Subject: BMJ - Decision on Manuscript ID BMJ.2015.027448

Body: 27-Jul-2015

Dear Dr. Rodrigues

Manuscript ID BMJ.2015.027448 entitled "Adjunctive intra-arterial mechanical thrombectomy versus medical care alone for ischemic stroke – a systematic review and meta-analysis"

Thank you for sending us this paper, which we discussed at a recent manuscript meeting

We recognise the value and importance of your study, but identified some important issues that need to be clarified before we make a final decision about publication.

Would you be willing to revise and let us take another look?

Our biggest concern, shared by reviewers, was that results were so different for trials published in 2013 and 2015. We felt this reflected differences in the patient populations studied in the 2013 and 2015 trials. Some editors felt it was inappropriate to combine all 8 trials from both years, when the heterogeneity between 2013 and 2015 studies was so obvious. Please justify your approach better, and emphasise sensitivity analyses combing 2013 and 2015 trials separately.

A more detailed summary of our discussion is below, along with reports from reviewers. Please revise to respond to all comments by editors advisers and reviewers. We hope you find the reports constructive

I'm afraid we can't promise to publish the revision, but we should be in a position to make a quick decision

If you are happy to proceed with the BMJ, please let us have the revised paper back within a month or so.

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And finally, we also require a copy of the manuscript with changes highlighted. Please upload this file with file designation 'Revised Manuscript Marked copy'.

Many thanks again. We look forward to seeing your revised paper

With best wishes

Alison Tonks
associate editor BMJ
atonks@bmj.com

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were:Elizabeth Loder [chair] Angela Wade [statistician] Wim Weber, Georg Roeggla, Rubin Minhas, Tiago Villanueva

Decision: request revisions

Detailed comments from the meeting:

We agreed this was an interesting, timely, and potentially useful contribution, but with important limitations:

One of our US editors , Jose Merino, made the following comments:

Disclosure: I was an investigator (while at the NIH) at the leading enrolling site for MR RESCUE, one of the studies published in 2013 and included in the MA. This was an NIH-funded trial.

I think the authors should be clearer about two points that differentiate the studies published in 2013 and 2015.

1. The new trials used new devices (the reviewers raised this issue. The retrievers used in 2015 were more rapid to deploy and more succesful at recanalizing occluded vessels)

2. The trials in 2013 and 2015 include DIFFERENT patients.

Point #2 is very important and it is the reason why the authors should present their results in two groups (as some of the Forest plots show). The key issue is that stroke is a dynamic process. When a vessel is occluded a small area of brain is infarcted and a larger area is at risk of infarction. As ischemia persists, the area of the infarction grows. This means that there is more to gain with early treatment.

The trials published in 2013 all included patients in later stages of the process. Some went up to 8 hours, and in these trials patients who were not candidates for IV tPA, often because of time from onset of symptoms, or who had IV tPA without improvement were enrolled in the study (only a few patients had IV tPA before the endovascular procedure). Patients were not selected based on imaging criteria. Patients received endovascular therapy late. The idea (and hope) behind these studies was that endovascular therapy could be used for many patients who could not benefit from standard tPA because of time or other contraindications.

The studies published in 2015, on the other hand, enrolled patients who were treated early after onset of symptoms. In two of the studies, all patients had to be treated with IV tPA in the standard time window. In the other trials most patients also received standard tPA. In all these trials the mean or median time to endovascular treatment was less than 4.5 hours, the standard IV tPA time window. In all the trials published in 2015 patients had demonstrated vascular occlusion on pre-treatment imaging. The trials required evidence of a small ischemic core and because patients had moderately severe strokes, a large penumbra (rescuable tissue) could be inferred. Some of the trials also required imaging documentation of the penumbra (a large perfusion deficit).

The 2015 studies show that those who already benefited from standard therapy can now benefit more from additional interventions while those for whom there was no acute therapy (with a few exceptions) still do not have an acute therapy.

This means that the 2013 studies enrolled patients later after onset of symptoms, presumably with a larger infarct and less salvageable tissue and without documented target pathology (clot). The 2015 papers enrolled patients with small core, much salvageable tissue and a documented target pathology.

The new AHA stroke guidelines acknowledge that "Certain endovascular procedures have been demonstrated to provide clinical benefit in selected patients with acute ischemic stroke." (http://www.ncbi.nlm.nih.gov/pubmed/26123479)

I would like the authors to make these differences between early and late studies much clearer and take into account the features of the included populations in their discussion when recommending endovascular therapy.

One of our European editors, Wim Weber, made these further comments

I took part in one MRCLEAN, and I noticed two weaknesses: this trial was retrospectively registered (http://www.controlled-trials.com/ISRCTN10888758), and the Rankin scores were obtained through telephone interview.

Looking at the other trials, at least two other studies were retrospectively registered, and no trial describes how Rankin assessments were done (Direct/ video/ telephone/ blinding etc.).

Please note (perhaps in a table) which studies were prospectively registered and mention retrospective registration as a major weakness in some of the included trials, especially since some of the outcomes were subjective and not all trials had blinded assessors.

IMPORTANT CHECKLIST FOR ALL BMJ PAPERS. Make sure your revision complies fully.

Title: this should include the study design eg "systematic review and meta-analysis"

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found

Results
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Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
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Footnotes and statements

What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

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inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:

did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)

was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)

were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)

are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:
COMMENTS FOR EDITOR:

This systematic review and meta-analysis comes truly at the time when such ones are needed. The authors have properly collected published data and used appropriate analyses. The results are clearly presented and the conclusions are valid and based on them. The manuscript is easy to read. The message of the manuscript is clinically important and will influence daily practice, but as the authors properly say, AIMT as standard care will require restructuring comprehensive stroke centers and training of many more interventional neuroradiologists before it can be delivered on 24/7 basis to those who need it and benefit from it.

The authors have included all 8 RCTs that have studied AIMT, which is appropriate. Including trials published before 2015 is obviously the reason for the fact that the authors used such wordings as "there exists uncertainty" and "there is moderate quality evidence" because all trials published in 2015 have been positive and did not leave any uncertainty. The authors should tell this more clearly, otherwise the present meta-analysis can discourage clinicians and delay wider use of AIMT in care of patients with large anterior vessel occlusions.

The results of the present meta-analysis verify that AIMT is superior to conventional IV alteplase in properly selected patients. Busy clinicians may not have read the original papers published in NEJM and therefore, the present systematic review and meta-analysis will help them to become well informed.

Furthermore, the authors describe the patients who could benefit from AIMT.

My suggestions for revisions are easy to execute if the authors are allowed to revise their manuscript. I think that they deserve that possibility.

COMMENTS FOR AUTHORS:

The idea of the study is very good. The authors have properly collected published data and used appropriate analyses. The results are clearly presented and the conclusions are valid and based on them. The manuscript is easy to read. The message of the manuscript is clinically important and will influence daily practice, but as the authors properly say, AIMT as standard care will require restructuring comprehensive stroke centers. They could also add that use of intra-arterial therapies asks for training of many more interventional neuroradiologists before it can be delivered on 24/7 basis.

The authors have included all 8 RCTs that have studied AIMT, which is appropriate. Including trials published before 2015 is obviously the reason for the fact that the authors used such wordings as "there exists uncertainty" and "there is moderate quality evidence" because all trials published in 2015 have been positive and did not leave any uncertainty. The authors should tell this more clearly, otherwise the present meta-analysis can discourage clinicians and delay wider use of AIMT in care of patients with large anterior vessel occlusions resembling the situation to that of the first meta-analysis of thrombolysis. The efficacy of thrombolysis in these meta-analyses was weakened by the three negative RCTs in which the active study drug was streptokinase. When the meta-analyses and pooled analyses only included RCTs in which the active study drug was alteplase, the results were different and led to daily use of intravenous alteplase in care of patients with ischemic stroke.

The systematic review and meta-analysis of the authors is truly needed at present when clinicians treating stroke patients need more effective therapies for patients with large anterior vessel occlusions. The results of this meta-analysis verify that AIMT is superior to conventional IV alteplase in properly selected patients. Busy clinicians may not have read the original papers published in NEJM and therefore, the present systematic review and meta-analysis will help them to know the cutting edge of recanalization therapies.

There are a few points, which need to be revised.

Major comments:

In the Background of the Abstract and in the Conclusions and implications of key findings on page 3, the authors downplay the efficacy of intra-arterial recanalization treatments saying that there exists uncertainty and that there is moderate evidence that AIMT provides beneficial functional outcome after ischemic stroke secondary top anterior large vessel occlusion. The same holds true for the last paragraph of the Introduction on page 4 and the first paragraph of the Discussion, Summary of evidence, on page 9 where the authors say on the 2nd row that there is moderate quality evidence from RCTs that AIMT improves the outcome of patients. The trials published in 2015 do not leave any uncertainty about whether intra-arterial recanalization therapy improves the outcome of ischemic stroke patients with large anterior vessel occlusions compared with such patients treated with medical care alone.

Minor comments:

On page 3, on the 5th row in Findings of Abstract, after the word "rates" add the following: compared with patients having been randomized to receive medical care alone.

On page 7, in the second paragraph of Study characteristics, the authors say that most studies required a time from the symptom onset to thrombolysis of 4.5 hours. However, in 6 of the 8 trials included in the meta-analyses, the time window was longer than 4.5 hours and in 4 out of 6 positive trials the time window was from 6 to 12 hours.

In the same paragraph the authors list trials, which accepted patients not eligible for thrombolysis. They should add IMS III in the list because in intra-arterial therapy arm of IMS III the time window was 6 hours.

On page 9 in Limitations, the authors could add the following at the end of the 1st paragraph: Furthermore, in RCTs, the study sites are highly selected and their investigators well trained to the treatments studied. In daily practice after positive RCTs physicians providing these treatments to their patients are very often less well familiar with new therapies and not trained in using them well. As the authors properly say, patients treated outside RCTs often have disorders, which would have excluded them from RCTs, which could add the risks of major complications. This is especially so, when the new treatment is invasive and asks for appropriate training before it can be delivered safely.

On the title page, Dr. Joao Costa is missing from the list of authors and Dr. Ferreira Joaquim is mentioned twice.

Additional Questions:
Please enter your name: Markku Kaste

Job Title: Emeritus Professor of Neurology and Past Chairman

Institution: University of Helsinki and Department of Neurology of Helsinki University Central Hospital

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
The authors have shared the results of a metaanalysis comparing mechanical thrombectomy with best medical management. On the basis of their inclusion criteria, they selected 8 studies: IMS III, SYNTHESIS, MR RESCUE, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, and REVASCAT. They concluded: "Cost-effectiveness analysis should be pursued before widespread implementation of mechanical thrombectomy and restructuration of comprehensive stroke centers".

An important aspect of such an analysis is based on the understanding of mechanical thrombolysis. It is the device , patient selection, and experience that determine the ease, safety, and success of the procedure.

The earlier trials, IMS III, SYNTHESIS expansion, and MR Rescue were conducted with older technology. These trials mostly used MERCI retrievers or the EKOS Micro-Infusion Catheter. The authors have included these trials in the current analysis along with the newer studies (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, and REVASCAT). The latter trials used mainly the latest stent retriever technology (Solitaire and Trevo) with CT perfusion imaging (SWIFT-PRIME and EXTEND-IA) in the decision-making tree.

The following aspects need to be considered:
1. IMS III, SYNTHESIS, MR RESCUE did not show a significant difference in functional independence with endovascular therapy after intravenous t-PA as compared with intravenous t-PA alone, whereas all the trials published in 2015 unanimously showed superiority of endovascular therapy over best medical management.
2. The authors must statistically explain the results when the 3 trials of 2013 are compared with the 5 trials of 2015.
3. Endovascular neurointervention is one field where disruptive innovation is an issue. Worldwide, older-generation retrievers have been replaced by the Solitaire/Trevo stent retrievers. Aided by superior imaging (CT perfusion), the results have been impressive, clearly in favor of endovascular.
4. A detailed subanalysis based on device selection (older generation/Merci vs. newer/Solitaire) needs to be shared and discussed with the readers.
5. The conclusion should mention the change in the outcome of 2013 versus 2015 results.
6. Ideally, the authors should have compared the results of 2015 only, as the technology used was similar.

Is the research question or study objective clearly defined? Yes
Is the abstract accurate, balanced and complete? Yes
Is the study design appropriate to answer the research question? Yes
Are the methods described sufficiently to allow the study to be repeated? N/A
Are research ethics (e.g. participant consent, ethics approval) addressed appropriately? N/A
Are the outcomes clearly defined? Yes
If statistics are used are they appropriate and described fully? Yes
Are the references up-to-date and appropriate? Yes
Do the results address the research question or objective? Yes
Are they presented clearly? No
Are the discussion and conclusions justified by the results? No
Are the study limitations discussed adequately? No
Is the supplementary reporting complete (e.g. trial registration; funding details; PRISMA checklist)? Yes
To the best of your knowledge is the paper free from concerns over publication ethics (e.g., plagiarism, redundant publication, undeclared conflicts of interest)? Yes
Is the standard of written English acceptable for publication? Yes
Does the paper require specialist statistical review? Yes
Specific Comments: (see above)
Recommendation: Reject - solely on the basis of including outdated technology proven ineffective in this analysis.

Thank you for asking us to participate in this review.
Ashish Sonig MD MS MCh and Elad I Levy MD MBA FACS FAHA

Additional Questions:
Please enter your name: Elad I. Levy MD MBA

Job Title: Professor and Chair of Neurosurgery

Institution: University at Buffalo, State University of New YOrk

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: No

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END

Date Sent: 27-Jul-2015