Intraarterial Multi-Modal Reperfusion Therapy for Acute Ischemic Stroke: A 10 year Single-Center Experience

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ABSTRACT: **Background:** Only 0.5% of stroke patients in Israel are treated with endovascular multi-modal reperfusion therapy (MMRT) each year.

Objectives: To assess our experience with MMRT over the last decade.

Methods: We analyzed data from our stroke registry of patients undergoing MMRT during 2002–2011. All patients underwent multi-parametric imaging studies including subtraction angiography according to a predetermined algorithm. Stroke severity was measured with the National Institutes of Health Stroke Scale (NIHSS). Disability was measured with the modified Ranking Scale (mRS) and classified as favorable (mRS ≤ 2) or unfavorable. Target vessel recanalization was determined with the thrombolysis in myocardial infarction (TIMI) scale.

Results: During the study period 204 patients were treated; 166 of them had complete data sets including mRS scores at 90 days and were included in the analysis. Favorable outcomes at 90 days post-stroke were observed in 37% of patients and the mortality rate was 25%. Patients with favorable outcomes were younger, had significantly lower NIHSS scores on admission and discharge, and more often had complete target vessel recanalization (TIMI 3). On regression analysis the only factor associated with favorable outcome was TIMI 3, whereas increasing age and NIHSS scores on admission and discharge were predictors of poor outcome.

Conclusions: Our data show that MMRT can be successfully implemented in patients with severe stroke in Israel. More than a third of our patients with severe ischemic strokes who could not receive acute treatment were functionally independent after MMRT, demonstrating that this procedure is an important alternative for patients who are not candidates for intravenous tissue plasminogen activator (tPA) or do not achieve recanalization with tPA.

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Ischemic stroke is a complex disease incorporating several subtypes with different underlying pathologies that have many corresponding treatment options. These options should be individually tailored for each specific patient. Systemic thrombolysis with recombinant tissue plasminogen activator is the gold standard of acute ischemic stroke therapy [1-3]. However, this treatment option is limited due to a time window of only 3–4.5 hours from start of symptoms until infusion of the drug [1-3]. Because many patients arrive at the emergency department more than 4.5 hours from stroke onset, only a small fraction of stroke patients are eligible for this treatment [4]. Endovascular multi-modal reperfusion therapy is advantageous in that it selectively treats large vessel occlusions by reducing the amount of thrombolytic agents or preventing the need of thrombolytics altogether by using mechanical revascularization techniques such as thrombectomy or stenting [5-16]. This selective approach results in a larger therapeutic time window with up to 6 hours for intraarterial thrombolysis, and up to 8 hours for the use of mechanical devices in anterior circulation infarcts and up to 24 hours in posterior circulation infarcts [5-16].

However, only patients with occlusion of relatively large arteries such as the basilar, carotid or middle cerebral, typically undergo MMRT. The potential benefit of intraarterial therapy must be balanced against the risks of peri-procedural complications (5%–7%) and symptomatic intracranial hemorrhage (6%–15%) [5-16]. The question as to which treatment modality should be favored, systemic tPA or MMRT, is highly controversial as we await the results of large randomized clinical trials such as the International Management of Stroke III (IMS III) [17], which will compare the two options .

However, non-randomized clinical data suggest that success rates in restoring perfusion may be higher with intraarterial MMRT [5-16]. With unsuccessful reperfusion or with contraindications to thrombolytics, the prognosis appears to be dismal in patients with intracranial large vessel occlusions [9,18]. Therefore, a sequential combined treatment approach could be promising [13].

For ischemic stroke patients with intraarterial MMRT

MMRT = multi-modal reperfusion therapy
tPA = tissue plasminogen activator

Table 1. Imaging and treatment algorithm for patients with acute stroke

Time from symptom onset (hr)	Suspected involved artery	NIHSS	Imaging	Suggested procedure
0–3 (4.5)	MCA/ACA/PCA	1–4	CT+CTA	IV tPA if proximal occlusion
		5–12	CT+CTA	IV tPA
		13–18	CT+CTA	IV or MMRT
0–3 (4.5)	ICA	> 18	MRI	MMRT
0–3 (4.5)	Vertebral Vertebral/basilar	1–10 11–22	CT+CTA MRI	IV MMRT
0–3 (4.5)	Small vessel	1–18	CT	IV
3–6	MCA/ACA/PCA	1–4	CT	Conservative if large vessel occlusion is not present
		5–12	MRI	MMRT if MM > 1.4 conservative otherwise
		13–22	MRI	MMRT if MM > 2 conservative otherwise
3–6	ICA	>22	MRI	Conservative
3–6	Vertebral/basilar	1–22	MRI	MMRT
3–6	Small vessel	1–22	CT	Conservative
6–9	MCA/ACA/PCA	1–4	MRI	MMRT if MM > 2 and proximal occlusion
		1–18	MRI	MMRT if MM > 2.6
		>18	CT or MRI	Conservative
6–9	ICA	>22	CT or MRI	Conservative
6–9	Vertebral/Basilar	1–22	MRI	MMRT if occlusion
6–9	Small vessel	1–22	CT	Conservative

MCA = middle cerebral artery, ACA = anterior cerebral artery, PCA = posterior cerebral artery, ICA = internal carotid artery, CTA = computerized tomography angiography, MMRT = multimodal endovascular reperfusion therapy, MM = diffusion weighted–perfusion weighted MRI mismatch

the treatment is highly complex and involves numerous subspecialties. A multidisciplinary team consisting of neurologists, interventional neuroradiologists, endovascular neurosurgeons, anesthesiologists and neuro-intensivists is essential due to the complex needs of patients undergoing MMRT procedures. Currently, only a few facilities in Israel are able to administer such therapy. In this paper we describe our experience performing these procedures for a wide variety of ischemic stroke patients over the last 10 years.

PATIENTS AND METHODS

In 2002 we implemented a multidisciplinary stroke service at the Hadassah-Hebrew University Medical Center as a referral center for MMRT candidates. Local emergency services (Magen David Adom and TEREM), hospitals and primary physicians were approached to collaborate with our center's urgent stroke care system. Patients with suspected acute ischemic stroke were treated according to our Acute stroke imaging and treatment algorithm [Table 1].

Consecutive patients presenting with ischemic stroke who underwent MMRT over the span of 10 years were entered continuously into our stroke registry and the data were retrospectively analyzed. The institutional review board granted a general permission to collect routine anonymous data on all stroke patients.

The diagnosis of acute large vessel occlusion was established according to clinical findings and proven on computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography in all patients. All the endovascular procedures were performed by one or both of the senior angiographers (J.E.C or J.M.G). MMRT was performed in patients who were ineligible for systemic thrombolysis because of presentation later than 3 hours from symptom onset, or having an international normalized ratio > 1.7, or who did not improve significantly on the National Institutes of Health Stroke Scale (< 4 points) within one hour of intravenous tPA administration. MMRT was not performed in patients with hypodensity larger than one-third of the involved territorial supply on non-contrast CT, or lack of diffusion-perfusion mismatch on multi-parametric stroke MRI. MMRT was not performed in patients presenting with deep coma (Glasgow Coma Scale < 5), in patients with absent brainstem reflexes, or in those with primary intracerebral or subarachnoid hemorrhage.

We accrued clinical and demographic characteristics including age, gender, year the procedure was performed, and localization of occluded artery. Stroke etiology was determined according to the TOAST classification as: 1 = cardioembolic, 2 = large vessel atherothrombotic, 3 = small vessel, 4 = other known etiology such as dissection or vasculitis, and 5 = unknown etiology (cryptogenic).

MMRT was defined as any combination of two or more therapeutic modalities from a list that included intraarterial lytics, angioplasty, stenting, intrarterial GPIIbIIIa antagonists, mechanical clot disruption, and application of clot retrieval devices and stent retrievers. The number and types of procedural modalities were also documented and studied in all patients. Treatment complications including post-procedure hemorrhage and clinical deterioration without hemorrhage were also documented.

Neurological deficits were classified with the NIHSS (range 0–42; higher scores denote larger clinical deficits) at admission and discharge. Functional deficits before admission and at 90 days post-infarct were evaluated with the modified Rankin scale score (0 = completely independent with no complaints, 1 = mild complaints but no objective signs and no impairment, 2 = mild symptoms and signs with mild

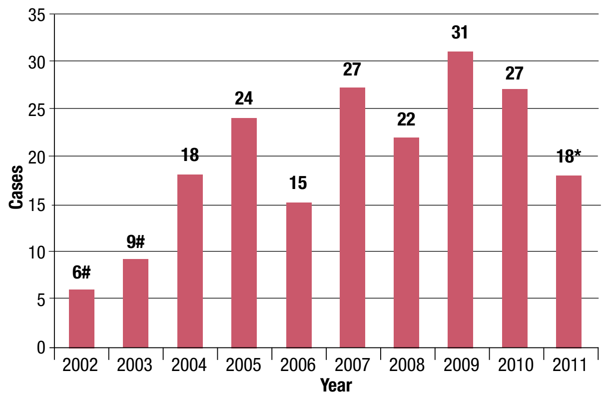
NIHSS = National Institutes of Health Stroke Scale

Table 2. Descriptive analysis of clinical and radiological data according to functional outcome

	Favorable outcome mRS 0–2(N=61)	Unfavorable outcome mRS 3–6(N=105)	*P* value
Age (± SD)(Median)	53.6 ± 14.7 (55)	66 ± 14.4 (69)	< 0.001
Gender male (%)	45 (64%)	61 (36%)	0.063
Occlusion location (%)			**0.203**
BA	12 (19.7%)	33 (31.4%)	
Vertebral	3 (4.9%)	2 (1.9%)	
ICA	24 (39.3%)	30 (28.6%)	
MCA	22 (36.1%)	41 (39.0%)	
TOAST (%)			**< 0.001**
Cardio-embolic	25 (41.0%)	52 (49.5%)	
Atherothrombotic	18 (29.5%)	48 (45.7%)	
Lacunar infarcts	0 (0%)	0 (0%)	
Other	16 (26.2%)	3 (2.9%)	
Unknown	2 (3.3 %)	2 (1.9%)	
TIMI (%)			
0–1	9 (14.8%)	40 (38.1%)	
2–3	52 (85.2%)	65 (61.9%)	< 0.001
3	48 (78.7%)	49 (46.7%)	0.003
Mean NIHSS at admission (± SD) (Median)	12.4 ± 9.1(12.5)	24.0 ± 9.1 (23)	< 0.001
Mean NIHSS at discharge (± SD) (Median)	4.3 ± 3.7 (4)	21.4 ± 14.2(16)	< 0.001

BA = basilar artery, ICA = internal carotid artery, MCA = middle cerebral artery, ACA = anterior cerebral artery, TOAST = Trial of ORG in Acute Stroke Treatment, TIMI = post-procedural thrombolysis in myocardial infarction score, NIHSS = National Institute of Health Stroke Scale

Figure 1. Patients who underwent intraarterial MMRT



In the first 2 years patients had to have an NIHSS ≥ 18 and undergo a prior MRI according to a special stroke protocol.
* Cases were counted until July 2011

Table 3. Multivariate analysis for variables associated with favorable outcome

Variable	OR	95% CI	*P*
Age	0.92	0.88–0.97	< 0.001
Gender	1.72	0.39–7.50	0.471
TOAST	1.27	0.55–2.92	0.577
NIHSS at admission	0.91	0.83–0.99	0.036
NIHSS at discharge	0.74	0.64–0.86	< 0.001
TIMI	4.93	1.16–21.00	0.031

impairment, 3 = moderate symptoms and signs with significant impairment but can still ambulate with help, 4 = wheelchair-bound, 5 = bedridden and totally dependent on others, 6 = dead). Good outcome was defined as mRS ≤ 2, and unfavorable outcome as mRS ≥ 3.

Post-procedural flow was classified with the TIMI system (0 = no flow, 1 = minimal flow, 2 = residual stenosis, and 3 = normal patent vessel).

STATISTICAL ANALYSIS

Descriptive statistical evaluations were performed with the Sigma-Stat package (Systat 12). Patients with favorable outcome were compared to those with unfavorable outcome using the *t*-test for continuous variables and chi-square test for categorical variables. We then performed a multivariable logistic regression analysis that included all variables that yielded a *P* value of < 0.2 on the univariate analysis.

mRS = modified Rankin scale
TIMI = thrombolysis in myocardial infarction

RESULTS

From May 2002 to June 2010, 204 patients (mean age 61.5, 64% male) underwent intraarterial MMRT [Figure 1]. Over the years a gradual increase in the use of MMRT was observed, with only six procedures performed in 2002 and an increase to 31 procedures in 2009. Of those, 166 patients had complete data sets, including 90 day mRS scores, and were included in the analysis. In 38 patients part of the data sets were missing (mostly due to loss to follow-up due to rehabilitation or long-term facility care outside the Jerusalem area).

Most patients (98%) were fully independent (mRS = 0) prior to their ischemic event. At 90 days after stroke onset 61 (37%) of our patients had good functional outcome, with an mRS ≤ 2, and 105 (63%) had an unfavorable outcome. Forty-one patients (25%) did not survive for 90 days post-stroke, with 41% (n=17) of them having suffered a stroke due to basilar artery occlusion. The most frequent etiology for ischemic stroke in our patient population was cardioembolism, accounting for 77 of the cases (46%), followed by large artery disease (n=66, 40%). Other causes were identified as resulting from dissections (n=19, 11%). Most vascular lesions involved the anterior circulation (117 patients, 70%). The middle cerebral artery (63 patients, 38%) was the most frequently occluded intracranial vessel followed by the basilar artery (45 patients, 27%).

Patients with unfavorable outcomes were compared with those who had favorable outcomes [Table 2]. The results show that patients with favorable outcomes were significantly younger, had lower NIHSS scores at baseline and discharge, more frequently had carotid dissections, and more often achieved complete target vessel recanalization. In contrast, patients with unfavorable outcomes more often had large vessel thrombosis or cardioembolic strokes.

Excellent target vessel recanalization (TIMI 3) was achieved in 58% of the patients. Only 49 patients (29.5%) did not have significant vessel recanalization (TIMI 0–1). Complete revascularization (TIMI 3) was associated with higher chances for good outcome ($P < 0.001$). On multivariate analysis controlling for age, admission and discharge NIHSS scores, gender, TOAST classification and TIMI score, the only variable to be associated with favorable outcome was complete target vessel recanalization (TIMI 3; odds ratio 4.93, 95% confidence interval 1.1–20.9) [Table 3]. In contrast, increasing age (OR 0.9, 95% CI 0.88–0.96) and increasing NIHSS scores on admission (OR 0.9, 95% CI 0.8–0.99) and discharge (OR 0.74, 95% CI 0.64–0.86) were associated with unfavorable outcomes.

DISCUSSION

More than a third of our patients had a favorable outcome at 90 days despite having large stroke lesions that would have led to a dismal outcome without treatment [15,18,19]. Of note, the only variable to predict a good outcome after MMRT was the achievement of complete target vessel recanalization, whereas increasing age and more severe neurological deficits at presentation and at discharge from the neurology department were associated with unfavorable outcomes. Our findings are confirmatory and comparable to those observed in previous MMRT studies performed in large volume centers in the United States and Europe, thereby providing support for the performance of MMRT in Israel [5,6,11,14,20-25].

Importantly, most of our patients were not eligible for systemic tPA treatment, emphasizing the suggestion that endovascular MMRT has an important role as an alternative or as an add-on treatment in acute ischemic stroke patients with large vessel occlusion, as shown in previous studies. To effectively guide an endovascular stroke service, a clearly defined "Acute stroke imaging and treatment algorithm" [Table 1] is essential and should be established in every center that provides such services.

OR = odds ratio
CI = confidence interval

Only 0.5% of stroke patients in Israel are treated with MMRT each year. This is due to the lack both of trained endovascular personnel and of an appropriate infrastructure for establishing a collaborative effort in Israel. The lack of centrally coordinated services results frequently in unnecessary loss of time and in multiple futile efforts to transport patients to the tertiary referral centers that utilize MMRT. Because current treatment protocols for MMRT include time windows of up to 8 hours for anterior circulation infarcts and up to 24 hours in cases of basilar artery occlusion, we believe that a nationwide centrally controlled referral system would increase the availability of MMRT to all areas of the country and minimize gaps in health services consumption. For proper infrastructure there is a need to train personnel, open dedicated units, and resolve issues of flow of clinical and radiological information and of rapid transportation. This is especially important because despite the extended therapeutic windows available with MMRT, vessel recanalization and tissue reperfusion should be done as soon as possible to minimize tissue loss.

In conclusion, the present study shows that MMRT can be safely and effectively performed in Israel in patients with large strokes and poor outcome. Since MMRT results in a good outcome in a large number of patients who would otherwise be dead or dependent, we believe that efforts to implement an appropriate infrastructure allowing for proper and timely availability of such therapy in the entire population of Israel should be centrally coordinated.

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