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The importance of time: Time delays in acute stroke

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ABSTRACT

Background: Endovascular treatment (EVT) of severe acute ischemic stroke (AIS) determined by large vessel occlusion (LVO) is effective and safe. Debate still goes on especially about time importance and utilization of advanced penumbra imaging at the expense of loosing valuable minutes.

Methods: We did a meta-analysis focused on time of randomized clinical trials (RCTs) that started to use methodically the new-tech stent retrievers. The chosen time interval was onset-groin time (from last seen well to sheath insertion in the cathlab). Primary outcome was good functional outcome (mRS of 0–2) at 90 days, and secondary outcomes were mortality at 90 days and symptomatic intra-cerebral hemorrhage (sICH). Furthermore, we did a sub-analysis of the EVT patients to find a correlation between faster times and outcomes. We did the same sub-analysis including also single-arm registries that used modern stent retrievers.

Results: Totally data from 1287 patients (5 RCTs) were analyzed, whose 634 EVT patients were divided into two groups based on time (faster/slower than 240 min). Furthermore 1501 EVT-treated patients (9 studies) were divided into two pre-specified groups (fast/slow) and analyzed. In both meta-analysis and sub-analysis, the fast group had better functional outcome at 90 days [log OR = −2.07, 95% CI (−3.00, −1.14)] and less deaths [log OR = −0.56, 95% CI (−3.66, −2.55)], demonstrating that onset-groin time has a strong impact even on mortality. On the other hand, sICH resulted to be more frequent in the slow group [log OR = 0.18, 95% CI (−1.36, −1.71)] emphasizing how delays could even worsen AIS.

Conclusions: This meta-analysis supports the "Time is brain" strategy in treatment of acute ischemic stroke. In general, fast endovascular treatment (groin puncture within <4 h) significantly improves patients' outcomes. Healthcare systems should develop maximal effort to shorten pre-hospital and in-hospital delays in acute stroke patients. The earlier the patient is presenting, the more important is the fast track, offering chance for full neurologic recovery.

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Introduction

Ischemic stroke is one of the most important causes of death and severe functional disability around the world nowadays, with a very high human price and a strong impact on healthcare systems.

Intra-venous rtPA (iv rtPA) initiated up to 4.5 h from symptom onset is indicated for acute ischemic stroke (AIS) based on the 2013 American Heart Association (AHA) Guidelines [1]. The latest 2015 update from AHA [2] introduced 1A indication for endovascular therapy (EVT) after five recent randomized controlled trials [3–8] (RCT) strongly supported the use of EVT in specifically selected patients, in particular those with evidence of large clots in the distal internal carotid artery (ICA) or in the middle cerebral artery (segment M1 or M2) and with a severe clinical presentation (high NIHSS). Before these successful RCTs, there were three neutral trials during 2013 [9–11] that were not able to demonstrate benefit from EVT due to suboptimal patient selection and old technology (modern thrombectomy retrievers used only in minority of patients).

Going through the recent RCTs, we can point out some differences in methodology and inclusion criteria that could be underestimated or misinterpreted.

The net benefit in terms of good functional outcome for EVT in comparison with the control iv rtPA-alone groups on the eligible patients is now confirmed by recent meta-analysis and review articles [12–16] and the importance of time to revascularization is highlighted by several studies about iv rtPA [17] or EVT [18–20].

We aimed to investigate the influence of time delays on the major outcomes of AIS treated by EVT in the current stent retrievers' era.

Methods

Data sources

We searched PubMed, Cochrane CENTRAL, Web of Science, and the National Institutes of Health Clinical Trials from 1 January 1995 (year of publication of the NINDS rtPA Stroke trial) through 30 October 2015, for English language, peer-reviewed publications. The following Medical Subject Heading terms and/or keywords were used for database searches: 'acute ischemic stroke', 'intra-arterial therapy', 'endovascular treatment', 'endovascular therapy', 'thrombectomy', and 'catheter-based treatment'. Related reviews, clinical trial databases and the reference lists of all retrieved articles were also searched manually for relevant studies. Any disagreements were resolved by discussion.

Study selection and eligibility criteria

We included trials with at least 12 weeks of follow-up, both double-blind and open-label trial designs were eligible for inclusion. We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of RCTs for our protocol [21].

We decided to analyze manuscripts that started to use mechanical thrombectomy with modern stent-retrievers, excluding the neutral 2013 RCTs for their methodology limits already highlighted in other papers [22,23], in particular for their limited use of these last generation devices.

Choice of times and outcomes

We decided to compare the time from the stroke onset (or last seen well) to the sheath insertion in the cathlab (onset-groin time) because it is the most relevant time interval across the studies and the only one always present in all the EVT arms.

The primary specified outcome was the proportion of patients with a good functional outcome defined with the modified Rankin Scale (mRS of 0–2) at 90 days from stroke onset. Secondary outcomes included mortality at 90 days and symptomatic intra-cerebral hemorrhage (sICH). Asymptomatic ICH was defined in different ways across the RCTs so it was excluded from the analysis.

Statistical analysis

Key statistical analysis was conducted by an external independent statistician (B.P.).

To compare the results in different studies the forest chart from metaphor package of program R was used (http://cran.r-project.org/). The problem for quantitative data was that for the same variables were used different descriptions in the different studies: mean and SD, or median and quartiles, or median and minimum and maximum. To solve this problem, we supposed normal distribution and estimated mean as median and we estimated SD from normal distribution with appropriate quartiles, respect to maximum and minimum.

The estimated median onset-groin time was 229.9 min for the EVT arm patients so we decided to dichotomize them in two pre-specified groups (fast/slow): faster or slower than 4 h (240 min) to see the impact of time on outcomes.

For representation of the results we use forest plot (for all, iv rtPA/EVT arms, fast/slow groups) of logarithmic odds ratio (log OR) and their 95% confidence interval (95% CI). To compare the impact of iv rtPA/EVT arms or fast/slow groups we used bootstrapping ANOVA model with nuisance categorical parameter [24]. For the qualitative variables we used the forest charts and the Mantel–Haenszel test with nuisance categorical parameter [25].

Moreover, we made crude odds ratio (OR) to directly compare fast/slow groups inside the EVT arms, using analysis of contingency tables (chi-square or Fisher's test) to calculate the association between qualitative variables thus correlating outcomes with the two pre-specified groups [25]. We considered significance level of 5% ($p < 0.05$).

Results

Included studies

Totally 3741 articles were found in the databases and only 27 met eligibility criteria for full text evaluation. Of these, we did a meta-analysis of the five recent trials starting from the

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