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Original article

Number needed to treat for stroke thrombectomy based on a systematic review and meta-analysis

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ABSTRACT

The positive results of recent clinical trials examining endovascular treatment of acute stroke were the culmination of nearly two decades of studies of endovascular stroke treatment. We systematically reviewed this body of work, evaluated the strength of evidence, and performed a meta-analysis to define the clinical impact of these investigations. Terms were entered into search engines in a systematic fashion. Articles were reviewed independently by study authors, graded for level of evidence, and combined in a meta-analysis. The overall body of evidence was evaluated using GRADE criteria. Our search yielded 948 articles. Twenty-five met predefined inclusion criteria. We identified 12 grade I, 1 grade II, 5 grade III, and 7 grade IV studies ($\kappa = 0.86$). Meta-analysis for independence at 90 days showed a benefit of endovascular treatment (grade I studies OR 1.58 [1.20–2.07]). When limiting the analysis to studies using stent retriever, the OR increased to 2.44 (1.77–3.36). The number needed to treat (NNT) was 8. Endovascular treatment was not associated with increased symptomatic intracranial hemorrhage, and forgoing endovascular treatment was associated with death at 90 days. The quality of evidence according to GRADE criteria was "moderate." In summary, we found impressive evidence for a benefit of endovascular treatment of acute stroke, particularly when using stent retriever devices. Our meta-analysis is unique in that it includes all studies related to this topic and defines the clinical impact of the data, providing NNT. We show that thrombectomy is among the most effective stroke treatments currently available.

1. Introduction

Ischemic stroke is a major cause of death worldwide, which has defied treatment efforts well into the era of modern medicine [1]. Beginning in the 1990s, the NINDS rt-PA trial revolutionized medical management of acute ischemic stroke, demonstrating that rt-PA started within 3 h of symptoms results in improved outcomes at 90 days (OR 1.7 [1.2–2.6]) [2]. Three years later, the ECASS III trial showed similar results for rt-PA given within 4.5 hours [3]. The number needed to treat (NNT) for rt-PA administered with 4.5 h is between 4 and 13 [4].

While these dramatic changes in medical management of ischemic stroke were occurring, early studies of endovascular treatment for this disease were being performed [5,6]. Initial efforts primarily involved intra-arterial (IA) thrombolysis and were not successful. Improvements in devices, techniques, and patient selection ultimately resulted in several positive trials in 2015 [7–12].

Meta-analyses have summarized recent clinical trials [13–15]. These studies indicated that mechanical thrombectomy is superior to standard medical management when examining contemporary randomized controlled trials. None of these reviews attempted to summarize the past 20 years of studies in a comprehensive systematic review and meta-analysis. We sought to perform a comprehensive review and meta-analysis, summarizing and examining progress in endovascular treatment of ischemic stroke since the earliest efforts. Furthermore, we aimed to highlight the clinical impact of these treatments by calculating NNT and evaluating the body of evidence as a whole, and we sought to identify where future research may be most fruitful.

2. Methods

Key search terms "stroke," "endovascular," "interventional," "embolectomy," "thrombectomy," "retriev*" were included in our search. We used the Medline and Cochrane databases. We also reviewed references of key articles. A librarian with expertise in systematic review was consulted at the beginning of the search process.

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Table 1
Articles identified in the systematic review [5–12,24–40]. RCT, randomized controlled trial; IAT, intra-arterial thrombolysis; S, stent retriever; C, other/combination.

Study (by year)	Study design	Grade	Risk of bias	N	Technique
del Zoppo 1998 (PROACT)	RCT	II	Allocation concealment	46	IAT
Furlan 1999 (PROACT II)	RCT	I		180	IAT
Ducrocq 2005	RCT	IV	Allocation concealment, unmasked assessment	27	IAT
Burns 2008	Cohort study	IV	Dissimilar groups, unmasked assessment, primary outcome not stated	63	C
Mazighi 2009 (RECANALISE)	Cohort study	III	Unmasked assessment, primary outcome not stated	160	IAT
Ciccone 2010 (SYNTHESIS Pilot)	RCT	I		54	IAT
Meiner 2012	Case control	IV	Unmasked assessment, primary outcome not stated	28	C
Broderick 2013 (IMS III)	RCT	I		656	C
Ciccone 2013 (SYNTHESIS Expansion)	RCT	I		362	C
Kidwell 2013 (MR RESCUE)	RCT	I		127	C
Qureshi 2013	Case control	IV	Dissimilar groups, unmasked assessment, primary outcome not stated	104	C
Sallustio 2013	Cohort study	III	Dissimilar groups, unmasked assessment	97	C
Abilleira 2014	Cohort study	III	Dissimilar groups, unmasked assessment	1179	C
Saeed 2014	Cohort study	IV	Unmasked assessment, primary outcome not stated	2313	C
Tütüncü 2014	Cohort study	III	Dissimilar groups, unmasked assessment	30	C
Berkhemer 2015 (MR CLEAN)	RCT	I		500	S (81.5%)
Bracard 2015 (THRACE)	RCT	I		414	C
Campbell 2015 (EXTEND-IA)	RCT	I		70	S
Goyal 2015 (ESCAPE)	RCT	I		316	S (86.1%)
Hwang 2015	Cohort study	IV	Unmasked assessment	156	C
Jovin 2015 (REVASCAT)	RCT	I		206	S
Meyne 2015	Case control	IV	Dissimilar groups, unmasked assessment	82	S
Mocco 2015 (THERAPY)	RCT	I		108	C
Paciaroni 2015 (ICARO-3)	Case control	III	Unmasked assessment	648	C
Saver 2015 (SWIFT PRIME)	RCT	I	Allocation concealment	196	S

The pre-specified inclusion criteria were studies that compared endovascular and medical treatment arms, reported clinical outcome data, included >25 patients, and were written in English. We excluded studies of predominantly posterior circulation stroke, stroke due to dissection, and stroke in children. Two study authors (EC, AG) independently reviewed each article and assigned a grade of evidence to each. The articles were graded according to the classification scheme recommended by the American Academy of Neurology [16–18]. A senior study author (SS) resolved any discrepancies in the article ratings.

Pre-planned outcome measures included independence (modified Rankin Score [mRS] 0–2) at 90 days, symptomatic intracranial hemorrhage (ICH) and death at 90 days. Data were included in meta-analyses combining all articles meeting inclusion criteria, grade I studies only, stent retriever studies only, and studies using other techniques. The inverse variance method and a random effects model were employed for the meta-analysis. Analyses were performed using RevMan 5.3 software from the Cochrane Informatics and Knowledge Management Department. A P value <0.05 was considered significant. Throughout the review and meta-analysis, PRISMA methodology was employed [19].

We evaluated the total body of evidence using the GRADE system [20–23]. A GRADE designation was achieved by consensus after discussions involving study authors as recommended by GRADE guidelines. Beyond evaluating individual studies, this system assesses the total body of evidence. Criteria include study design, risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, dose response, and all plausible residual confounding. Four possible designations are specified: high, moderate, low, and very low quality.

3. Results

3.1. Systematic review

Our strategy for inclusion of studies is outlined in Fig. 1. The search strategy yielded 948 studies. Upon reviewing the abstracts, we found 923 studies that did not meet our predefined inclusion/exclusion criteria. Twenty-five studies were candidates for inclusion in our qualitative and quantitative syntheses. [5–12,24–40]. We identified 12 grade I, 1 grade II, 5 grade III, and 7 grade IV studies (κ = 0.76, weighted κ = 0.86). Included studies are listed in Table 1.

3.2. Meta-analysis

The meta-analysis for mRS 0–2 at 90 days showed a benefit of endovascular treatment, OR 1.69 (1.31–2.19), P < 0.0001 (Fig. 2). The NNT was 31. When repeating the analysis for grade I studies, the OR was 1.58 (1.20–2.07), P = 0.0010, NNT 38 (Supplemental Fig. I). Finally, we limited the analysis to stent retriever studies, and the OR increased to 2.44 (1.77–3.36), P < 0.00001 (Fig. 3). The NNT for stent retriever studies was 8. When including all studies, heterogeneity was substantial, $I^2 = 71\%$. However, heterogeneity was moderate in the limited analysis (e.g., $I^2 = 35\%$ for stent retriever studies).

We performed meta-analyses for symptomatic ICH and death at 90 days in the grade I studies. For symptomatic ICH, the point estimate suggested an association between endovascular treatment and hemorrhage, but this was not significant, OR 1.13 (0.80–1.60), P = 0.50 (Supplemental Fig. II). On the other hand, we found a significant association between medical management (forgoing endovascular treatment) and death, OR 0.70 (0.54–0.91), P = 0.007 (Supplemental Fig. III). The number needed to harm was 92.

In order to examine the effect of endovascular technique on the results, we analyzed mRS at 90 days for the IA thrombolysis studies as well as combination technique studies. Unlike stent retriever studies, there was no significant effect of IA thrombolysis, OR 1.38 (0.97–1.97), P = 0.08. Additionally, there was no effect for combination technique studies, OR 1.36 (0.82–2.25), P = 0.23. The earliest studies tended to use IA thrombolysis or combinations of techniques (Table 1). Therefore, we performed a regression analysis of year versus effect size. We found that study year was not associated with effect ($R^2 = 0.019$, P = 0.57).

3.3. Body of evidence quality (GRADE rating)

The risk of bias in the individual studies is presented in Table 1. Having rated articles according to individual strengths and weaknesses, we graded the overall body of evidence using the system described by Guyatt et al. [20–23]. The GRADE method proposes