10-Nov-2016

Dear Dr. Thorlund

Manuscript ID BMJ.2016.035734 entitled "Patient-reported outcomes in patients undergoing arthroscopic partial meniscectomy for traumatic or degenerative meniscal tears: A comparative prospective cohort study"

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, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

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, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Tiago Villanueva
Assistant Editor
tvillanueva@bmj.com

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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: Wim Weber (Chair), Angie Wade (Statistician), Georg Roggla, Elizabeth Loder, Rubin Minhas, Amy Price, Daoxin Yin, John Fletcher, Tiago Villanueva

Decision: Put points

Detailed comments from the meeting:

First, 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.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:
Some points to note (probably nothing fatal):

1. The treatment of missing data is unclear and requires some amendment. Baseline observation carried forward has been shown to bias results and should not be used. The authors state that this was in addition to the imputation incorporated in the main analyses, the form of which is not specified, as they state that analytic techniques were selected to avoid missing value issues.

2. Although the authors have made amendments from the protocol, they give justification and this does not appear to have substantially affected the results.

3. As noted by Harris, there is an inconsistency between the difference used in the power calculation (8 points) and the difference used for excluding clinically important effects in the results (10 points).

4. Including in the sensitivity analyses only the participant characteristics from table 1 that are significant at 10% level may potentially miss associations. The excluded variables should be checked for association after adjustment for the other factors.

5. Some individuals are lost to follow up. The numbers presented in table 2 suggest that the losses may be a biased subsample and this should be investigated. For example, the average change from 3 to 12 months of KOOS4 in the TT group is 61.8-57.4 = 4.4 and for the DT group this is 66.2-58.7 = 7.5, a difference of 4.4-7.5 = -3.1, which is quite different to the difference of -5.3 in those that completed both assessments.

- One editor felt it was difficult to get a view on how much this added to the existing literature, but felt it read easily and seemed straightforward.

- Several editors were supportive and felt the paper was clinically relevant.

- Another editor said that until there is a trial this looks like it may be the best we have and it's good to cover an orthopaedic topic that is also relevant to primary care doctors.

- Our patient editor (who didn't participate in the meeting) wrote in a note that she couldn't see in the patient involvement box a description of how you had decided which outcomes to get patients to report. She wondered that if

you had no involvement, how do you know these are relevant outcomes? Finally, she added that if by contrast the outcomes were actually set by patients in any way, why have you not described that in the patient involvement box?

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:
The study is a comparative cohort study comparing the outcomes of arthroscopic partial meniscectomy (APM) in those with traumatic meniscus tears to those with degenerative meniscus tears (TT vs DT). The question is an important one because APM surgery is common and because although many previous studies have compared APM for DT to alternative treatments, there have been no such trials for TT.
A potential problem with this study is the poor definition of the type of tear (TT vs DT). The authors address this by providing several sensitivity analyses using different definitions, however this still requires some clarification (see below). The comments below mainly concern clarity of definitions as I found this somewhat confusing at times. I have no major issues with the methodology.
1. The definition of TT vs DT is unclear, and possibly varies from the published study protocol. The protocol states that all patients aged 18-34 and those aged 35-55 with 'violent' tears are TT – the rest being DT. The definition used in the study is not clear. The authors provide the definition (TT is defined as "Participants aged 18-34 years and replying that symptoms evolved as a result of a 'specific incident' or 'violent incident' AND participants aged 35-55 years replying symptoms evolving as a result of a 'violent incident'") but then state that it was changed "to include all participants aged between 18-55". All patients aged 18-55 were always included in all definitions, it is how they were divided into TT and DT that needs clarification. Was the definition changed prior to analysis (as stated)? Please provide a clear definition of the definition used in the analysis.
2. The authors provide several sensitivity analyses based on the definition of TT vs DT, which strengthens the study. However, I would have expected one of those definitions to be the definition used in the original published protocol in order to better address bias due to selective outcome analysis.
3. There is inconsistency between the power analysis and the primary outcome. The power analysis is based on a difference of 8 points in KOOS but the threshold for clinical importance chosen was a difference of 10 points.
4. For the sensitivity analysis using "null responder imputation" (which used baseline value carried forward, I cannot see how this was done "in addition to" the imputation methods used in the main analysis. Surely, it can only be one or the other. I also question the validity of using last observation carried forward using baseline observations. This may require input from a statistician.
5. Terminology around KOOS vs KOOS4 vs KOOS subscales vs KOOS4 subscales is confusing. If KOOS4 was used, then please define it once and use the term "KOOS4" throughout the results.
6. In table 3, the term "NTT" (a term used in the protocol for non traumatic tears) is used instead of "DT" (used throughout this manuscript)
7. The protocol lists many other outcomes, such as SF36, global perceived effect and adverse events. Are these to be reported in separate publications? This information would be helpful.

Additional Questions:
Please enter your name: Ian Harris

Job Title: Professor of Orthopaedic SUrgery

Institution: UNSW Australia

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: 2

Recommendation:

Comments:
The paper is very well written in all sections with respect to language and grammar. The script satisfies most of the STROBE criteria. However, I have a few comments and queries about the paper to the authors.

To Editor:
Statistics is not my forte so I would recommend the editor to evaluate the study with the help of a professional statistician for the validity and relevance of the sttistical tests used.

The paper is very well written and may be recommended after satisfactorily addressing the queries raised.

To the authors:

Details of structural pathology of menisci was collected in the methods and presented in the tables but not presented under results nor discussed the results in discussion with respect to the type of tear in relation to outcome. Salient findings and their relevance may be discussed for these as well as associated pathology in the knee.

What was the effect of tear type on the main outcome? Please discuss.

Did the authors have a chance to look at the effect of duration of symptoms and outcome?

Sensitivity analysis was mentioned to have been performed by adding degree of cartilage defects in addition to age, sex and BMI for the main outcome under the methods section. What was the outcome? Please discuss findings in the discussion. Although cartilage loss was presented under results, other parameters were not discussed.

Data and its meaning is not clear in supplementary table 1. What do the authors want to convey here? The legend of table indicates baseline data but why add assessed at 52 weeks here? Is the data baseline or at 52 weeks?

Under the unanswered section, the authors imply that APM is not useful in traumatic tears. I submit that this topic was not researched in this paper and preliminary glance indicates more than 50% patients were satisfied after APM in this group at 1 year and KOOS score seems to have significantly improved from preop status to 52 weeks post op. So the conclusion is not acceptable although the recommendation to conduct further study on that topic may be accepted

Authors seem to have given more weightage to the single item questions in the above recommendation. These questions were asked at 1 year and hence may suffer a retrospective memory bias and also these responses are subjective. There is definite improvement in KOOS scores assessed in these patients compared to the preoperative levels. Hence not recommending surgery to traumatic tears may not be appropriate, in my opinion, with the results presented by the authors.

Main difference in results between TT and DT may be related to presence of degenerative meniscal changes. If degenerative menisci are included in both groups, the results would probably be equal/ not significant. Have the authors considered this point and if yes, how did they exclude this effect? This would bring accuracy of visual assessment of meniscus through scopy into question.

How accurate is assessment of degenerative meniscus through arthroscope? Has this been validated with histological appearances? The authors note that majority are degenerative in the DT group. It would be interesting to see how many patients below age 40 and 45 are included in each group. This data is not presented and may be included in the supplementary data for those who are interested.

Additional Questions:
Please enter your name: Srinivas B S Kambhampati

Job Title: Consultant Orthopaedic Surgeon

Institution: Sri Dhaatri Orthopaedic Center

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Reviewer: 3

Recommendation:

Comments:
Thank you very much for asking me to review this interesting paper entitled: "Patient-reported outcomes in patients undergoing arthroscopic partial meniscectomy for traumatic or degenerative meniscal tears: A comparative prospective cohort study".

This group has spearheaded orthopaedic research in the recent decade, systematically addressing pivotal issues on the knee surgery, including the role of APM/knee instability/surgery of a torn ACL on knee symptoms and development of patient reported outcome instruments (including the primary outcome of the study) to study the efficacy of various interventions on knee function. Specifically regarding arthroscopic surgery for knee pain (which APM essentially is), the authors have recently published a meta-analysis (ref. #2) summarizing the evidence base on the efficacy of APM. These studies that can be considered efficacy trials, addressed whether APM is superior to physiotherapy or sham surgery under idealized ("can it work") circumstances. The authors demonstrated a small inconsequential benefit of APM for the degenerative knee (at best), an effect that was limited in time and absent at one to two years after surgery.

It probably comes as no surprise to anyone that many of our contemporary medical (particularly surgical) practices base on nothing but intuitively logical rationing: With no support aside from biological rationale, the indication for APM crept from locked knees in young patients to all patients of all ages with knee pain and "meniscus tears" of any sort. Once we started to assess our common practices more prudently, these "tears" seen either on magnetic resonance imaging or at arthroscopy, proved poorly associated with symptoms. Later, APM was also shown to be no better than conservative treatment or even sham surgery.

The submitted manuscript describes a study that I consider a comparative effectiveness "trial", assessing the effects of arthroscopic partial meniscectomy (APM) on traumatic vs. degenerative meniscus tears. This is one of the most pressing issues in the orthopaedics, as: a) APM is still (one of the) most common surgical procedures performed in the western world, b) recent evidence has seriously questioned the foundations (indications) of the procedure. In fact, traumatic tears are among the very few indications that still remain unchallenged (disputed) with respect to this particular procedure – most others have recently failed under scrutiny.

As noted, the authors have used a more pragmatic "real-life" approach of prospectively collecting all patients undergoing APM and then comparing the outcome for those with a traumatic tear (allegedly, those who should respond) to those with a non-traumatic / degenerative tear.

After a thorough review of the paper, here are my remarks, first using the PICO format (although the PICO format does not truly fit to this design, a prospective cohort):

P: Population is well-defined, represents a very generalizable (representative) group of patients (those for whom the APM surgery is generally recommended/performed), is well characterized (appropriate eligibility criteria and means to characterize the disease), and appropriate criteria are used to divide patients into "traumatic" and "degenerative" (although this aspect also represent the weakness of the study).

I: APM is a highly standardized procedure performed to millions of patients world-wide each year to treat a "symptomatic meniscus lesion".

C: The comparison between "active" (traumatic) and control (degenerative) is a reasonable one.

O: KOOS is probably the most widely used PROM in studying the efficacy of various interventions on patients with knee complaints/pain. 52-weeks is a reasonable follow-up period for such a minor surgery as the APM is.

The authors also provide a comprehensive protocol for the study, although they have chosen to tweak the statistical analysis somewhat from that described in the paper. However, the rationale for doing this is well argued and they also provide us with a number of sensitivity analyses to convince the reader that there seems to be no foul play due to the deviations from the original protocol.

Having said all this, there are some issues that I need to point out about the study:

1) Terminology: As we can all appreciate, definition of terms lies at the heart of any study and this is particularly pertinent to the study under scrutiny, as there is no universal consensus on the definition of the terms "trauma(tic)", non-traumatic/degenerative, mechanical symptoms (locking, catching). Having said that, this also highlights how obscure the situation is in clinical orthopedics: Surgeons commonly use these definitions in clinical decision-making despite the fact that they are vague, at best. Nevertheless, from a scientific perspective, this situation introduces an obvious source of bias, which the authors have attempted to address by having predefined (rationale) definitions for "symptom onset" and "mechanical symptoms" (page 7). As much as I appreciate the approach, I still wonder whether the authors should talk about "acute onset" vs. "gradual, non-traumatic onset", rather than "traumatic" vs. "degenerative". The downside of doing this, I must admit, is that the term "traumatic" is so commonly used (with no universal definition, I must add) that this fact almost justifies its' use here. Perhaps, the authors could still elaborate

on this in their discussion? Also, although the authors have provided us with a number of different sensitivity analyses, one potentially clinically-relevant analysis would be to divide patients based on the tear type/morphology, as advocates of APM commonly argue that meniscus tears with longitudinal tear pattern, bucket handle tear or flap are "unstable" (indication for APM), whereas radial, horizontal and complex were determined as stable (less optimal for the APM).

2) Conceptual remark: As noted above, the entire practice of carrying out APM for patients with knee pain basis on nothing but an intuitively rationale: The alleged link between symptoms and "meniscus tears" has been refuted - there is no way to determine whether a "tear" seen at arthroscopy or on MRI is symptomatic (causing pain), the performance of the clinical (meniscus) tests is equivalent to a coin toss… Should the onset of symptoms (see above) be the crux of this paper?

3) Observational vs. RCT data: An obvious concern related to this design is the observational nature of the study. Although the authors have provided us with a considerable amount of data suggesting that the analyses (comparison) are (is) valid, maybe a few words on the potential biases and on how they were addressed would be warranted.

After this lengthy elaboration, below please find my specific (minor) remarks on the paper:

1. What is already known about the subject, second bullet point: "above placebo", what is the study that has shown APM to provide a benefit (even short-term) above placebo?

2. Discussion, page 13: Prior evidence on "traumatic vs. degenerative": The authors already provide a few studies on this topic, but these two should probably also be included (and their results briefly discussed) given that the evidence on the topic is indeed so sparse (and surprisingly uniform).
a. Kim et al. 1
b. Ghislain et al. 2
1. Kim JR, Kim BG, Kim JW, et al. Traumatic and non-traumatic isolated horizontal meniscal tears of the knee in patients less than 40 years of age. Eur J Orthop Surg Traumatol 2013;23(5):589-93. doi: 10.1007/s00590-012-1028-6
2. Ghislain NA, Wei JN, Li YG. Study of the Clinical Outcome between Traumatic and Degenerative (non-traumatic) Meniscal Tears after Arthroscopic Surgery: A 4-Years Follow-up Study. J Clin Diagn Res 2016;10(4):RC01-4. doi: 10.7860/JCDR/2016/16686.7569

Additional Questions:
Please enter your name: Teppo Järvinen

Job Title: Professor

Institution: University of Helsinki

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

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g. Footnotes and statements

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