Endovascular Treatment for Acute Large Artery Occlusion Stroke: Implications for Israel

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KEY WORDS: acute stroke, reperfusion, thrombectomy, endovascular treatment

IMAJ 2016; 18: 569–570

Acute ischemic stroke affects about 9000 patients admitted annually in Israel [1-3]. Although incidence rates have declined over the last decade, the overall burden of stroke in Israel remains just as high. Stroke is a syndrome with multiple possible causes and a wide range of symptomatic presentations from mild and transient to devastating and fatal. Overall, it is the leading cause of adult long-term severe disability.

The current treatment paradigm for acute ischemic stroke is straightforward: restore blood flow as soon as possible, and do it as safely and completely as possible in order to save the ischemic penumbra and minimize disability. Intravenous thrombolytic therapy was proven effective more than two decades ago and was introduced successfully in Israel in 2002 [4,5]. Currently, about 20 centers in Israel provide intravenous recombinant tissue plasminogen activator (rt-PA) therapy. Based on the National Acute Stroke ISraeli (NASIS) registry, conducted triennially during 2 month periods since 2004, there was a ~15-fold rise in the utilization of intravenous rt-PA therapy, from 0.5% in 2004 to 7.4% in 2013 [6].

Fast reperfusion is the key to good outcome. Every 15 minutes of expediting reperfusion can provide on average an equivalent of 1 month of healthy life for each patient treated [7]. With multiple strategies it is possible to cut the median in-hospital door-to-needle time to only 20 minutes [8]. The key is to do as little as possible after the patient has arrived at the emergency department, and as much as possible before that while the patient is being transported. Achieving such a goal requires stroke-workflow efficiencies not yet in place in many hospitals in Israel. During 2003, door-to-needle time among patients receiving thrombolysis in Israel was less than 1 hour in only a quarter of patients [1]. In recent years therefore, there has been a heightened awareness of the importance of time. The Ministry of Health has set, as part of the national program of quality indices, several prehospital and acute hospital care indices focusing on efficiency in acute stroke management.

Ischemic stroke may be caused by large or small artery occlusions. For small artery occlusions and distal large artery occlusions the only reperfusion treatment option is intravenous rt-PA. Proximal large artery occlusion ischemic stroke, such as proximal middle cerebral artery occlusion, is associated with particularly high disability, yet reperfusion rates with intravenous rt-PA for such large clots are relatively low. Early mechanical thrombectomy for large artery occlusion ischemic stroke significantly improves clinical outcomes, as proven in five randomized controlled clinical trials published in the *New England Journal of Medicine* between December 2014 and April 2015 [9-13], and the HERMES collaboration meta-analysis combining individual patient data from these trials [14]. Overall, this is the most clinically significant advancement in acute stroke care since the introduction of intravenous rt-PA two decades ago, changing the standard of care. Endovascular treatment complements treatment with intravenous rt-PA, providing overall a more complete reperfusion strategy for acute ischemic stroke.

The dominant themes for success are the use of neurovascular imaging with careful selection of appropriate candidates for treatment, speed of management, early treatment, and the use of more effective new-generation thrombectomy devices. Stent-retriever device technology results in faster and more complete recanalization as compared with earlier-generation thrombectomy devices. In a meta-analysis and review of the literature of stent-retriever thrombectomy for anterior circulation stroke published in the current issue of *IMAJ*, Sivan-Hoffmann and colleagues [15] report that thrombectomy using a stent retriever in selected patients restores perfusion to the brain in four of five treated patients, allowing favorable clinical outcome in about one of two patients with large vessel occlusion acute stroke. This important success of mechanical thrombectomy clearly raises new questions regarding benefit versus harm in other patient populations (such as those with relatively large infarcts at baseline, posterior circulation occlusions, presentation beyond 6–12 hours or wake-up strokes [16], and those with substantial disability before stroke).

Although a relatively limited number of patients with ischemic stroke are candidates for endovascular treatment, these patients may gain considerable clinical benefit by salvaging brain tissue. The best strategy and neurovascular imaging modality for patient selection is still a matter of debate. By choosing a more restricted selection-based strategy some

patients who may benefit may not get the treatment, while choosing a more inclusive strategy may lead to a greater number of futile recanalizations.

Endovascular treatment for acute ischemic stroke in Israel is currently on the rise with utilization rates of about 0.9% in 2010, 1.4% in 2013, 1.8% in 2014 (overall ~160 cases annually) and an estimated gradual increase in 2015 and 2016. The infrastructure required for acute stroke care in Israel should assure modern care for the 9000 acute ischemic strokes admitted annually, of which a reasonable annual target for endovascular treatment nationwide is about 800–1200 cases. Therefore, there are still substantial opportunities to increase the treatment rate in Israel. In Catalonia, for comparison, with a comparable population of 7.5 million, the endovascular treatment rate in the metropolitan area of Barcelona was ~10/100,000 in 2015 [17]. In peripheral areas where accessibility was limited, treatment rates were lower and time to treatment longer.

Critical organizational changes in the systems of care are required to ensure that all eligible patients nationwide have the opportunity to receive this treatment in a timely manner. Not every hospital, however, can or should perform endovascular stroke therapy, since it requires not only a well-trained neuro-interventionalist, but an infrastructure and multidisciplinary teams that only comprehensive stroke centers may provide. The efficacy of endovascular stroke therapy has therefore major implications both for triaging decisions by emergency medical services and for the infrastructure of comprehensive stroke centers.

Even in a trial where workflow metrics were the fastest reported to date (the ESCAPE trial) there are still major opportunities for improvement in workflow from brain imaging to reperfusion that may substantially improve outcome [18]. Based on preliminary findings from NASIS-REVASC, a registry of reperfusion therapy in Israel, the median time from door of a primary stroke center to that of the comprehensive stroke center (door-to-door time) among patients transferred is much too long (~3 hours), leading to diminished treatment effectiveness. Prehospital identification of suspected large artery occlusion by Emergency Medical Services in Israel (MADA) is therefore required for direct referral to comprehensive stroke centers. The Ministry of Health in collaboration with the relevant medical specialties and MADA are currently working to assure a protocol for direct shipment of patients with suspected large artery occlusion strokes (by a simple clinical prehospital scale) to comprehensive stroke centers ("mothership"), and for assuring speedy "drip-and-ship" with intravenous rt-PA to those requiring transfer from a primary to a comprehensive stroke center. This paradigm shift evidently leads to more stroke patients admitted to comprehensive stroke centers, particularly more challenging severe stroke patients, requiring an infrastructure with large enough dedicated multidisciplinary stroke teams and departments. Moreover, modern comprehensive stroke centers require integrated diagnostic, preventive, therapeutic, research and rehabilitation resources to meet the extensive needs of stroke patients and to provide integrated care.

These are exciting times in the field of Stroke Medicine and Vascular Neurology. The field has matured over the last decade into a modern field using sophisticated technology for neurovascular imaging, stroke prevention, hyper-acute stroke treatment, and stroke rehabilitation. The whole spectrum of transient ischemic attack and stroke – ranging from minor to major symptoms – has the potential to be catastrophic and necessitates timely expert care management.

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