14-May-2022

BMJ-2022-070730 entitled "Surgical versus non-surgical treatment for sciatica: a systematic review and meta-analysis of randomised controlled trials"

Dear Dr. Liu,

Thank you for sending us your paper and for your patience while we have been considering it.

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.

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Dr Navjoyt Ladher Research Editor nladher@bmj.com

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Report from The BMJ's manuscript committee meeting

At the manuscript meeting the Editor makes the final decisions on accepting original papers submitted to the journal. Each article is discussed by The BMJ's international team of research editors and one statistician. When making decisions we take into account each paper's originality, scientific merits, and interest to a general readership in comparison with other submitted papers. We take reviewers' reports fully into account too, but the final decision on acceptance or rejection of a paper rests with the editors.

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Navjoyt Ladher (chair), Tim Cole (statistical editor), John Fletcher, Jessica Kimpton, Elizabeth Loder, Joe Ross, Di Wang, Wim Weber

Decision: Put points

Editors felt that your paper covered an important topic relevant to a broad clinical readership. However, there were several aspects of the research question that we felt needed clarifying in order to move forward with your paper - in particular what this review adds to earlier work. All the queries from research and statistical editors are listed below in the detailed comments from the meeting.

We ask that you please revise your paper to respond to the comments by the editors, and also the reviewers. Their reports are available at the end of this letter. 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.

Detailed comments from the meeting:

Statistical editor -

* All languages, all alternative interventions, focused patient groups, recent search – looks well done.

* One of 24 included papers a conference abstract [52] - surprising that this would include sufficient information for a meta-analysis. Can the authors clarify please?

* Last sentence of conclusion states: "Discectomy may be an option for people who require rapid leg pain relief and disability improvement." - how helpful is this as surely all patients want rapid leg pain relief?

Research editors -

*The 2007 Cochrane review on "Surgical interventions for lumbar disc prolapse" included 40 trials and 2 non-randomised studies - many more than were included in this systematic review. The conclusions were similar. There are another 16 Cochrane reviews in the library evaluating treatments for sciatica. How much does this new review add?

*Looks to be a well done meta-analysis on this research question, but there are many published meta-analyses, including network meta-analyses, with very similar conclusions. Can the authors clarify what this study adds to earlier work, and should the major earlier reviews be referenced?

* This is an important and still contentious issue. However, I thought it's currently well acknowledged that nonsurgical care remains the mainstay of initial treatment for most patients with lumbar disc herniation, while those with persistent symptoms despite adequate conservative therapy are considered for surgery[Int J Spine Surg. 2020 Feb; 14(1): 1–17]. Thus I would be more interested in a slightly modified RQ: how well does surgery work for patients who have failed the initial non-surgical treatment (rather than "any patient").

* The publication of included studies spans 1983~2021- could any evolvement of either non-surgical or surgical therapies modify the results?

* The title: "surgical versus non-surgical treatment for sciatica", is it more accurate to use "lumbar disc herniation with Radiculopathy"?

* The "non-surgical (non-pharmacological or pharmacological) treatment" seems to cover a wide range of different therapies and varied greatly across studies (table 1). Should this be further categorized to more homogeneous subgroups to see how the findings might change?

* Nonsurgical treatment approaches vary widely. I agree with the reviewer who wonders why the authors are so careful to distinguish various interventional/surgical techniques but lump all nonsurgical treatments together. Looking at Table 1, some nonsurgical groups got bedrest, others got various unusual types of massage, educational booklets, or various medications. I would like to know what the "analgesics" used might have been. I wonder if, as doctors use fewer opioids, patients who are suffering from severe pain are more likely to choose surgery. If nonsurgical treatment were standardized, intensive, and timely, perhaps fewer people would need surgery.

* It's surprising to see so many RCTs did not report loss-to-follow-up and cross-over (table 1), which is very important. Is this information obtainable?

* The crossover rates are tremendously high. Perhaps this is unsurprising since as one of the reviewers notes, these are patients with imaging findings suggesting a need for surgery. On the other hand, who would agree to be randomized to surgery vs nonsurgical approaches? They must be people who would like to avoid surgery if possible, or perhaps have less severe pain. This makes the crossover numbers even more concerning. I agree with the authors that this may end up underestimating the benefits of surgery.

* Adverse events - there were quite a few dural tears in the discectomy groups. I wonder how carefully participants were followed up for long term problems from these and other AEs. The interpretation could do a better job of incorporating information about adverse events with information about benefits.

* given that nearly all of these studies did not blind patients or the assessors, it's difficult to conclude the superiority of discetomy. Is more caution required around the conclusion?

* It is difficult to get a feel for the magnitude or clinical importance of the pain relief or disability reductions achieved with discectomy. Is it possible to make these outcomes more understandable for patients or lay readers?

*Ref. 14 is not a systematic review, as stated on p.5 and 13.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

This is a very comprehensive review on an important subject. There is a lot of information here and the conclusions seem reasonable. There are a few issues, some major, that I believe warrant attention and perhaps a very major revision.

1. There may be some 'bias' in that there are people from major specialties but no pain medicine physicians on this. That said, I do think the conclusions are objective, but here's how it affects these findings. The authors divide the surgeries into types of surgeries, but they do not do the same for

comparators. For example, there are different types of epidural steroid injections, but the authors do not specify the type unless it's listed in the title. This is important because particularly for a herniated disc which is more likely to cause unilateral pain, transforaminal ESI are generally acknowledged to be more efficacious. The same hold true for pharmacological treatments, with antidepressants have the strongest evidence for efficacy (but not strong), gabapentinoids having conflicting evidence, and very little evidence for NSAIDs and muscle relaxants, which are often used (not even mentioned on guidelines for neuropathic pain).

2. The authors consider treatments such as plasma disc decompression, ozone ablation and chemonucleolysis to be "surgical", but many people would disagree. In fact, the websites Wikipedia and Spine-Health specifically refer to chemonucleolysis as non-surgical. They are percutaneous like ESI and involve injections into disc that radiologists and pain doctors do (like platelet-rich plasma injected into discs, older intradiscal ablative treatments that were modified to treat herniated disc and treatments such as nucleoplasty or disc DeKompressor). These percutaneous treatments are also only indicated for small herniations (and often "contained").

3. Page 5, introduction: Minor point, but it is contestable (and probably not true) that HNP accounts for 90% of cases of sciatica. It certainly depends on the population, but as IASP recommends, "sciatica" is non-specific (really a lay term) and usually refers to radicular pain, which can be caused by HNP, stenosis or even degenerative disc degeneration with complete annular tears (chemical irritation). Moreover, HNP and spinal stenosis often co-occur, with one recent study finding this happens almost 25% of the time (Mutubuki et al. Eur J Pain 2020).

4. Page 6, line 30: You probably mean "radiologic" rather than radiographic, as x-rays cannot identify disc herniation.

5. Page 7, lines 12-14: I would defer to a statistician but I'm not sure that "borrowing" SDs from similar studies is valid (since they may vary significantly and they are very important for statistical analysis).6. Bottom of page 8: Please note whether (or which) of the surgeries included fusions or instrumentation (often used for multi-level procedures or those accompanied by instability). It is also likely that single vs. multi-level procedures have different outcomes.

7. Dividing symptoms duration into < or > 3 months doesn't seem to be a good cutoff besides that that is the cutoff that IASP uses to separate acute from chronic pain. Some payers (and guidelines) don't authorize or recommend injections or surgeries for acute pain because the natural course is for improvement. In a validated instrument evaluating ESI (Bicket et al. Reg Anesth Pain Med 2016, AQUARIUS), the international panel concluded that studies should ideally not be done in those with < 3 months of pain, while similar problems arise in people with long-standing (> 2 years) of pain (i.e. central sensitization).

8. In the text, I would note mortality or serious complication rates between groups. It will of course not be statistically significant because of the low numbers, but the deaths of a few people is incredibly important & clinically relevant- and few people ever view supplemental files.

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Recommendation:

Comments:

This systematic review and meta-analysis examines the efficacy/effectiveness and safety of surgical versus non-surgical treatment for people with sciatica. Based on 24 included studies (of mostly high risk of bias), the authors report that there is low to very low certainty evidence that discectomy is superior to non-surgical treatment in reducing leg pain and disability in people with sciatica. These effects seem to decline over time.

Overall, this review is methodologically sound, including pre-registration and carefully written. The authors have gone into much detail in organising and presenting their data and I particularly like the details available in the supplementary files.

My main concerns are the following:

1. Currently the emphasis is strongly on discectomy with only limited information in the main paper about other surgical options. This does not fit with the title or the objective of the manuscript which includes any type of surgery. I would advise the authors to put less emphasis on discectomy, and potentially include an overall meta-analysis, independent of type of surgery (see my comment below). 2. The authors point out the very high cross-over rates in many studies, which may well influence the interpretation of this review. These are included in table format, but I suggest mentioning them in text in the results section as well, as this is a major problem in this literature that limits (or prevents?) interpretation. Would it be possible to do a sensitivity analysis, excluding those papers with high cross over? Or had all papers such high cross over?

3. My third and most important concern is a clinical one: as the authors correctly mention in the introduction and discussion, current care for patients with sciatica is a stepwise model of care starting with conservative treatment which is then escalated to injections or surgery. This means that if a patient is considered for surgery, in most instances they will have had a course of 'failed' non-surgical care (unless there is significant motor deficit). Second, patients who can ethically be put forward for surgery have to have a clear indication for surgery (e.g, clear disc herniation). However many patients with sciatica do not have a clear MRI finding which indicates surgery. Therefore, studies using surgery already involve a highly select group of patients. So my question is: how valid is the comparison of surgery and non-surgical care in a population that has a) a clear indication for surgery and b) is likely to already have failed conservative care? Is that really a fair (and useful) comparison?

In order to address this important issue, I suggest the authors carefully evaluate the inclusion criteria of the included studies. How were these populations defined? Did they have standard care (e.g., had to fail non-surgical care to be considered for surgery), or did studies indeed include patients who did not have previous non-surgical treatment (I suspect this is highly unlikely as potentially unethical). Did they have a clear indication for surgery? Importantly, I suggest that this point is added in the discussion to put the results (and the potentially biased question) in perspective. E.g, the authors' recommendation to encourage clinicians to discuss potential rapid relief of leg pain with surgery and the potential need for delayed surgery seems supported by their review findings, however this is most likely based on a population that has already failed conservative care and has a clear indication for surgery and is therefore unlikely to be generalised to the broader population of 'sciatica'. Pending the findings of the analysis of the inclusion criteria, but I would predict that this statement is likely overstating the actual clinical implications of this review.

Additional comments:

Methods:

Page 7, line 12: when it was not possible to estimate SD, the authors borrowed them from a similar study included in the review. Why were authors not contacted for data? How was 'similar study' defined? Also, in how many instances was this the case?

I commend the authors for including industry funding without declaration of autonomy as part of their risk of bias assessment.

Why were continuous pain and disability outcomes transformed to a 0-100 scale? The use of standardized mean differences would have corrected for the differences in scales. For interpretability

particularly of the well-established disability scales I think the actual numbers would be more useful rather than a transformed number (particularly for clinicians who I think will be the main audience for this review). What was the reasoning of using transformation rather than standardised mean differences and reporting raw data?

Subgroup analyses: The original protocol only included one subgroup analysis for duration of symptoms. Therefore, the additional subgroup analyses reported in the paper should be declared as post-hoc analyses.

The authors decided to use the ACP guidelines for low back pain to classify the size of effects as they did not was to adopt an approach on arbitrary minimum clinically important thresholds. Can you explain why you consider these effect sizes to be less arbitrary?

Results:

There are inconsistencies in the flow diagram, the numbers do not add up. For instance, the total records identified from all databases add up to 3765. Duplicates add up to 1169. 3765-1169=2596. However, the flow chart says 2569 studies were screened. Then again, 64 studies were assessed for eligibility, and 38 excluded. This would amount to a total of 26 studies included in the review, however only 24 were included. Can you please check these discrepancies?

Apparently 18 trials did not blind participants and personnel. Can you clarify whether that was indeed 'AND'? Blinding of participants is not possible in e.g., a surgery vs pharmacology trial and only potentially achievable in sham surgery trials. But blinding of personnel is essential. Is it too strict to downgrade a study if patients were not blinded in such study designs but personnel was?

The review title is "surgical versus non-surgical treatment for sciatica". However, the study focusses strongly on discectomy as a type of surgery with most other analyses moved to supplemental data and given little room in discussion and abstract. To address the study title, I would have expected an overall meta-analysis independent of type of surgery and non-surgical treatment. This could have been followed by the currently presented subgroup analyses, as I agree that in particular the conservative treatments are heterogenous and worthwhile to explore separately.

In the results section, results are divided into subgroup and sensitivity analysis. I suggest that this is also separated in the methods section: which analyses were sensitivity analyses and which subgroup analyses.

Discussion: I suggest pointing out that the non-surgical comparison group is highly heterogenous (e.g, including pharmacology, physiotherapy, advice, combination therapy). I agree it is not worthwhile splitting them up, but this should at least be pointed out in the discussion to recognise the complexity/heterogeneity.

Table 1: please correct Table title: comparing

Supplemental material:

Supplemental file 1: The search terms contain several spelling mistakes, which could have led to missing studies. E.g., discectomy which is the main surgical procedure of interest in this review is misspelt with a k in several searches. Further, dickectomy is included in the search terms (thank you for the giggle, I wonder what the searches revealed on this term). I would recommend to rerun the searches where these spelling mistakes were made to assure no studies were missed.

Supplemental file 10: Meta-regression Why was the mean duration of symptoms analysed as a dichotomised variable in the meta-regression and not a continuous variable? Also for study size: why dichotomising rather than leaving the measure continuous to avoid losing information?

Overall: in several places discectomy is misspelt as diskectomy, e.g., Supplemental file 2.

Not all abbreviations added to legends of tables, e.g., NR

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