had good outcomes, 1 (11%) had mild and 3 (33%) had moderate to severe disability. **Conclusion:** Clot angioplasty can potentially shorten recanalization times in well-selected patients and can be an effective complimentary procedure in patients with tPA resistant clot. Angioplasty can be performed with a very low complication rate using the technique described and may be associated with good outcomes.

RÉSUMÉ: Accident vasculaire cérébral aigu dans le territoire de la circulation antérieure: repermeabilisation par angioplastie du caillot. Contexte et objectif: Différentes stratégies, dont l'administration intraveineuse et intra-artérielle de t-PA, ont été utilisées pour repermeabiliser l'artère cérébrale moyenne (ACM) et la carotide interne (CI) en phase aiguë de l'accident vasculaire cérébral (AVC). Cependant, la thrombolyse pharmacologique seule peut être inefficace chez des patients qui ont des caillots volumineux (CI terminale, M1 complète). Nous rapportons notre expérience initiale de fragmentation du caillot par voie endovasculaire, au moyen d'un ballonnet mou composé de silicone, associée à la thrombolyse intraveineuse ou intra-artérielle par le t-PA. **Méthodes:** Il s'agit d'une revue rétrospective de neuf patients présentant des symptômes d'AVC aigu thrombotique dans le territoire de l'ACM ou de la CI qui ont été traités par angioplastie intracrânienne par ballonnet. Tous les patients ont consulté moins de six heures après le début des symptômes pour un AVC aigu par occlusion de la circulation antérieure. Les patients chez qui l'angiographie de soustraction a confirmé la présence d'un gros caillot (CI terminale, M1 ou M2 proximale) ont été inclus dans l'étude. Le volume, le flot et le temps moyen de transit sanguin cérébral ont été cartographiés par tomodensitométrie avec perfusion. Si moins de trois heures s'étaient écoulées depuis le début des symptômes, le patient recevait également du t-PA intraveineux. Le t-PA intra-artériel était injecté directement dans le caillot. Si le volume du caillot était jugé important par le neurointerventionniste, il procédait à un essai limité de t-PA intra-artériel suivi d'une angioplastie par ballonnet du caillot résiduel. Le temps écoulé entre l'imagerie et la repermeabilisation était noté. L'issue clinique était évaluée au moyen de l'échelle modifiée de Rankin et de l'indice de Barthel. **Résultats:** Une tomodensitométrie avec perfusion a été effectuée chez 7 (78%) des patients qui tous avaient une quantité appréciable de tissu viable selon le neurointerventionniste et le neurologue traitant. La repermeabilisation (TIMI 2 ou 3) a été possible chez 8 patients (89%). Aucun cas d'hémorragie intracrânienne symptomatique n'a été observé et 2 patients (22%) ont subi des hémorragies asymptomatiques. Le temps moyen écoulé depuis la tomodensitométrie d'urgence jusqu'à la repermeabilisation était de 2,1 heures et le temps moyen depuis le début des symptômes jusqu'à la repermeabilisation était de 4,1 heures. Cinq patients (56%) ont eu un bon résultat. L'invalidité était légère chez un patient (11%) et de modérée à sévère chez 3 patients (33%). **Conclusion:** L'angioplastie du caillot peut abréger le temps de repermeabilisation chez des patients bien choisis et peut constituer une intervention complémentaire efficace chez des patients qui présentent des caillots résistants au t-PA. L'angioplastie peut être effectuée par la technique que nous décrivons, avec de bons résultats et peu de complications.

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Since the National Institute of Neurological Disorders and Stroke (NINDS) trial,¹ intravenous tissue plasminogen activator (iv-tPA) has become the standard of care in treatment of acute stroke between 0-3 hours. However, iv-tPA may be ineffective in patients with significant thrombus burden in the middle cerebral artery (MCA).² One randomized trial has shown benefit for patients with acute MCA occlusion treated with intra-arterial pro-urokinase.³ However, the experience with intra-arterial tPA (ia-tPA), as an alternative drug to recombinant pro-urokinase(rpro-UK), is limited. Intra-arterial thrombolysis with tPA can be time-consuming and ineffective in patients with large thrombus burden.⁴ This can lead to delays in recanalization, thereby significantly decreasing good outcomes.⁵ Mechanical recanalization using balloon angioplasty for acute middle cerebral artery (MCA) and internal carotid artery (ICA) thrombus has been investigated with studies suggesting benefit.⁶⁻¹⁴ In theory, prompt restoration of diminished blood flow to salvageable brain should increase the likelihood of tissue survival. This report describes our preliminary experience, technique and outcomes of balloon angioplasty in acute anterior circulation stroke. Our recanalization rates, outcomes, and complications are compared to the literature.

PATIENTS AND METHODS

The study population consisted of a retrospective review of nine consecutive patients who underwent balloon angioplasty in the MCA/ICA for acute stroke. All patients presented with symptoms of acute anterior circulation stroke less than six hours from onset. There were five males, four females with a mean age

of 71 (median 69). All had a non-enhanced CT (NECT) scan with 5 mm thick slices. Patients with ischemic stroke were excluded if there was more than a 1/3 acute changes (blurring of grey-white, hypodensity, swelling of gyri) in the ICA territory. A CT angiography from the neck to the circle of Willis was performed followed by a 2 cm CT perfusion slab at the level of the basal ganglia and third ventricle. Computed tomography perfusion scans were analyzed using an imaging workstation (Advantage Windows; GE Medical Systems) with commercial CT perfusion analysis software (CT PERFUSION; GE Medical Systems) to generate maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT). Patients who presented with stroke prior to three hours were considered for bridging therapy with iv-tPA therapy who had evidence of large vessel (distal ICA, M1 or proximal/M2) occlusion confirmed on CT angiography were considered for acute interventional recanalization (AIR). Tissue destined to infarct was defined as areas demonstrating significantly decreased cerebral blood volume (CBV). Tissue at risk was defined as areas showing decreased cerebral blood flow and prolonged mean transit time (MTT) but normal CBV. The "penumbra" was judged to be significant or non-significant based on the difference in area involved between tissue at risk (low CBF, high MTT) and tissue destined to infarct (low CBV) (Table 1).

The risks of intra-arterial therapy for acute stroke, the background of literature suggesting benefit in limited series in patients treated with balloon angioplasty, the lower recanalization rates in patients with significant clot burden and the risks of angioplasty including vessel rupture and death were

Table 1: Characteristics, imaging and outcomes of patients with acute MCA/ICA Stroke treated with balloon angioplasty

Pt#	AGE	Symptoms	Site of Occlusion	tPA administered prior to angioplasty	CT-perf	Penumbra	CTR (hrs)	Symptom onset-recanalization (hrs)	TIMI grade post angioplasty	MRS	BI
1	53	1a, 3	ICA/MCA	20 mg ia	y	y	3	2	3	4	35
2	51	1b, 2	ICA/MCA	17 mg ia	y	y	3	5	2	0	100
3	61	1a,2,3	MCA	40 mg iv, 4 mg ia	y	y	2	3.75	3	1	100
4	82	1b	MCA	none	y	y	2	4.5	2	3	60
5	69	1a,4	MCA	3 mg ia	y	y	1.75	5	3	2	95
6	69	1b, 2	ICA/MCA	50 mg iv, 4 mg ia	y	y	N/A	N/A	0	5	25
7	78	1b, 2, 3	ICA/MCA	none	n	N/A	1.5	5.5	3	5	15
8	82	1b, 5	MCA	36 mg iv, 4.5 mg ia	y	y	2.5	3.5	3	1	100
9	91	1b, 5	MCA	none	n	N/A	2	3.5	3	1	100

1a- rt Hemiparesis, 1b- lt hemiparesis, 2- facial weakness, 3- aphasia, 4-dysphasia, 5-slurred speech, CT-perf = CT perfusion, CTR = CT-to-recanalization-time, MRS = Modified Rankin Scale, BI = Barthel Index, ia = intra-arterial, iv = intravenous

explained to patients and their families. Consent was obtained by the neurology and neuroradiology team. Two-thirds of the maximal dose (0.6 mg/kg) of tPA was given intravenously en route to angiography, for patients presenting with stroke onset less than three hours. The groin was punctured using a micropuncture set and six French sheath was placed. A 6 Fr guiding catheter was exchanged and placed in the ICA. The patients were heparinized with 2500 units. Tissue plasminogen activator (tPA) for intra-arterial injection into the large vessel clot was diluted 1:2 with heparinized saline. Thrombolysis was performed through a microcatheter or a balloon catheter and an attempt was made to embed the catheter tip within the thrombus. One mg aliquots of tPA were given over two minutes to three minutes. If the volume of clot was judged to be significant (complete M1, terminal ICA) by the treating neuro-interventionist, then a limited trial of tPA was administered intra-arterially followed by angioplasty of persistent clot. In order to shorten the CTR, if ia-tPA did not appear to be effective then an appropriate length of a compliant silicone balloon (Hyperglide, Micro Therapeutics, Irvine, CA) catheter was chosen dependent on the size of the thrombus and location (10mm, 15mm, 20mm). Angioplasty of the thrombus was performed after verification of balloon catheter placement. The degree of angiographic recanalization was graded using the Thrombolysis in Myocardial Infarction (TIMI) scale.¹⁵ Patients with complete recanalization were assigned a TIMI grade of 3, while recanalization of some but not all the occluded arteries, partial recanalization, was assigned a TIMI grade 2. Follow-up CT scans to determine the presence of intracranial hemorrhage, defined as hyperdensity persisting beyond 24 hours post therapy were performed. Clinical outcome was evaluated using the modified Rankin scale (mRS) and Barthel indices (BI). Good outcomes were assigned a mRS ≤ 2 and BI ≥ 90 .

RESULTS

The results of patients who had angioplasty of thrombus causing symptoms of acute MCA or ICA stroke are summarized in Table 1. Between March 2002 and March 2003, a total of nine consecutive patients, who had attempted angioplasty of acute thrombus in the ICA/MCA distribution, formed the study group. The patient group consisted of four females and five males. Seven of nine patients had diagnostic CT angiography and CT perfusion studies. In all seven cases, CT perfusion demonstrated a significant penumbra as judged by the treating neuro-interventionist and neurologist. Three patients had distal internal carotid, and six patients had MCA thrombus. Six of the nine patients received concomitant intra-arterial tPA, three patients received iv-tPA while three patients had only balloon angioplasty (one patient received prior thrombolytics for an acute MI, one patient had recent surgery and one patient had a prior stroke within three months). Thrombolysis in Myocardial Infarction 2 or 3 flow was achieved in eight patients (89%). The average CT-to-recanalization time was 2.1 hours. The average time from symptom onset to vessel recanalization was 4.1 hours. Two patients had asymptomatic intra-cranial hemorrhage. There were no procedure-related complications and no cases of symptomatic intra-cranial hemorrhage. Five patients (56%) had good outcomes (mRS ≤ 2), 4 (44%) of which were excellent outcomes

(mRS ≤ 1), none died. 3(33%) patients had moderate to severe disability (mRS 4 or 5), 1 (11%) had mild to moderate disability (mRS 3).

CASE STUDY

Case 1: This 51-year-old male presented at three hours after sudden collapse from left sided hemiparesis. Figure 1 CT scan showed a hyperdense right MCA sign and no early signs of infarct. The CT angiography demonstrated a right internal carotid "T" occlusion of the right M1 and A1 segments. The CT perfusion showed a small area of diminished CBV and a large area of diminished CBF and prolonged MTT consistent with a significant penumbra. Angiography confirmed the thrombus. A micro-catheter could be passed into the M1 thrombus and intra-arterial thrombolysis was attempted with a total of 17 mg of tPA. Check angiogram revealed persistent internal carotid T-occlusion. A soft silicone balloon catheter was advanced into the thrombus and inflated to 3 mm diameter multiple times along the length of the thrombus with subsequent successful angioplasty of the thrombus and TIMI 2 flow. The patient suffered a small insular cortex stroke but had no deficits at discharge and at 30 day follow-up.

DISCUSSION

The PROACT II study³ was the first randomized controlled study comparing intra-arterial thrombolysis of acute MCA thrombus with placebo. It found a 15% absolute difference in good outcomes (40% vs 25%) for patients treated with intra-arterial rpro-UK compared to placebo. As rpro-UK is no longer available, intra-arterial tPA has been substituted, however, large randomized trials are lacking. There have been many case series describing results of ia-tPA in acute stroke.^{13,16,17} The outcome in our study (56% good outcomes, 44% excellent outcomes) is comparable to PROACT II (40%). A summary of studies investigating angioplasty for treatment of acute stroke is provided in Table 2. The largest study of patients treated by angioplasty of thrombus was by Nakano⁶ in which 36 patients were treated with percutaneous transluminal angioplasty (PTA). In this study they had 74% good outcomes (mRS ≤ 2) in the angioplasty group of which 53% had excellent outcomes. In that group, there was no functional data used to help triage patients. Nonetheless, their results are impressive. Yoneyama⁷ prospectively evaluated direct PTA combined with low-dose iv-tPA for acute MCA thrombus. In their study, MCA trunk occlusions with early CT changes of hypodensity or involvement of the lenticulostriate arteries had PTA followed by iv infusion of tPA to lyse any distally migrated thrombus fragments. There was a significant improvement in NIH scores for patients treated with this protocol. Ringer et al⁸ reported on their use of angioplasty in nine patients. Five of their patients survived and showed some improvement in NIHSS scores of 4.2 +/- 7.8 points. Ueda et al¹⁰ reported their use of rescue angioplasty for seven patients. They commented on the practicality of rescue angioplasty in patients with documented failure of thrombolysis expressing concerns on the "salvageability of tissue considering the time delay associated with recognition of failed thrombolysis and initiation of rescue therapy". In our protocol we have aimed to achieve

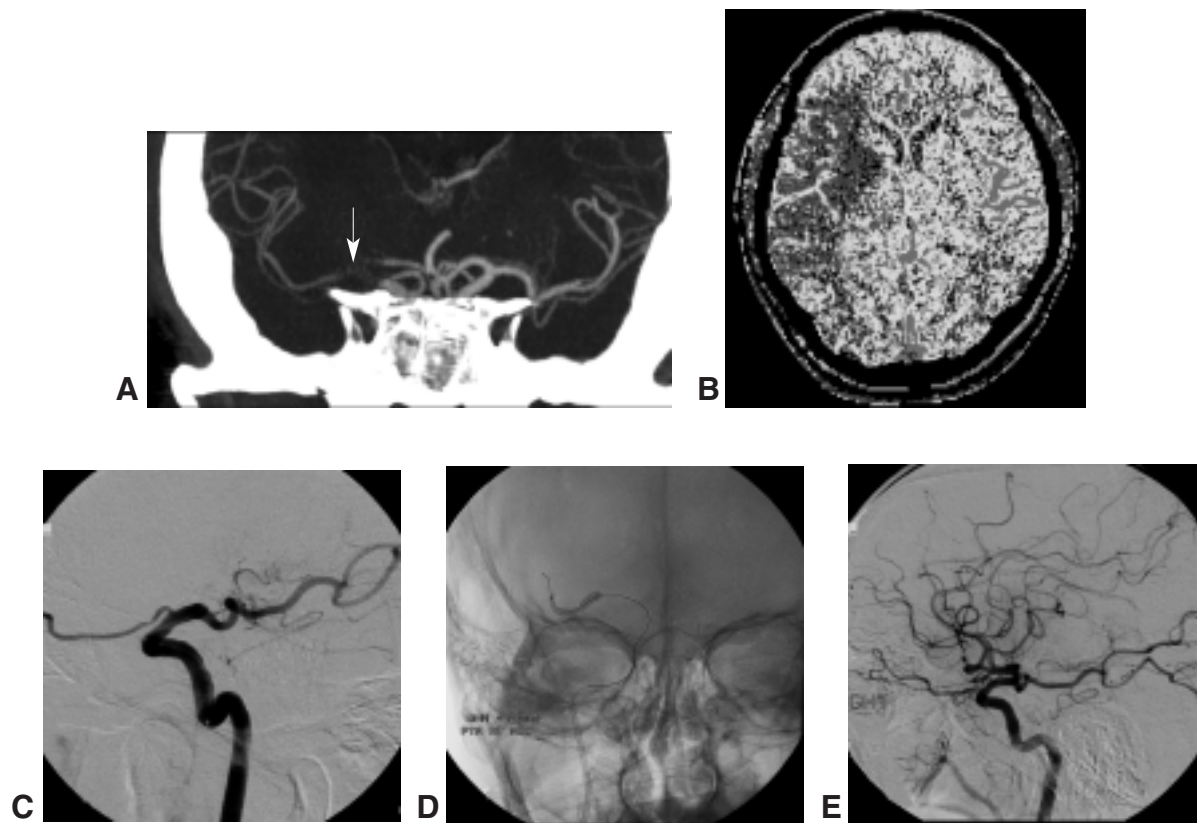


Figure: Fifty-one year old male presents with sudden collapse and left hemiparesis. A) The coronal multi-planar reconstructed CT angiogram image (MIP) showed occlusion of the distal right internal carotid artery at its bifurcation (arrow). A few branches of the right MCA are filling. B) There is decreased CBF indicating a large area at risk C) Lateral angiogram demonstrates the completely occluded supraclinoid ICA. D) Anteroposterior angiogram demonstrates the balloon inflated. E) Lateral angiogram demonstrates successful balloon angioplasty and recanalization of the supraclinoid ICA, MCA and ACA.

recanalization as quickly as possible without significant delay in evaluating the efficacy of intra-arterial thrombolysis. Our study, unfortunately, does not prove that rapid recanalization leads to more tissue saved compared to conventional pharmaceutical thrombolysis. This is a hypothesis which will need to be studied in larger comparative studies with control groups. However, it does demonstrate that balloon angioplasty can be effective in rapid recanalization and is relatively safe. Literature suggesting that earlier treatment with thrombolytics is associated with improved outcome^{5,18,19} supports an initiative to open the vessel quickly. Subgroup analysis of the NINDS trial suggests better outcomes for patients treated earlier in the 0-60 minute window from stroke onset compared with the 90-180 minute cohort.⁵

We were able to achieve TIMI 2 or 3 flow in 89% of patients. The recanalization rate was greater compared to the PROACT II trial (66%) and similar to Nakano's group at 91.2%. Most of our patients (six) experienced recanalization after only a few inflations. However, there were three patients in which multiple inflations were necessary and one patient in which PTA was unsuccessful. We were able to achieve recanalization in four patients with distal ICA occlusions. One of these patients had a

remarkable recovery. We feel that PTA helped in patients with significant thrombus burden, in whom persisting with thrombolysis would have been ineffective and perhaps harmful. Prompt recanalization is important to optimize salvage of tissue-at-risk. Rapid thrombolysis in patients treated with iv-tPA resulted in dramatic recovery, defined as a decrease in NIHSS score ≥ 10 points or NIHSS score ≤ 3 at the end of the infusion, in patients who had documented trans-cranial doppler evidence of ICA/proximal MCA thrombus dissolution.²⁰ In this publication they provided two models of pathophysiology for dramatic recovery. In the first model, if thrombus is initially obstructing the origin of collateral vessels and subsequently lysed, this could lead to improved perfusion to ischemic areas from collaterals and improved function. The second model hypothesized lysis of thrombus blocking the perforators to the basal ganglia and thalamus leading to restoration of function in these areas.

A short "CT to recanalization" time (CTR) is important. It is during this interval that the interventionist may choose to use additional tools to hasten thrombolysis - a time when potentially salvageable brain can be rescued if the perfusion is restored. Studies have recorded different parameters, such as the time to

initiation of therapy^{1,3,17} and time to thrombus lysis,¹⁶ however, we have no direct comparisons for our CTR. The mean CTR time for our patients was 2.1 hours. This included time for a limited trial of ia-tPA. Our median time from onset of symptoms to vessel recanalization was 4.1 hours, similar to Nakano who recorded an average of 4.1 hours from onset to time of termination of PTA. However, in Nakano's paper, angioplasty was performed as first-line therapy. The more resistant thrombus is, the longer the time required for thrombolysis during which brain is potentially dying. The success of recanalization with tPA likely depends on a number of factors, including thrombus location and composition as well as total volume of thrombus burden. The quicker thrombus can be dissolved, the greater the likelihood of tissue preservation. It is for this reason we feel that balloon angioplasty is a valuable adjunct to conventional intra-arterial thrombolysis. We recognize the potential for distal migration of thrombus to smaller branches, however, these usually only cause small segmental infarcts and in some cases the leptomeningeal collateral vessels may be sufficient to prevent infarct. These smaller branch occlusions may also respond to the adjunctive thrombolytic therapy.

The CT perfusion has been helpful in assessing tissue at risk²¹⁻²⁷ especially when more aggressive recanalization strategies such as balloon angioplasty are being considered. Studies have demonstrated^{21,26,27} that areas of diminished CBV are likely to infarct, whereas areas of diminished CBF and prolonged MTT indicate areas at risk. Matched CBV and CBF/MTT changes suggest that there is no more tissue to salvage. In these cases, treatment is probably better withheld.

Our current microcatheter of choice is a soft silicone balloon catheter used over a 0.010" micro-wire (Expedion, Microtherapeutics, Irvine, CA) for treatment of acute stroke. The catheter is advanced over the micro-wire and through the thrombus with the wire projecting 5-10 cm distal to the thrombus. The micro-wire is then withdrawn into the catheter

and a small injection of contrast is made through the end-hole of the catheter to confirm a safe position. The catheter is then withdrawn into the distal portion of the thrombus and a few mg of tPA is infused. In our experience, some thrombus responds favourably to tPA while others are resistant, likely depending on its composition and volume. If thrombus lysis occurs promptly with tPA, the process continues. However, if the thrombus appears resistant to tPA then early balloon angioplasty is performed after confirming the size of the parent vessel. The soft-silicone balloon is deliberately underinflated using a one-cc graduated pressure inflation syringe, usually to about 3 mm in the M1 and 2 mm in the M2 segments. The balloon is deflated and check angiograms are performed through the guiding catheter to assess vessel patency and flow. The aim is to achieve good distal perfusion and not necessarily a perfect angiographic result. Other authors have described acute angioplasty of thrombus^{6,10-14} however they used high-pressure balloons or the technique was not described at all. The risks associated with direct PTA include vessel rupture, hemorrhage and death. We feel that our technique using a low-pressure compliant balloon and verification of the calibre of the vessel distal to the thrombus reduces the likelihood of complications.

We had no symptomatic hemorrhage with neurological deterioration in our PTA patients, however 2 of 9 (22%) patients did have small asymptomatic bleeds. The rate of symptomatic bleed in the PROACT II trial was 10.2%. The rates in our study may be lower because of the small sample size. As well, using balloon angioplasty can result in faster recanalization and potentially limits the risk of reperfusion hemorrhage into infarcted brain.

Recently, the safety and efficacy of mechanical embolectomy in acute ischemic stroke has been reported.²⁸ The primary outcomes were recanalization and safety. Recanalization was achieved in 46% with a clinically significant procedural

Table 2: Studies evaluating angioplasty of clot in acute stroke

Author	No. patients	TIMI 2 or 3 Recanalization N(%)	Outcome mRS<2 N(%)	Symptomatic bleed N(%)	Death N(%)
Nakano(6)	34	31 (91)	25 (74)	1 (3)	N/A
Ringer(8)	11	N/A	3 (27)	N/A	4 (36)
Ueda(9)	11	N/A	6 (55) Excellent or good	0	2 (18)
Nakano(11)	10	10 (100)	5 (50) Excellent or good	0	0

complication rate of 7.1%, a comparable risk to intravenous¹ and intra-arterial³ thrombolysis. This potentially provides an additional tool for revascularization in acute stroke. More investigation is needed to determine which strategy or combination of strategies is necessary for the treatment of acute stroke.

In conclusion, this study demonstrates that PTA can be a safe, effective procedure in well-selected patients. It can be complimentary in patients with large vessel thrombus resistant to thrombolysis, who may otherwise have large, possibly life-threatening infarcts. A PTA can potentially be performed with a very low complication rate using the technique described and may be associated with good outcomes. A larger scale study would be ideal to evaluate the efficacy of this combined treatment compared to conventional pharmaceutical thrombolysis.

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