Subject: BMJ - Decision on Manuscript ID BMJ-2019-049230

Body: 25-Jun-2019

Dear Dr. Tu

Manuscript ID BMJ-2019-049230 entitled "Comparative efficacy and safety of new surgical treatments for benign prostatic hyperplasia: A systematic review and network meta-analysis"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers and would lik to offer publicationin the BMJ if you are able to revise to our satisfaction.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting. We are looking forward to reading the revised version in due course.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

John Fletcher
Dr John Fletcher
Associate Editor
The BMJ
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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: Jose Merino (chair), Richard Riley (statistician), Tiago Villanueva, Tim Feeney, Elizabeth Loder, John Fletcher

Decision: Put points

Detailed comments from the meeting:

1. This is a clinical topic relevant to many of our readers and your review appears to have a clear message.

2. Our main reservation at the moment is the complex and somewhat unclear presentation of the results. Please see our statistician's report for guidance on revision.

3. Please can you provide an illustration or perhaps a text box that describes how each of the procedures is carried out. We appreciate this will be obvious to surgeons but our general readers may appreciate a little more explanation.

4. Our patient editor noted that there is no PPI declaration or dissemination plan. Please include these in your revision.

5. Please can you explain or discuss a little more to what extent patients have a real choice about surgery? Will it be down to what the local surgeons offer or are good at?

6. Please can you elaborate a little how the outcome measures in your review translate into symptomatic improvement for patients? How noticable is a change in QMax of 3 ml/sec?

7 Please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Thank you for the opportunity to review this systematic review comparing various contemporary treatment modalities to monopolar TURP for BPH. This is a comprehensive meta-analysis with rigorous methodology. I only have minor comments:

Minor:
-There are various grammatical/syntactical errors throughout the paper, for example:
line 16: should read "the year 2000"
line 19: should read "benign prostatic hyperplasia"; should be corrected throughout the manuscript
-I am confused by the authors use/meaning of "blood clot tamponade" throughout the paper.
-The authors appear to lump bipolar electrocautery into the enucleation group during their discussion. This should be avoided as bipolar TUR is not traditionally regarded as an "enucleation" technique.
-Lastly, it would have been nice to see comparisons between the various laser techniques as I'm not convinced that monopolar TURP remains the "gold standard" in outlet procedures. While this comment is not directly related to the manuscript, the authors should consider this in future studies.

Additional Questions:
Please enter your name: David Friedlander

Job Title: Research Fellow

Institution: Brigham and Women's Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
This manuscript tried to describe and compare different new surgical techniques in the efficacy and safety of BPH by applying frequentist network meta-analysis. I believed that Authors should spend lots of time on data collection and analysis, while in my opinion, the work still has no novelty in terms of methodology and conclusion. I do not think the manu. should be suitable for publication in the BMJ. Anyway, I have some comments or suggestions as following:

1. The updated searching date needs to avoid missing searches to the greatest extent(In the manuscript, the searching date was only updated to Mar. 2018).

2. In Supplementary figure 2, the blank area is supposed to be yellow, indicating unclear risk of bias? Maybe, authors are not familiar with the statistical software.

3. The authors mentioned the search strategy of grey literature by manual search in the method part. However, the information was missed in the parts of flow diagram and results.

4. It seems that the authors selectively reported surgical outcomes, for the key outcome of PVR was not included in the final analysis, while it was mentioned and planed in the protocol.

5. The authors have included IPSS and Qmax as the primary outcomes, however, it is suggested that the primary outcomes should be consisted of both outcomes of efficacy and safety. How about the primary endpoints of safety? Please describe in the context. In addition, the total number of primary outcomes is suggested no more than three (see Chochrane Handbook).

6. Patients and Urologists often face the challenge in selecting the optimal intervention among various treatments of BPH, so GRADE approach is suggested to classify evidence into different recommendation levels based on single outcome.

Additional Questions:
Please enter your name: Hao Zeng

Job Title: Prof.

Institution: Department of Urology, West China Hospital, Sichuan University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 3

Recommendation:

Comments:
BPH is a common condition that affects aging men. As authors point out, there are several surgical treatments available for it. The authors compare and rank 9 surgical treatments. The authors are congratulated for undertaking this substantial project. The study is well done.

A few points to consider.

MAJOR:
1. Did any of the trials included in this network meta-analysis report on length of hospital stay? This should be considered an endpoint too, if available.
2. Did any of the trials included in this network meta-analysis report on the individual IPSS scores? This maybe helpful as nocturia is a multifactorial entity and does not always relate to BPH. Further, certain IPSS questions pertaining to 'urgency' and 'frequency' after treatment of BPH may reflect permanent detrusor overactivity (from BPH or not) and thus may falsely inflate IPSS scores, and mask the effectiveness of the treatment. Therefore looking at individual scores is sometimes helpful.
3. In the sensitivity analysis, the authors should strongly consider including IPSS QoL. This is probably the most important component of the IPSS score that governs patients' decision to undergo treatment and postoperative satisfaction.

MINOR:

1. Please clarify this statement in the results "However, only seven methods reported outcomes for 24-36-month postoperative follow-up, and these were predominantly pairwise comparisons of bipolar TURP with monopolar TURP."
2. I could not find in the text what was considered a significant p-value? Was it <0.05? If so, then should the authors consider using correction for multiple corrections such as Bonferroni etc?

Additional Questions:
Please enter your name: Akshay Sood

Job Title: Senior Resident

Institution: Henry Ford Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Funds for a member of staff?: No

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Reviewer: 4

Recommendation:

Comments:
Very good paper reporting the results of a meta-analysis about a hot topic.
The only one limitation of this study is that the authors did not analyze early postoperative urinary symptoms such as urgency, or post-micturition pain: this factor represents the main concern of some of the reported procedures. Tha authors stressed this limitation in the discussion.

Additional Questions:
Please enter your name: Fabrizio Dal Moro

Job Title: Associate Professor

Institution: University of Udine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 5

Recommendation:

Comments:
Thank you for the opportunity to review this interesting paper, on clearly an important topic. I have been through this from a statistical perspective, and have a number of comments and suggestions for improvement, as follows.

1) The authors should use PRISMA-NMA, not PRISMA (http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis.aspx)

2) I-squared is not a test of heterogeneity, and indeed is a poor direct measure of heterogeneity. (Rucker G, Schwarzer G, Carpenter JR, et al. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol 2008;8:79)

3) The authors use Stata and the mvmeta module; do they actually mean they used the network module (which uses mvmeta in the background)?

4) If relevant, how were multiple intervention effects from the same study handled in the analysis (i.e. was their correlation accounted for)?

5) What assumptions were made about the specification of the between-study variance matrix components? E.g. were between-study variances made equal and correlations set to 0.5, as is standard?

6) Was a random effects meta-analysis used in the network meta-analysis, as in the pair-wise analyses? Was the uncertainty of between-study variance estimates accounted for when deriving subsequent CIs for summary results? E.g. using Hartung-Knapp Sidik-Jonkman approach?

7) What estimation method was used for the network meta-analyses? REML?

8) STATA should be Stata

9) “We applied a 0.5 zero-cell correction only in the pairwise meta-analysis as a default of the Stata meta command but not in the network-meta-analysis to obtain a more unbiased estimation.” – I don’t think adding 0.5 in the pair-wise analysis is as appropriate as using the Sweeting correction. (Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med 2004;23(9):1351-75)

Moreover, I do not think the 2-stage framework is correct when outcomes are rare, and a 1-stage model is more exact and appropriate. That is, the mvmeta module in Stata requires treatment effect estimates and their variances to be calculated for each study, and these are then pooled in a meta-analysis. However, when the event rate is low, there is a concern that such effect estimates are not normally distributed and variances are poorly estimated. This, a one-stage network meta-analysis that uses the exact binomial likelihood might be preferred. Did the authors consider this, or evaluate if their conclusions are robust to this issue?

See for example:
1. Riley RD, Jackson D, Salanti G, Burke DL, Price M, Kirkham J, et al. Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. BMJ. 2017;358:j3932.
2. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. Stat Methods Med Res. 2008;17(3):279-301.

10) Page 12: met-analysis should be meta-analysis

11) “We evaluated the potential inconsistencies… “ – more details are needed on what criteria they used to confirm consistency or inconsistency. These results should also be provided in the main text, as this is a fundamental part of a network meta-analysis.

12) It is not clear if the meta-regression described in the methods relates to the network meta-analysis or the pair-wise meta-analysis.

Regardless, meta-regression is very prone to study-level confounding, so I would class these as an exploratory analysis. In particular, the association of mean prostate volume and overall treatment effect is at the ecological level – what we really need is the association between individual prostate volume and individual treatment response.
This could only be ascertained from IPD and within-trial information, and so I strongly suggest the meta-regression of prostate volume is downplayed.

A nice paper in the BMJ on this recently is Fisher (Fisher DJ, Carpenter JR, Morris TP, et al. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? BMJ 2017;356:j573). Also see: Hua H, Burke DL, Crowther MJ, et al. One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. Stat Med 2017;36(5):772-89. doi: 10.1002/sim.7171

13) Multiple time-points are considered. Was the correlation across time-points accounted for? Or was a separate network meta-analysis done at each time-point? If the latter, then were most time-points available in most studies, such that missing time-points is not a big issue?

14) I find Table 2 hard to follow. Why are the authors using dichotomised values of prostate volume here?

15) Sometimes in the text the comparator group is difficult to identify

16 We need ranking plots added, and information about mean rank and SUCRAs, to help summarise the network meta-analysis results in more detail.

17) For the continuous outcomes, we need more details on whether the effect estimates were appropriately derived from analysis of covariance (i.e. after adjusting for baseline) in each trial, as this is the best method.[1] If not, then were effect estimates based on change scores or final value only? And if so, how might this influence the findings?

Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. Bmj. 2001;323(7321):1123-4.

18) Abstract conclusion says: ""The efficacy of vaporization in large prostates seems Questionable" – no results in the abstract relates to this point as far as I can tell? Also, see my comment about the concern of meta-regression of prostate volume above.

19) Moreover, the definition of large is arbitrary. "In the large prostate group (mean PV >70 gm), … " – we need to be looking at prostate volume as a continuous variable within trials before making strong conclusions

I think this is a sufficient set of comment for the authors to consider going forward and to inform the BMJ's decision. I hope my comments are ultimately helpful to all parties going forward, and will enhance the hard work of the authors to this point.
Best wishes, Prof Richard Riley

Additional Questions:
Please enter your name: Richard Riley

Job Title: Professor of Biostatistics

Institution: Keele University

Reimbursement for attending a symposium?: No

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A fee for organising education?: No

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