Multi-Modal Reperfusion Therapy for Patients With Acute Anterior Circulation Stroke in Israel

Ronen R. Leker, MD; Roni Eichel, MD; David Arkadir, MD, PhD; John M. Gomori, MD; Guy Raphaeli, MD; Tamir Ben-Hur, MD, PhD; Jose E. Cohen, MD

Background and Purpose—We aimed to delineate prognostic variables in Israeli patients with anterior circulation strokes treated with endovascular multi-modal reperfusion therapy (MMRT).

Methods—Clinical and radiological data from consecutive tpa-ineligible stroke patients with large anterior circulation infarcts involving either the entire internal carotid artery or the proximal middle cerebral artery territory were analyzed. Stroke subtypes were categorized according to TOAST criteria. Neurological deficits were assessed with the NIH stroke scale (NIHSS), and vessel recanalization was determined using the thrombolysis in myocardial infarction (TIMI) scale at the end of MRRT. Good outcome was defined as a modified Rankin score (mRS) ≤2.

Results—Fifty patients were included with a median age of 68. Thirteen patients died and 17 patients achieved an mRS ≤2 at 90 days. Variables associated with survival on multivariate analysis were admission NIHSS <20 (OR 15 95% CI 1 to 230) and postprocedure TIMI score 2 to 3 (OR 35.5 95% CI 2.3 to 603.9). Variables associated with good outcome included admission NIHSS <20 (OR 9.4 95% CI 1.3 to 71.3), day 1 NIHSS <15 (OR 6.4 95% CI 1.1 to 38.4), and postprocedure TIMI 3 (OR 7.4 95% CI 1.1 to 50.3).

Conclusions—MMRT resulted in high survival and good outcome rates in these critically ill patients. Lower baseline impairment and vessel recanalization increase the chances for good outcome. Our results suggest that the benefits of MMRT may merit further study and could be generalized to centers outside the United States and Europe. (Stroke. 2009;40:3627-3630.)

Key Words: reperfusion ■ stroke ■ internal carotid artery ■ middle cerebral artery ■ multimodal ■ endovascular

Large hemispheric ischemic stroke occurs in about 10% of all strokes and carries a mortality rate of close to 80%.1 Most of these patients suffer from internal carotid artery (ICA) T occlusions, and some have proximal middle cerebral artery (MCA) territory occlusions involving the M1 segment. The value of systemic thrombolysis in such patients remains unclear2,3 as we await the results of larger randomized studies such as the International Stroke Trial 3, but the chances of recanalizing the occluded vessel and restoring perfusion appear to be somewhat higher with endovascular multi-modal reperfusion therapy (MMRT).4–8 However, with unsuccessful reperfusion4 or with contraindications to thrombolysis, the prognosis appears to be dismal.9 In most cases mortality is caused by brain herniation secondary to stroke-associated edema.10 The only treatment that may prevent such a malignant course of events seems to be rapid tissue reperfusion. Importantly, most studies examining the efficacy of MMRT were performed in the United States, Europe, or Japan. Therefore, we aimed to evaluate which patients stand to benefit most if such therapy could become widely available worldwide.

Patients and Methods

We recruited consecutive patients presenting with hemispheric stroke that underwent MMRT over the span of 4 years into our stroke registry and the data were retrospectively analyzed. The institutional review board has granted a general permission to collect routine research data on all stroke patients. The diagnosis of complete acute ICA or proximal MCA occlusions involving the M1 segment was established according to clinical findings and proven on CT angiography (CTA), MR angiography (MRA), or digital subtraction angiography (DSA) in all patients. We did not use any specific radiological inclusion criteria other than stroke with large vessel occlusion. Included patients were ineligible for systemic thrombolysis because of presentation later than 3 hours from symptom onset (n=46) or having an INR >1.7 (n=4). Patients with hypodensity larger than 1/3 of the involved territorial supply on noncontrast CT were excluded as were patients that underwent multi-parametric stroke MRI and had no evidence for diffusion-perfusion mismatch. Patients presenting in deep coma (GCS <5) with absent brain stem reflexes and those with primary intracerebral or subarachnoid hemorrhage were excluded. Patients presenting more than 8 hours from symptom onset were not included. Clinical and demographic characteristics accrued included cerebrovascular risk profile, concomitant medications, time from symptom onset to initiation of endovascular procedure, and time onset to reperfusion. Infarct etiology was classified according to TOAST.
criteria as cardioembolic, large artery atherothrombotic, other classified (eg, dissection) or unclassified.

Neurological deficits were determined with the NIH stroke scale (NIHSS) and functional deficits before admission and at 90 days postinfarct were evaluated with the modified Rankin scale score (mRS). Good outcome was defined as an mRS $\leq 2$.

Radiological parameters were evaluated on entry CT/MRI and on the diagnostic and therapeutic angiography and follow up CT/CTA. Flow was classified with the TIMI system (0 no flow, 1 minimal flow, 2 residual stenosis, and 3 normal patent vessel). The presence and extent of collateral flow was evaluated by an experienced angiographer (J.E.C.) on DSA and determined to be present if backflow from one or both posterior communicating arteries or from the anterior communicating artery or from meningeal vessels sufficiently perfusing the distal MCA trunk was present. The collateral flow was arbitrarily scored according to the DSA as very good, good, or insufficient. We also determined the length of occlusion, vessel tortuosity, and lesion complexity (eg, calcified, ulcerated etc).

The number and types of procedural modalities were documented and studied in all patients. MMRT was defined as any combination of 3 or more therapeutic modalities from a list that included IA lytics.

### Table 1. Univariate Analysis of Clinical, Radiological, and Procedural Variables Associated With Favorable Outcome

<table>
<thead>
<tr>
<th>Variable/Group</th>
<th>Good Outcome (17)</th>
<th>Poor Outcome (33)</th>
<th>All</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, ±SD (median)</strong></td>
<td>51.2±16.4 (48)</td>
<td>66.5±15.1 (70)</td>
<td>61.8±17.7 (68)</td>
<td>0.002</td>
</tr>
<tr>
<td>Gender, n male (%)</td>
<td>9 (53)</td>
<td>13 (39)</td>
<td>23 (46)</td>
<td>0.31</td>
</tr>
<tr>
<td>Internal carotid occlusion</td>
<td>6 (35)</td>
<td>17 (52)</td>
<td>22 (44)</td>
<td>0.43</td>
</tr>
<tr>
<td>Middle cerebral occlusion</td>
<td>11 (65)</td>
<td>16 (48)</td>
<td>28 (56)</td>
<td>0.43</td>
</tr>
<tr>
<td>Involved hemisphere –left (%)</td>
<td>13 (76)</td>
<td>25 (76)</td>
<td>38 (76)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (29)</td>
<td>18 (55)</td>
<td>23 (46)</td>
<td>0.16</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3 (18)</td>
<td>13 (39)</td>
<td>16 (32)</td>
<td>0.21</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (35)</td>
<td>12 (36)</td>
<td>18 (38)</td>
<td>0.81</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (41)</td>
<td>8 (24)</td>
<td>15 (30)</td>
<td>1</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7 (41)</td>
<td>12 (36)</td>
<td>19 (39)</td>
<td>0.98</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (53)</td>
<td>8 (24)</td>
<td>17 (34)</td>
<td>0.04</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>4 (24)</td>
<td>15 (45)</td>
<td>19 (38)</td>
<td>0.23</td>
</tr>
<tr>
<td>TOAST classification (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>12 (71)</td>
<td>20 (61)</td>
<td>33 (66)</td>
<td>0.70</td>
</tr>
<tr>
<td>Large vessel</td>
<td>3 (18)</td>
<td>10 (30)</td>
<td>12 (24)</td>
<td>0.50</td>
</tr>
<tr>
<td>Small vessel</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1 (6)</td>
<td>0</td>
<td>1 (2)</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (6)</td>
<td>3 (9)</td>
<td>4 (8)</td>
<td>1</td>
</tr>
<tr>
<td>Onset to treatment (median)</td>
<td>5.9±2.1 (5.5)</td>
<td>6.3±2.8 (5)</td>
<td>6.04±2.5 (5)</td>
<td>0.61</td>
</tr>
<tr>
<td>Admission NIHSS (median)</td>
<td>15.4±6.9 (16)</td>
<td>22.1±3.8 (23)</td>
<td>19.7±6.0 (20.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 1 NIHSS (median)</td>
<td>10.2±6.2 (9)</td>
<td>19.6±6.3 (19.5)</td>
<td>16.1±7.8 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 90 NIHSS (median)</td>
<td>2.9±1.5 (2)</td>
<td>9.7±2.5 (9)</td>
<td>6.8±4.04 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Postprocedure TIMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>3 (18)</td>
<td>19 (58)</td>
<td>22 (44)</td>
<td>0.017</td>
</tr>
<tr>
<td>2–3</td>
<td>14 (82)</td>
<td>14 (42)</td>
<td>28 (56)</td>
<td>0.017</td>
</tr>
<tr>
<td>3</td>
<td>12 (71)</td>
<td>7 (21)</td>
<td>19 (39)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic hemorrhage</td>
<td>1 (6)</td>
<td>8 (24)</td>
<td>9 (18)</td>
<td>0.04</td>
</tr>
<tr>
<td>Symptomatic hemorrhage</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (2)</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (18)</td>
<td>15 (45)</td>
<td>18 (36)</td>
<td>0.10</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1 (6)</td>
<td>4 (12)</td>
<td>5 (10)</td>
<td>0.65</td>
</tr>
<tr>
<td>Neurological deterioration</td>
<td>2 (12)</td>
<td>6 (18)</td>
<td>8 (16)</td>
<td>0.70</td>
</tr>
<tr>
<td>Decompressive hemicraniectomy</td>
<td>2 (12)</td>
<td>4 (12)</td>
<td>6 (12)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Day 90 modified Rankin score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (18)</td>
<td>0</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14 (82)</td>
<td>0</td>
<td>14 (28)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>9 (27)</td>
<td>9 (18)</td>
<td></td>
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<tr>
<td>4</td>
<td>0</td>
<td>11 (33)</td>
<td>11 (22)</td>
<td></td>
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<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>13 (40)</td>
<td>13 (26)</td>
<td></td>
</tr>
</tbody>
</table>
angioplasty, stenting, IA GPIIbIIIa antagonists, mechanical clot dissection, and application of clot retrieval devices.

Included patients presented less than 6 hours from symptom onset were eligible for any of the above treatment modalities, whereas those presenting between 6 and 8 hours from symptom onset were not eligible for IA lytics but remained eligible for clot retrieval devices, mechanical lysis, angioplasty, and stenting. Treatment options were left to the discretion of the treating interventionalist. Treatment complications including postprocedure hemorrhage and clinical deterioration without hemorrhage were documented.

Patients younger than 60 were referred for craniectomy following the publication of a recent meta-analysis if MMRT failed to recanalize the artery and they experienced worsening neurological symptoms with clear evidence of worsening edema or imminent herniation on noncontrast CT.

Statistical evaluations were performed with the Sigma-Stat package (Systat). For univariate analysis patients with good and bad outcomes were compared using Student t test or χ² tests. We then used multivariate logistic regression analysis models that included variables that yielded a probability value of less than 0.2 on the univariate analysis to determine the effects of such variables on survival and good outcome.

Results

Fifty consecutive patients fulfilling entry criteria were included. The baseline clinical and radiological characteristics are presented in Table 1. All patients were independent before the procedure (mRS <2). Patients were divided (Table 1) according to day 90 mRS scores into those with good (mRS ≤2, n=17) and poor outcomes (mRS 3 to 6, n=33). Patients with good outcome significantly differed from those with poor outcome in that they were younger, more often achieved good to excellent vessel recanalization, and had lower NIHSS scores on admission and on the first postprocedural day. Patients with good outcome also tended to smoke more often but did not significantly differ from those with poor outcome in other risk factors (Table 2). Of note, procedure-related variables including type and site of vessel occlusion, onset to treatment time and time to vessel recanalization, number and types of procedural modalities used, collateral flow pattern, and lesion length did not differ between the groups.

Mechanical clot disruption was performed in 38 patients (76%), 23 (46%) received intraarterial urokinase, and 13 (26%) received GPIIbIIIa antagonists. Angioplasty was performed in 13 (26%) and stents were placed in 10 (20%). The number of modalities used or their individual types did not influence outcome.

Good reperfusion (TIMI 2 to 3) was achieved in 28 (56%) patients with 19 patients (38%) having excellent reperfusion (TIMI 3).

At 7 days poststroke only 13 of our 50 patients had died (26%). There were significantly more asymptomatic intracranial hemorrhages in patients who had poor outcome but the number of symptomatic hemorrhages was very low and did not differ between the groups (Table 1). Postprocedural infections were more common in patients with poor outcome but this trend did not reach significance (Table 1).

Eight of our patients had neurological deterioration attributable to massive brain infarction, and 6 of them underwent decompressive hemicraniectomy with no fatalities. However, this treatment had no effect on favorable outcome (Table 1). Follow-up data showed that 11 of the 37 surviving patients had an mRS ≤2 at this time point and 26 patients had an mRS ≤3 (67%), including 5 of the 6 patients that had decompressive hemicraniectomy, leaving only 4 patients in a dependent state with an mRS of 4. At 90 days poststroke the number of patients with good outcome increased to 17, and 20 patients remained with poor outcome.

Multivariate analysis (Table 2) identified vessel recanalization (TIMI 3) as the only variable that was associated with increased likelihood of both survival and good outcome. Admission and day 1 NIHSS scores (<20 and <15 respectively) were associated with good outcome. However, age, hypertension, and smoking did not show a significant impact on outcome.

Discussion

Our results demonstrate that MMRT resulted in high survival and good outcome rates in patients with malignant strokes. Good reperfusion status and lower NIHSS score on admission and on the day after the procedure were identified as good prognostic factors in these patients.

Our results reiterate the importance of recanalization as a potent mediator influencing outcome as shown not only for MMRT but also for studies using systemic thrombolysis. Of note, good outcome was obtained in some of our patients despite relatively late treatment onset, emphasizing the importance of tissue reperfusion.

Our findings are confirmatory to those observed in previous MMRT studies performed in large volume centers and suggest that MMRT can be further studied worldwide in multicenter studies. Furthermore, our study also represents the usual clinical practice outside large industry supported studies. Therefore, our results may provide further stimulus to train more interventional neuroradiologists and neurologists to provide for the growing demand for MMRT.

Our study has several limitations. First, the number of included patients was relatively small limiting its power. Furthermore, because the small sample size may introduce inadequacies in the multivariable analysis our results should be viewed as tentative. Second, this was an observational study and not a randomized clinical trial comparing MMRT with controls. Therefore, our results should be viewed as hypothesis generating that suggest the justification of future randomized studies. Nevertheless, the current study further expands the existing knowledge regarding the efficacy of MMRT in patients with large and often deadly strokes.

In conclusion, MMRT can be beneficial for patients with large hemispheric strokes. Furthermore, our results are in agreement with previous studies performed in the United States and Europe suggesting that MMRT can be equally...
effective when performed in smaller centers and outside of
the United States or Europe.

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Disclosures
None.

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