Intra-arterial treatment in acute ischemic stroke

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PART I

Development of intra-arterial treatment in the Netherlands

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Intra-arterial treatment of acute ischemic stroke: better outcome with stentretrievers?

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ABSTRACT

Background: Intra-arterial treatment is increasingly used in acute ischemic stroke. Recently, new devices have become available, aiming at better recanalization rates and outcome. We present a series of patients with acute stroke of the anterior circulation treated with intra-arterial therapy using intra-arterial thrombolysis and different types of mechanical devices.

Methods: We prospectively gathered clinical and radiological data of all patients with acute anterior stroke who were treated with intra-arterial therapy in a Dutch teaching hospital between 2009 and 2011. Patients were grouped according to the intra-arterial treatment strategy and analyzed for poor outcome (modified Rankin Scale score >2 or death), complications and recanalization rate with the Poisson regression.

Results: Eighty-four patients were treated with intra-arterial therapy, 13 with intra-arterial thrombolysis only (ND group), 22 with a Merci device (MERCI group) and 49 with a stent retriever (SR group). Overall, 52 patients (62%) had poor outcome of whom 17 (20%) died. There was a trend towards poorer outcome in the ND group (adjusted RR 1.18; 95% CI 0.74-1.88) and the MERCI group (adjusted RR 1.17; 95% CI 0.79-1.74) compared with the SR group. Furthermore, failed recanalization occurred more often in the ND group (adjusted RR 2.59; 95% CI 1.50--4.49) and MERCI group (adjusted RR 2.32; 95% CI 1.33-4.05) compared with the SR group.

Conclusion: We found higher recanalization rates with SRs. However, this resulted only in a trend towards better clinical outcome.

INTRODUCTION

Recently, three randomized controlled trials have failed to show improved clinical outcome after intra-arterial treatment in acute ischemic stroke patients, compared with standard care and intravenous thrombolysis (IVT).[1-3] By contrast, previous randomized studies have suggested a beneficial effect of intra-arterial thrombolysis compared with intravenous thrombolytic therapy both in clinical outcome[4,5] and recanalization rates.[6] Furthermore, studies using thrombectomy devices ('stent retrievers') showed highly favorable clinical outcome and recanalization rates.[7-9]

The discrepancy between the results of the recent trials and the earlier, promising results of intra-arterial treatment of acute ischemic stroke may have several reasons. First, the higher recanalization rates achieved in intra-arterial treatment compared with IVT need not to be accompanied by better clinical outcome, as the relation between successful recanalization and good clinical outcome is not clear.[10-12] Second, the recently published trials have reported on patients mainly treated with locally applied intra-arterial thrombolysis. The recently developed stent retrievers (SRs), which may achieve high recanalization rates and good clinical outcome, have been used only in few cases in the trials.[1-3] Third, time to treatment may have been longer than necessary because of the trial design, which prescribed intravenous treatment as the first line of treatment.[1,3]

Given these new insights, we assessed outcome and recanalization rates in patients with an acute stroke of the anterior circulation treated intra-arterially in our center, with the focus on the transition from intra-arterial thrombolysis towards mechanical thrombectomy. Therefore, we studied a cohort that was treated with intra-arterial treatment in every day routine as this probably gives a more realistic view of the real-life clinical practice and avoids selection bias that might occur in the setting of a clinical trial.

MATERIAL AND METHODS

We included all patients with an acute ischemic stroke who underwent intra-arterial treatment in a Dutch teaching hospital in the period from January 2009 to November 2011. Clinical and radiological data were prospectively collected in a database. The local ethics committee reviewed the research protocol and considered formal approval not indicated because this follow-up study was based on routinely collected data. Intra-arterial treatment was performed only after obtaining consent from the patient or his relatives.

On admission, all patients were examined by a neurologist or a resident in neurology and all underwent nonenhanced CT scanning of the head and computed tomography angiography (CTA) of the intra- and extracranial vessels (GE Lightspeed 64 slice). Demographic and clinical data were recorded at baseline (age, sex, time of symptom onset, baseline NIHSS, history of coronary artery disease, atrial fibrillation, diabetes, hypertension, peripheral artery disease). If the patients had no clinical or laboratory contraindications, no hemorrhage on nonenhanced CT scanning, a NIHSS ≥4, isolated aphasia or failed on intravenous treatment (alteplase: 0.9 mg/kg, max. 90 mg, 10% given as bolus and 90% by continuous infusion) or were ineligible for intravenous treatment, and CTA showed an occlusion of the internal carotid, middle or anterior cerebral artery, a neurointerventionalist was consulted immediately to arrange for intra-arterial treatment.

Intra-arterial treatment consisted of local intra-arterial thrombolysis, mechanical thrombectomy or a combination of both. For intra-arterial thrombolysis, urokinase, heparin or abciximab or a combination of these was used. Mechanical thrombectomy was performed with either a Merci retriever (Concentric Medical, Mountain View, Calif., USA), a Solitaire device (EV3, Irvine, Calif., USA), a Trevo device (Concentric Medical), a Revive device (Micrus Endovascular, San Jose, Calif., USA) or a combination of these. The neurointerventionalist decided which intra-arterial treatment was chosen. As newer devices became available over time, decisions on which intra-arterial treatment was used were influenced by availability of devices. Four interventionalists performed all intra-arterial treatments. All procedures were carried out only with local groin anesthesia except for 1 patient with extreme agitation who was put under general anesthesia. For each treated patient, the ASPECT score[13] on the initial CT scan, site of occlusion or stenosis on CTA, time to intra-arterial treatment (time from the start of symptoms until the start of angiography), dosage of thrombolytics (both intravenous and intra-arterial) and devices used were recorded. All patients underwent a CT scan 24 h after treatment or after any clinical impairment. Secondary preventive treatment was initiated according to the European guidelines.[14]

The primary outcome measure was poor outcome after 90 days measured by the modified Rankin Scale (mRS).[15,16] Poor outcome was defined as an mRS score of 3 or higher. All mRS scores were assessed by one investigator (A.D.R.) and based on outpatient clinical reports by the treating neurologist, rehabilitation physician or the treating physician at the nursing home. For analysis, patients were divided into

groups according to the type of mechanical device used initially: no device (ND), Merci device (MERCI) or SR (including the Solitaire, Trevo and Revive devices).

Secondary outcome measurements included death within 90 days after treatment, any cerebral hemorrhage within 30 days after treatment, and the recanalization rate. Intracerebral hemorrhages were graded according to the ECASS grading system.[17,18] Recanalization was scored at the end of the angiography by means of the TICI score.[19] If the TICI score at the end of the angiography was below 2b, recanalization was defined as failed. Both the ECASS grading and the TICI score were assigned by two neuroradiologists (G.J.L.N. and B.F.v.d.K.).

Statistical Analysis

For analysis, time to initiation of intra-arterial treatment was trichotomized as follows: 0--3, 3--6 and 6--9 h. Furthermore, we defined vascular history as positive if a patient had coronary artery disease, atrial fibrillation, diabetes, hypertension or peripheral artery disease. Descriptive statistics were used for baseline characteristics in the three treatment groups. Frequencies of poor outcome and failed recanalization were compared between the three treatment groups with risk ratios (RRs) and 95% confidence intervals (CI). Since the SR group was the largest, we used it as reference in both analyses. Adjusted RRs were calculated with the Poisson regression. As patients could have been treated with more than one device (both Merci device and SR) in order to reach recanalization, we also calculated adjusted RRs for the different treatment groups according to the last device used.

RESULTS

In the period from January 2009 to November 2011, 84 patients with an acute stroke of the anterior circulation were treated with intra-arterial therapy at our center. Baseline characteristics of these patients are given in table 1.

Thirty-three patients (39%) were women and the median age was 64 years. Thirteen patients were treated with intra-arterial thrombolysis only (ND), 22 with the Merci device (MERCI) and 49 with SR. Eight patients primarily treated with the Merci device received additional treatment with an SR. No patients in the SR group received additional treatment with the Merci device.

Baseline NIHSS did not differ between groups. In 90% of the patients, intra-arterial treatment was started within 6 h after symptom onset. In the MERCI and SR groups, more patients had an internal carotid artery occlusion leading to prolonged treatment times. Almost all patients (n = 11, 85%) in the ND group

received intra-arterial urokinase. By contrast, in the SR group, only 57% of the patients received urokinase. Abciximab was most often administered in the MERCI group (68%).

Overall, 52 patients (62%) had poor outcome (mRS >2) of whom 17 died (20%; table 2). As shown in figure 1, poor outcome (mRS >2) occurred less frequently in the SR group. Table 3 shows the RRs for poor outcome for the three treatment modalities. After adjustment for clinical and treatment parameters, we found no significant differences in the RRs for poor outcome between the three treatment modalities. Neither did we find a change in the RR for poor outcome after adjustment for recanalization. Nevertheless, there was a trend towards poorer outcome in the ND group compared with the SR group (adjusted RR 1.18; 95% CI 0.74-1.88). A similar trend was observed in the comparison between the MERCI and SR groups (adjusted RR 1.17; 95% CI 0.79-1.74). If patients were grouped according to the last device used, these trends partially resolved (table 4).

Intracerebral hemorrhage was the most frequent complication of intra-arterial treatment. We were able to retrieve the posttreatment CT scans of 82 patients (98%). For 2 patients, no follow-up scans were made, 1 patient suffered from end-stage lung cancer and died soon after the intervention. The other patient was transferred back to the primary referring center after intra-arterial treatment, where no follow-up scans were made.

Overall, 33 patients (40%) developed an intracerebral hemorrhage. Patients primarily treated with the Merci device or SR showed more intracerebral hemorrhages (43 and 44 vs. 23% in the ND group), although these were mostly hemorrhagic infarctions without a space-occupying effect (table 2) and not leading to additional symptoms. Severe parenchymal bleedings with a space-occupying effect (PH-2) were least seen in the SR group.

Three patients (all in the MERCI group) developed a groin hematoma; 1 patient deteriorated because of accumulation of clot material in the intracranial vessels caused by manipulation of the catheter; 1 patient developed rectal blood loss after treatment, and 1 patient experienced an epileptic seizure during the intra-arterial procedure. In 1 patient, the Solitaire stent detached from the pusher wire and could not be retrieved resulting in a permanent occlusion of the middle cerebral artery.

Overall, recanalization failed in 46% (n = 39) of the treated patients. In the ND group, recanalization failed in 77% (n = 10), in 68% (n = 15) in the MERCI group and in 29% (n = 14) in the SR group (table 2). The RRs for failed recanalization at the end of the intra-arterial treatment showed significantly more failures in the

ND group compared with SR treatment (adjusted RR 2.59; 95% CI 1.50-4.49) and the Merci device (adjusted RR 2.32; 95% CI 1.33-4.05; table 5).

If the patients were analyzed according to the last device used, those treated without device experienced significantly more failed recanalization compared with the SR (adjusted RR 2.22; 95% CI 1.45-3.40), and there was a trend towards more failed recanalization in those treated with the Merci device versus the SR (RR 1.31; 95% CI 0.69-2.47; table 4).

DISCUSSION

In this paper, we presented a large single-center cohort of patients with an acute ischemic stroke of the anterior circulation treated with intra-arterial therapy in every day clinical practice. Our study group reflects the developments in intra-arterial treatment of acute ischemic stroke, with a shift from local intra-arterial thrombolysis towards mechanical thrombectomy. Our results confirm the findings in recent reports showing higher recanalization rates with SRs.[7,8,20] However, we did not find a significant difference in clinical outcome between the different treatment modalities. Nevertheless, there was a trend towards better clinical outcome in patients treated with SRs compared with thrombolysis alone and Merci device.

Overall, 62% of our patients had poor outcome at 3 months after treatment and 20% had died. These outcome rates are similar to those in the IMS III and SYNTHESIS trials (poor outcome in 59.2 and 58%, respectively)[1, 2] and more favorable compared with the MR RESCUE trial (poor outcome in 86% in the penumbral group and 91% in the nonpenumbral group).[3] Death rates after 3 months were comparable to those found in the SYNTHESIS and MR RESCUE trials (19.1% and 18% for the penumbral group and 20% for the nonpenumbral group, respectively).[2,3] In our population (40%), bleeding complications were similar to those seen in the Multi-MERCI study (40.2%)[21] and less frequent compared with the MR RESCUE trial (64.7% in the penumbral group and 76.7% in the nonpenumbral group).[3] From previous studies, it is known that only PH-2. hemorrhages influence outcome and death after 3 months.[22,23] We found PH-2 hemorrhages in 7% of our patients which is comparable to the IMS III study (6.0%)[1] and the TREVO 2 trial (6.7%)[7].

Successful recanalization was reached in 54% of the patients with the highest recanalization rates found (71%) in the SR group. By contrast, in the MERCI group, 32% of the patients reached successful recanalization. Previous studies have also shown higher recanalization rates in patients treated with an SR compared with

the Merci device, confirming that the SR is currently the most powerful tool to achieve recanalization.[7,8,20]

A possible limitation of our study is the selection of our patients. Intra-arterial treatment was initiated after counseling between the vascular neurologist and the neurointerventionalist, which may have led to selection bias. However, this is also a strength because it reflects real-life clinical practice. Another limitation is that this study is a single-center study, possibly limiting generalization of our findings. On the contrary, due to the single-center design, all patients were treated according to the uniform emergency and stroke unit protocols resulting in a good comparability between the treatment groups.

Our study has several strengths. First, only four interventionalists carried out all intra-arterial treatments, and all procedures were performed in the same angiography room and with the same angiography setting. Second, there was a 24/7 availability of intra-arterial therapy during the whole study period resulting in relatively short treatment times. Third, we also included patients who were treated with the SR device only. Last, we adjusted the calculated RRs for possible confounders resulting in a valid comparison between the treatment groups.

The fact that the higher recanalization rates in our study did not result in a better clinical outcome may have several causes. First, TICI 2b was scored as successful recanalization, but this does not represent a complete reopening of the vessel. Previous studies have shown that reocclusion occurs in 17-18% of intra-arterially treated patients.[24,25] Reocclusion seems to occur more often after incomplete recanalization and is associated with poor outcome.[25] Another factor may be the time to the start of the intra-arterial treatment. In 10% of our study population, intra-arterial treatment was initiated 6 h or more after the start of complaints. In these cases, recanalization may have been reached, with the ischemic damage already being irreversible. However, the ASPECTS scores were rather high in all groups indicating little ischemic damage before the start of the intra-arterial therapy.[13] Another explanation might be that the TICI score has limitations in grading whether a treatment was successful. The TICI scoring system specifically evaluates recanalization at the primary occlusion. During intra-arterial treatment, distal emboli or emboli to other parts of the cerebral circulation might occur as a result of the clot manipulation. These occlusions, other than the primary occlusion, are not included in the TICI score.

CONCLUSIONS

Up to date, intra-arterial treatment has not been proven to be superior to IVT. Nevertheless, the recent large trials addressing this issue have mainly used local intra-arterial thrombolytics instead of the probably more effective SRs. Our study suggests that, given the higher recanalization rates achievable with SRs, future trials, including SRs as main treatment strategy, may show a benefit from intra-arterial treatment.

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TABLES

TABLE 1 Baseline characteristics according to the mechanical device used

	All (n = 84)	ND (n = 13)	MERCI (n = 22)	SR (n = 49)
Median age (min–max), years	64 (23–89)	67 (44–87)	72 (23–89)	60 (26–80)
Female sex, n	33 (39%)	5 (39%)	11 (53%)	17 (35%)
History of vascular disease[a], n	50 (60%)	9 (69%)	9 (41%)	32 (65%)
Mean NIHSS (min–max)	18 (4–38)	18 (4–32)	17 (6–35)	18 (7–83)
Intravenous thrombolysis, n	66 (79%)	12 (92%)	15 (68%)	39 (80%)
Treatment interval[b], h				
0–3	33 (39%)	3 (23%)	10 (46%)	20 (41%)
3–6	43 (51%)	7 (54%)	10 (46%)	26 (53%)
6–9	8 (10%)	3 (23%)	2 (9%)	3 (6%)
ICA occlusion, n	26 (31%)	2 (15%)	6 (27%)	18 (37%)
Mean ASPECTS score[c] (min–max)	9.2 (3–10)	9.2 (5–10)	9.1 (7–10)	9.2 (3–10)
Intra-arterial urokinase, n Median IU (min–max)	56 (67%) 200,000 (0–900,000)	11 (85%) 300,000 (0–750,000)	17 (77%) 325,000 (0–900,000)	28 (57%) 100,000 (0–850,000)
Abciximab, n	22 (26%)	3 (23%)	15 (68%)	4 (8%)
Heparin, n	13 (16%)	2 (15%)	10 (46%)	1 (2%)
Treatment time (SD)[d], min	106 (44)	75 (22)	112 (43)	111 (47)

[a] Either diabetes, coronary artery disease, peripheral artery disease, hypertension or atrial fibrillation. [b] From the start of symptoms until the start of angiography. [c] Initial ASPECTS score; n = 83. [d] Duration of the intra-arterial treatment from the start of angiography until the end of the procedure.

TABLE 2 Outcomes according to the mechanical device used

	All (n = 84)	ND 0(n = 13)	MERCI (n = 22)	SR (n = 49)
Poor outcome[a]	52 (62)	09 (69)	15 (68)	28 (57)
Intracerebral hemorrhage[b]	33 (40)	03 (23)	09 (43)	21 (44)
HI 1	11 (13)	01 (8)	03 (14)	07 (15)
HI 2	15 (18)	00 (0)	04 (19)	11 (23)
PI 1	01 (1)	00 (0)	00 (0)	01 (2)
PI 2	06 (7)	02 (15)	02 (10)	02 (4)
Death	17 (20)	03 (23)	07 (32)	07 (14)
Failed recanalization[c]	39 (46)	10 (77)	15 (68)	14 (29)

Values are n (%). [a] Defined as mRS >2; [b] n = 82; [c] TICI <2b.

TABLE 3 Unadjusted and adjusted RRs for poor outcome according to the first device used

	ND vs. SR		MERCI vs. SR		MERCI vs. ND	
	ND (n = 13)	SR (n = 49)	MERCI (n = 22)	SR (n = 49)	MERCI (n = 22)	ND (n = 13)
Poor outcome[a], n	9 (69%)	28 (57%)	15 (68%)	28 (57%)	15 (68%)	09 (69%)
Unadjusted RR	1.21 (0.78–1.87)		1.19 (0.82–1.74)		0.95 (0.62–1.56)	
Adjusted RR						
Age	1.14 (0.72–1.79)		1.18 (0.81–1.71)		1.04 (0.64–1.66)	
Female sex	1.22 (0.78–1.91)		1.23 (0.86–1.78)		1.01 (0.64–1.61)	
History[b]	1.20 (0.77–1.89)		1.25 (0.85–1.85)		1.04 (0.64–1.70)	
NIHSS	1.22 (0.79–1.88)		1.20 (0.82–1.75)		0.99 (0.62–1.57)	
IVT	1.25 (0.81–1.92)		1.16 (0.80–1.70)		0.93 (0.59–1.49)	
IAT	1.21 (0.77–1.88)		1.19 (0.82–1.74)		0.99 (0.62–1.57)	
Treatment interval[c]	1.19 (0.75–1.88)		1.18 (0.81–1.72)		1.00 (0.60–1.65)	
Treatment time[d]	1.31 (0.80–2.13)		1.19 (0.82–1.74)		0.91 (0.55–1.51)	
ASPECTS	1.24 (0.79–1.95)		1.22 (0.85–1.76)		0.98 (0.62–1.56)	
Failed recanalization[e]	1.17 (0.73–1.87)		1.16 (0.77–1.74)		0.99 (0.63–1.57)	
Three factors[f]	1.18 (0.74–1.88)		1.17 (0.79–1.74)		0.99 (0.61–1.62)	

IAT =Intra-arterial therapy. [a] Defined as mRS >2. [b] Either diabetes, coronary artery disease, peripheral artery disease, hypertension or atrial fibrillation. [c] From the start of symptoms until the start of angiography. [d] Duration of the intra-arterial treatment from the start of angiography until the end of the procedure. [e] TICI <2b. [f] Adjusted for age, history of vascular disease, and intravenous thrombolysis.

TABLE 4 Unadjusted and adjusted RRs for poor outcome and failed recanalization according to the last device used

	ND vs. SR		MERCI vs. SR		MERCI vs. ND	
	ND (n = 12)	**SR (n = 57)**	**MERCI (n = 15)**	**SR (n = 57)**	**MERCI (n = 15)**	**ND (n = 12)**
Poor outcome[a], n	8 (67%)	33 (58%)	11 (73%)	33 (58%)	11 (73%)	08 (67%)
Unadjusted RR	1.15 (0.73–1.82)		1.27 (0.87–1.85)		1.10 (0.66–1.82)	
Adjusted RR for three factors[b]	1.10 (0.68–1.78)		1.16 (0.78–1.72)		1.05 (0.61–1.81)	
Failed recanalization[c], n	10 (83%)	21 (37%)	8 (53%)	21 (37%)	8 (53%)	10 (83%)
Unadjusted RR	2.26 (1.48–3.46)		1.45 (0.81–2.59)		0.64 (0.37–1.10)	
Adjusted RR for three factors[d]	2.22 (1.45–3.40)		1.31 (0.69–2.47)		0.59 (0.32–1.07)	

[a] Defined as mRS >2. [b] Adjusted for age, history of vascular disease, and intravenous thrombolysis.
[c] TICI <2b.

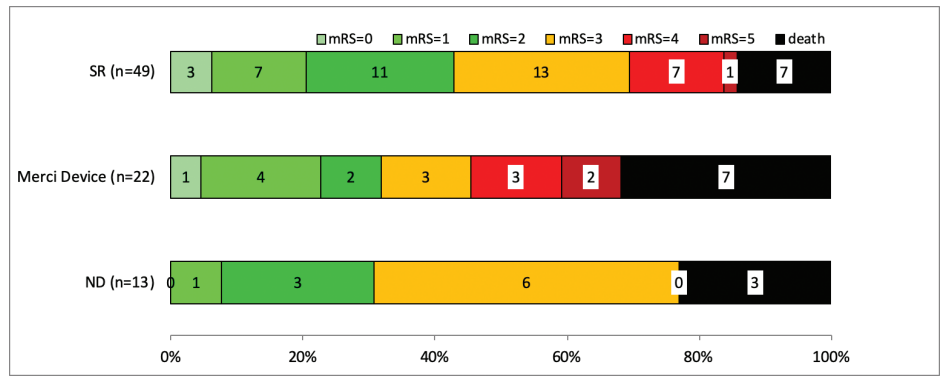
TABLE 5 Unadjusted and adjusted RRs for failed recanalization according to the first device used

	ND vs. SR		MERCI vs. SR		MERCI vs. ND	
	ND (n = 13)	**SR (n = 49)**	**MERCI (n = 22)**	**SR (n = 49)**	**MERCI (n = 22)**	**ND (n = 13)**
Failed recanalization[a], n	10 (77%)	14 (29%)	15 (68%)	14 (29%)	15 (68%)	10 (77%)
Unadjusted RR	2.69 (1.58–4.59)		2.39 (1.41–4.04)		0.89 (0.59–1.34)	
Adjustment RR for three factors[b]	2.59 (1.50–4.49)		2.32 (1.33–4.05)		0.90 (0.58–1.39)	

[a] TICI <2b. [b] Adjusted for age, history of vascular disease, and intravenous thrombolysis.

FIGURES

FIGURE 1 mRS score according to the treatment modality



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