2016

Effekt av trombolytisk behandling i intervallet 3 til 4,5 timer etter hjerneslag

Systematisk oversikt

Effect of thrombolytic treatment 3 to 4.5 hours after onset of stroke: a systematic review

This is an excerpt from the full technical report, which is written in Norwegian.
The excerpt provides the report's main messages in English.

folkehelseinstituttet

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Key messages

The Norwegian Knowledge Centre for the Health Services (now part of the Norwegian Institute of Public Health) were commissioned to update the evidence on effect of intravenous thrombolytic treatment administered 3 to 4.5 hours after stroke. There was already a Cochrane systematic review by Wardlaw et al from 2014. We searched for systematic reviews published after Wardlaw's review, but found none that fulfilled the inclusion criteria. Then we searched for randomised controlled trials published later than the search date for the Cochrane review, but we found no relevant trials. We have, therefore, conveyed the findings from Wardlaw and supplemented with data from an individual patient data meta-analysis. We have also graded our confidence in the estimates of effect using the GRADE tool (Grading of Recommendations Assessment, Development and Evaluation). The outcomes are assessed 3-6 months after the stroke and are compared with placebo.

We found that intravenous thrombolysis administered 3 to 4.5 hours after onset of ischemic stroke gives:

- Uncertain effect on the outcome «alive and independent» (very low quality/confidence)
- A positive effect on the outcome «alive with no functional impairment» (moderate quality/confidence)
- Between 37 fewer and 36 more per 1000 in risk of death (low quality/confidence)
- Uncertain risk of symptomatic intracranial haemorrhage (very low quality/confidence)

Title:

Effect of thrombolytic treatment 3 to 4.5 hours after onset of stroke

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Type of publication:

Systematic review

A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

Doesn't answer everything:

- Excludes studies that fall outside of the inclusion criteria
- No health economic evaluation
- No recommendations

Publisher:

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Updated:

Last search for systematic reviews: October 2015. Last search for primary studies: December 2015

Executive summary (English)

Background

Approximately 80 percent of strokes are ischemic, a result of blocking the supply of oxygen to the brain. If intracranial bleeding is not detected and there are no contra-indications, intravenous thrombolysis can be administered to dissolve the blood clot. Thrombolysis is a medical term for breakdown of blood clots by way of drugs. It is recommended to administer thrombolysis as soon as possible and preferably within 3 hours after onset of symptoms, but there is more uncertainty regarding the efficacy of thrombolysis up to 4.5 hours after stroke. The Directorate of Health in Norway is in the process of revising the national guideline for treatment and rehabilitation following a stroke, and they want to find out if there is new research on the efficacy of thrombolysis given during this time interval. Wardlaw et al published a systematic Cochrane review in 2014, and we searched for research published later than that.

Method

We had the following inclusion criteria:
Population: persons in the acute phase after ischemic stroke of all ages.
Intervention: intravenous thrombolytic treatment 3 to 4.5 hours after onset of symptoms of blood clot in the brain. Treatment received in the interval 0-3 hours and 3-6 hours is also included.
Comparison: placebo 3-4.5 hours after symptom onset, placebo 0-3 hours after onset, placebo more than 4.5 hours after onset, treatment as usual.
Outcomes: «Alive and independent» (= modified Rankin Scale score (mRS) 0-2 versus 3-6) with follow-up 3 to 6 months, "Alive with no functional impairment" (mRS 0-1 versus 2-6) with follow-up 3 to 6 months, mortality primarily with follow-up 3-6 months, secondarily 0-7 days, symptomatic intracranial bleeding (0-7 days).
Study design: systematic reviews of high quality. If we did not find any, we planned to include: randomised controlled trials.
Language: the literature search was not limited to specific languages. If publications in other languages than Scandinavian and English had been identified, we would, based on the English abstract, have considered translating them.
Publication date: later than November 2013.

In October 2015 we searched for systematic reviews in the *Cochrane Database of Systematic Reviews*, *Database of Abstracts of Reviews of Effects (DARE)*, *Health Technology Assessment Database* (HTA), *Epistemonikos*, *MEDLINE*, *Embase* and *PubMed*. Because we did not find any systematic reviews of high quality that fulfilled our inclusion criteria and that were newer than the Cochrane review by Wardlaw, we searched in December 2015 for randomised controlled trials published from 2013 and onward.

Two people went through the titles and abstracts of the hit list from the literature searches. We planned to acquire in full text the systematic reviews and articles that were considered appropriate and consider these in more detail in accordance with the inclusion criteria. For systematic reviews, two people were to independently assess their quality using the Knowledge Centre's checklist. Only systematic reviews of high quality were considered for inclusion.
Because we did not find relevant systematic reviews or randomised controlled trials, we have communicated the results of Wardlaw et al, and graded the quality of the documentation. We have also supplemented with data from a meta-analysis with individual patient data by Emberson et al (1).
We have assessed the quality of the overall documentation for each of the outcomes using GRADE (Grading of Recommendations Assessment, Development and Evaluation) (1). We describe the quality as high, medium, low or very low.

Results

The results described here are for the comparison between thrombolysis and placebo and assessed after three to six months follow-up. For the outcome "alive and independent" (Good stroke outcome = modified Rankin Scale score [mRS] 0-2 versus 3-6, there is probably an effect of thrombolysis administered within 3 hours after symptom onset (Odds ratio [OR]: 1.54, 95% CI: 1.26 to 1.88, moderate quality evidence). If thrombolysis is given between 3 and 4.5 hours after onset there is uncertain effect (OR: 0.93, 95% CI: 0.78 to 1.12, very low quality evidence). For the time interval 3-6 hours, there is probably a minor difference between thrombolysis and placebo (OR: 1.15, 95% CI: 0.96 to 1.38, moderate quality evidence).
For the outcome "alive with no functional impairment" [Good stroke outcome mRS 0-1 versus 2-6], there is probably a positive effect for thrombolysis administered within 3 hours (OR: 1.75, 95% CI: 1.35 to 2.27, moderate quality evidence) and also probably effective in the interval between 3 and 4.5 hours (OR: 1.26, 95% CI: 1.05 to 1.51, moderate quality evidence). For more than 4.5 hours there is probably a minor effect (OR: 1.15, 95% CI: 0.95 to 1.39, moderate quality evidence).
For the outcome "death" there is possibly a minor difference between administering thrombolysis within 3 hours after symptom onset and administering placebo (OR: 0.91, 95% CI: 0.73 to 1.13, low quality evidence). For thrombolysis given between 3 and 4.5 hours after onset there is possibly a minor difference (OR: 0.90, 95% CI: 0.54 to 1.49, low quality evidence). For the interval 3-6 hours, there is probably an increased risk of death compared to the placebo group (OR: 1.16, 95% CI: 1.00 to 1.35, moderate quality evidence).
For "symptomatic intracranial bleeding", there is possibly an increased risk when thrombolysis is administered within 3 hours after onset (OR: 5.71, 95% CI: 3.16 to 10.32, low quality evidence). For thrombolysis given between 3 and 4.5 hours after onset there is an uncertain effect on symptomatic intracranial bleeding (OR: 9.85, 95% CI: 1.26 to 77.32, very low quality of evidence). For the time interval 3-6 hours, there is probably an increased risk of intracranial bleeding (OR: 4.38, 95% CI: 3.12 to 6.14, moderate quality evidence).

Discussion

Thrombolysis administered within 3 hours is probably beneficial.
In the time interval 3 to 4.5 hours, the estimate is uncertain for the outcome "alive and independent", probably because there is a lack of data. There are more studies in the overlapping time interval 3 to 6 hours. Because a minor effect is found (with moderate quality evidence), this substantiates a minor effect also between 3 and 4.5 hours.
For the outcome «alive with no functional impairment», there is probably a positive effect for the time interval 3 to 4.5 hours.
For the outcome «risk of death», there is possibly no effect of thrombolysis in the time interval 3 to 4.5 hours, but the quality of evidence is low. In the overlapping time interval 3 to 6 hours,

there is probably an increased risk of death, and the quality of evidence is moderate. There is a need for more research on this outcome in this time interval.
The risk of symptomatic intracranial bleeding is uncertain in the time interval 3 to 4.5 hours because there is only one study. In the overlapping time interval 3 to 6 hours, there is probably an increased risk of intracranial bleeding, which substantiates an increased risk also for the former time interval.

Conclusion
We found for the time interval 3 to 4.5 hours that the results probably are positive when the outcome “alive and independent” is used. The risk of death does not seem to differ between the thrombolysis group and the placebo group, while there is an increased risk of intracranial bleeding in the thrombolysis group.