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Review Article

Intra-arterial thrombectomy in the management of acute ischemic stroke: evidentiary analysis over the past two years

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ABSTRACT

Stroke is one of the main causes of death and disability worldwide, and the ischemic modality is responsible for the majority of these events. Despite its high occurrence and potentially unfavorable prognosis, the management options were scarce and barely effective until recent times, when a relatively new endovascular intervention with demonstrated superior efficacy as compared with that of classic management was reported in the medical literature. The theoretical basis of this study was conducted through research in virtual databases Public MEDLINE (PubMed) and Scientific Electronic Library Online (SciELO) using associations among the keywords “acute ischemic stroke”, “ischemic stroke”, “thrombectomy”, “endovascular,” and “intra-arterial thrombectomy”. Clinical trials, meta-analysis, and pertinent literature reviews published in the last two years were reviewed and 14 articles were selected for complete and critical evaluations. The results of the randomized clinical trials, consequences of implantation of the intra-arterial thrombectomy as routine management for eligible groups, cost-effectiveness, and the most related complications and outcomes associated with the procedure are critically explored throughout this study.

Keywords: *Stroke; ischemic stroke; thrombectomy; endovascular*

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Stroke is one of the main causes of mortality and disability worldwide, and the ischemic stroke (usually with cardioembolic or arteroembolic etiologies) is responsible for the majority of these events[1]. Despite its high occurrence and potentially unfavorable prognosis, the management options were ineffective in many cases until recent times when a relatively new endovascular intervention associated with intravenous thrombolysis was reported to demonstrate superior efficacy as compared with that of the classic intravenous recombinant tissue plasminogen activator (IV tPA) management.

Simultaneously with the initial spread of intravenous thrombolytics after its approval, endovascular intervention techniques in acute strokes from large vessel occlusion were developed and tested in several medical centers, although data from methodologically consistent clinical trials were not yet available[2].

A set of clinical trials published mostly in 2013 indicated a weak significance of the endovascular intervention advantages. However, several biases were pointed out in these studies, such as the use of outdated devices and late medical interventions after the onset of the symptoms. Recent pertinent and well-designed clinical trials demonstrated different results and 2015 became considered as "the year of endovascular treatment"[3].

In this article, we discuss the results of the randomized clinical trials published in the field, the logistic consequences of the intra-arterial thrombectomy implantation as a routine management tool for eligible groups, cost-effectiveness, and the most related complications and outcomes associated with the procedure.

METHODS

The theoretical basis of this review was carried out through searches in virtual databases Public MEDLINE (PubMed) and Scientific Electronic Library Online (SciELO), using association between the keywords "acute ischemic stroke", "ischemic stroke", "thrombectomy", "endovascular" and "intra-arterial thrombectomy". Clinical trials, meta-analysis, and pertinent systematic literature reviews published in English in the last two years were included (figure 1). Articles with a non-convenient theme were excluded. A total of 13 articles were selected for complete and critical parsing. Complementarily, a total of 4 clinical trials were included, which, despite not meeting the inclusion criteria, were considered fundamental for an unbiased discussion of the proposed theme.

Current Concepts

Most acute ischemic strokes are caused by the occlusion of large vessels that are mostly components of anterior circulation at the proximal middle cerebral artery and the intracranial internal carotid artery, but also occur in posterior large vessels at the basilar artery[2]. It is important to note that the classic IV tPA has relatively low effectiveness in the proximal occlusion of large vessels[4].

The main purpose of any ischemic stroke treatment must be urgent revascularization of the affected area to save the parenchyma in the "penumbra area", an event optimized in the endovascular approach by recent technologies such as stent retriever apparatuses[5].

Intervention with a mechanical device appears to have advantages over the isolated use of chemical treatments, such as faster revascularization, a decreased hemorrhagic rate, and a considerably eligible intervention time.

Evidence from Clinical Trials

Although the purpose of this article is to review the main evidence published over the last two years, older clinical trials such as IMS III, SYNTHESIS, MR RESCUE and THERAPY are crucial for a full and unbiased overview of the subject.

In the IMS III[6] and SYNTHESIS[7] trials it was found that the endovascular therapy and intravenous t-PA groups were similar for mortality at 90 days and symptomatic intracerebral hemorrhage within 30 hours after initiation of t-PA. These studies indicated that endovascular therapy is not superior to standard treatment with intravenous t-PA. The MR RESCUE[8] trial demonstrated that mean scores on the modified Rankin scale did not differ between groups even when subdivided according to the presence of penumbral or a nonpenumbral pattern on computed tomography or magnetic resonance imaging of the brain.

Thus, there were those who believed that these studies had determined the non-superiority of the endovascular therapy when compared to intravenous t-PA. However, limitations pointed out in these studies and posteriorly published trials have refuted such conclusion. Assessments have criticized the common delay between symptom onset and treatment, suboptimal optimal rates of recanalization, prevailing use of outdated devices, inconsistent use of appropriate imaging as a inclusion criteria, and statistical inadequacies[3,9]. Five clinical trials published in 2015 demonstrated the viability of the endovascular approach in acute ischemic stroke.

In the study EXTEND-IA[10], researchers analyzed earlier intervention (4.5 h after the onset of the symptoms). Patients diagnosed with acute ischemic stroke, specified as penumbra area and ischemic parenchyma with a volume less than 70 ml, were evaluated with a computer tomography (CT) due to

occlusion of the internal carotid or middle cerebral artery. These patients received alteplase (0.9 mg/kg), and were either submitted to the intra-arterial thrombectomy group using a Solitaire FR stent retriever or a conservative group receiving only tPA. Patients in the treatment group experienced a greater area of vascularized penumbra tissue, earlier clinical neurologic improvement 3 days after the procedure, and better functional outcome at 90 days as compared with those in the conservative group. No differences were noted in the rates of death or symptomatic hemorrhage between the two groups.

The SCAPE[11] trial investigators also evaluated the benefits of endovascular treatment in association with intravenous thrombolysis. Subjects with a proximal intracranial arterial occlusion without a large ischemic area and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) between 6 and 10 were evaluated. The mean time from CT to reperfusion was 84 min. Better rates of functional independence and reduced mortality were observed when comparing the intervention with the control group.

In order to assess patients with proximal anterior intracranial occlusion without a large ischemic area, the SWIFT PRIME[12] trial was performed. After the initial clinical presentation of the stroke, patients received intravenous tPA for 4 h and 30 min and thrombectomy using a stent retriever for 6 h. The results indicated reduced disability at 90 days, higher functional independence in the intervention group, and no substantial differences related to mortality and intracranial symptomatic hemorrhage between the two groups.

The REVASCAT[13] trial investigators found that patients with confirmed proximal anterior intracranial circulation without a large ischemic area defined as ASPECTS of 7 to 10, who were treated up to 4-5 h after the ictus with intravenous alteplase associated with thrombectomy using solitaire stent retriever up to 8 h after the ictus, demonstrated a reduced severity in disability and improved functional independence, with no differences of intracranial symptomatic hemorrhage when compared to alteplase therapy alone.

Lastly, MR CLEAN[14] researchers applied, up to 6 h after the onset of symptoms, the intra-arterial thrombectomy associated (in eligible patients) with intravenous (between 4-5 h) and intra-arterial tPA in patients with confirmed proximal anterior arterial cerebral circulation occlusion. Improved rates of functional independence in the intervention group and no differences in the mortality or symptomatic intracerebral hemorrhage were reported between the intervention and no-intervention groups.

Additionally, In the THERAPY[15] trial it was found that it is possible that an alternate method of thrombectomy, without stents retrievers, can be effective for specific patients harboring large vessel occlusions. In the meantime, the authors argue that

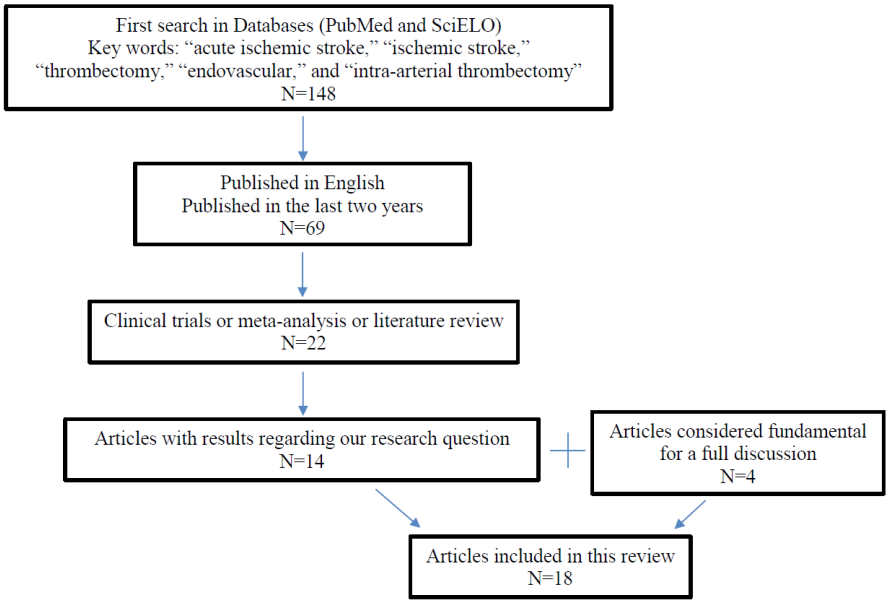

Figure 1: Article selection methodology.

Table 1: Main results of the randomized clinical trials published in 2015 that demonstrated the efficiency of the endovascular approach.

Clinical Trial	Number of patients	Eligibility time	Area of revascularized tissue	Functional outcome	Symptomatic hemorrhage rate	Death rates	Premature termination of research due to difference in efficacy
EXTEND-IA	70	6 h	Increased (100% vs. 37%)	Improved functional outcome at 90 days	No significant differences related	No significant differences related	YES
SCAPE	316	12 h	Increased (53.0%, vs. 29.3%)	The primary outcome favored the intervention	Most frequent in the intervention group (3.6% vs. 2.7%)	Reduced (10.4%, vs. 19.0%)	YES
SWIFT PRIME	196	6 h	Rate of substantial reperfusion at the end of the procedure is 88%	Reduced disability at 90 days	Lower in the intervention group (0% vs. 3%)	Reduced in 90 days (9% vs. 12%)	YES
REVASCAT	206	8 h	Higher in the thrombectomy group	Higher rates of functional independence at 90 days (43.7% vs. 28.2%)	No significant difference (1.9% vs. 1.9%)	Higher in the thrombectomy group (18.4% and 15.5%)	NO
MR CLEAN	500	6	Higher in the thrombectomy group	Higher in the thrombectomy group (32.6% vs. 19.1%)	No significant differences related	No significant differences related	NO

the results are not imperative, demanding further research.

DISCUSSION

Trials using more specific inclusion criteria had better clinical outcomes and prognosis than trials where patients were admitted with larger areas of penumbra and late presentations. It can also be noted that studies with simplified inclusion criteria showed unreliable results. CT angiography was performed in the ESCAPE Trial, resulting in a careful selection of patients, which had better outcomes with the procedure than those using only a conventional CT, such as MR CLEAN patients. These findings highlight the importance of criterion selection for intra-arterial thrombectomy. However, a simple and cheaper method is a more realistic possibility in the context of Brazilian public health, demanding an accurate search for possible radiological findings that indicate eligibility for the intervention.

It is evident that these five clinical trials demonstrated comparable methodology and compatible results. The reproducibility of the results indicates a high rate of confidence regarding the variable analyzed: the intra-arterial thrombectomy with stent retriever clinical outcomes after a proximal artery occlusion compared with the use of IV rTPa alone. It is noteworthy to mention that in three of the five studies, the research was stopped prematurely because of the discrepancy of efficacy between the approaches (table 1).

Cost-effectiveness, Complications, and Anesthesia Related to the Procedure

To assess the cost-effectiveness of intra-arterial thrombectomy implantation as the standard management of the ischemic event, Aronsson et al.[16] used a mathematical model (Markov model) to generalize the data arising from the five clinical trials discussed above from 90 days to a lifelong time period. The outcomes such as quality of life

and disability are closely related to the costs and benefits at a population level. Important financial benefits were estimated, such as savings around $221 per patient, including a big range of factors, such as rehabilitation, medicaments, follow-up, and home-care costs.

Since it is a very recent procedure, long-term studies that analyze long-dated clinical and economic factors of the intra-arterial thrombectomy in the management of acute ischemic stroke are not yet available. There are still substantial obstacles such as logistics, sedation, imaging exams, manpower, and financial aspects that need to be overcome to promote the implementation of endovascular management as a standard care.

Regarding the occurrence of atypical events and complications related to the procedure, the leading event was puncture site complications, followed by hemorrhagic events (hemorrhagic infarction or parenchymal hematoma), procedure-/device-related events (such as stent detachment, arterial dissection and vascular perforation) and late-onset occurrences (vascular stenosis, usually asymptomatic)[17].

Hemodynamic variables are clearly related to more severe outcomes, especially with huge variability in blood pressure and hypotension. A retrospective review[18] proposed that conscious sedation was associated with more favorable outcomes and related to a lower variability in systolic blood pressure when compared to general anesthesia. Therefore, it has been suggested that the anesthetic technique may play an important role in the clinical outcome.

CONCLUSIONS

The new findings in the literature clearly demonstrate that intra-arterial thrombectomy promotes important clinical and economic benefits pertinent to acute ischemic stroke management. However, it is indispensable to establish new functional logistic routines concerning acute stroke management in order to properly implement the new techniques. In the future, standardization of eligible criteria for the procedure needs to be determined.

There are many variables to be elucidated, in part due to the relatively low number of patients, which will impair subject division into subgroups for significant statistical analysis. The practical challenges for the dissemination of the approach remain to be studied, such as logistical aspects of imaging, sedation, and cost. However, endovascular therapy appears as a potential intervention technique for acute ischemic stroke with emphasis in large vessels occlusion.

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