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Response Letter to the Editor—Diamond et al, JBMR

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Response to Letter to Editor – Diamond T et al., JBMR

The ASBMR Task Force on vertebral augmentation stands by their recommendations that cast doubt on the clinical importance of vertebral augmentation procedures, including vertebroplasty, for the treatment of painful osteoporotic vertebral fractures (1). We also strongly refute bias in our report. The ASBMR Task Force commenced late in 2013, two years prior to the published protocol for the VAPOUR trial (2), and comprised experts from previously published blinded vertebral augmentation trials, biomechanics, epidemiology, physical therapy and rehabilitation, exercise, endocrinology, rheumatology and internal medicine. No member had any conflict of interest. The two ASBMR Task Force reports (1,3) both underwent the normal peer review process by *JBMR*, but were not sent out for external consultation prior to review, as is normal practice for ASBMR Task Force reports.

While the authors note that their complaint against the recent Cochrane review (4) has been published on the Cochrane website, they failed to acknowledge that a detailed response clearly refuting their claims of bias and misrepresentation of the published data, has also been published (5). We are not yet privy to their detailed rebuttal that has been accepted for publication, but we remain unconvinced that their arguments should sway us from our synthesis of the available evidence.

The Cochrane review considered the totality of the evidence about vertebroplasty by synthesising evidence from all available randomised controlled trials. It included 21 trials; five compared vertebroplasty with placebo (541 randomised participants), eight with usual care (1126 randomised participants), seven with kyphoplasty (968 randomised participants) and one compared vertebroplasty with facet joint glucocorticoid injection (217 randomised participants). While clinical and technical differences existed across many of the trials, the decision to pool the data appears to be vindicated by the consistency of the findings across the five placebo-controlled trials included, as can be seen by visual inspection of the forest plots that display almost no statistical heterogeneity. Excluding VAPOUR from these analyses would not have altered any of the ASBMR Task Force's recommendations.

As previously detailed (5), while VAPOUR found that the proportion of participants with pain scores <4 out of 10 favoured the vertebroplasty group at all time points, the point estimates of differences between groups with respect to mean pain as measured by the numerical rating scale (NRS) was only of clinical relevance at 2-3 days and there were no between-group differences at any other time point. There were also no between-group differences in mean pain measured by visual analog scale (VAS) in the subgroup who completed VAS assessments at 14 days and 6 months. This suggests that a slightly different cut-off for improvement (e.g. a NRS score of ≤4) may have yielded results more consistent with the null effect demonstrated in the pain data analysed as continuous

variables. The Cochrane review (4), as well as a published evidence-based review of VAPOUR (6), outline other potential biases that may have resulted in an overestimate of the benefit of vertebroplasty in this trial.

On well-grounded methodologic principles, the lack of an overall benefit of vertebroplasty over a placebo procedure indicates that subgroup analyses must be viewed cautiously. For the procedure to be effective in one subgroup, it follows it must be harmful for another group in order to sum to a null effect. While Diamond et al. note that VAPOUR included a study population with symptoms of <6 weeks' duration, they appear to dismiss the evidence from the other four placebo-controlled trials that also included participants with short symptom duration, none of which support their assertion that symptom duration is a significant treatment effect modifier (7-10).

Notwithstanding delays in receipt of trial intervention in VERTOS IV, which included participants with symptom duration of ≤9 weeks, the majority appear to have had duration of pain for ≤6 weeks (7). The VOPE trial, that Diamond et al. also appear to dismiss, is published as a PhD thesis and included 52 participants with symptom duration of ≤8 weeks (8). Neither trial found a clinically relevant benefit of vertebroplasty over placebo. The other two placebo-controlled trials (9, 10) included a total of 57 (27%) participants with pain duration ≤6 weeks, in whom the value of vertebroplasty was previously investigated in individual patient data meta-analyses (11). These adequately powered subgroup analyses also failed to show an advantage for vertebroplasty over placebo. As outlined in the Cochrane review (4), the 2016 open label trial by Yang et al. (12) appears to be unregistered and is at high risk of selection, performance and attrition bias, and therefore its results must be viewed with caution.

In reaching consensus on our recommendations regarding vertebral augmentation, the ASBMR Task Force also considered its potential harms. While we indicate there is uncertainty around the risk estimates of harms with vertebroplasty (1), clinically important harms including respiratory failure, cement perforation of the heart, cord compression, osteomyelitis and death have been reported. In an audit of outcomes among 850 patients with an average age of 78.9 years who underwent vertebroplasty or kyphoplasty in 2011-2012 identified from the American College of Surgeons National Surgical Quality Improvement Program database, 9.5% had any adverse event, 6.6% had a serious adverse event, 1.5% died, and 10.8% were readmitted within 30 days of the procedure (13). To put these data in perspective, the 30-day readmission rate among a large cohort of patients (>15,000) in a large US multicentre clinical registry who underwent lumbar spine surgery in 2012 was 4.4% (14).

The ASBMR Task Force report also indicated that an increased risk of incident symptomatic vertebral fractures arising due to vertebroplasty cannot be excluded (1). Data from six trials reported more incident symptomatic vertebral fractures arose in the vertebroplasty group

(48/418) compared with 31/422 in the control group, with an RR of 1.29 (95% CI 0.46 to 3.62).

After evaluating the totality of the evidence for vertebroplasty, we believe the potential harms of vertebroplasty outweigh any potential benefits. Similarly limiting the procedure to those with symptoms of ≤3 weeks, risks providing an unnecessary and potentially harmful treatment for the majority of patients whose symptoms are likely to improve quickly irrespective of treatment, consistent with the natural history of painful osteoporotic vertebral fractures.

We strongly consider that both clinicians and patients should be well-informed before choosing vertebral augmentation and believe our ASBMR Task Force reports provide this evidence. Efforts should now be directed towards identifying promising alternative approaches for people with painful osteoporotic vertebral fractures, including bracing and exercise. We should also ensure that such treatments are evaluated in high quality, randomized, placebo-controlled trials and be of proven benefit prior to their introduction into routine clinical care.
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References

1. Ebeling PR, Akesson K, Bauer DC, Buchbinder R, Eastell R, Fink HA, Giangregorio L, Guanabens N, Kado D, Kallmes D, Katzman W, Rodriguez A, Wermers R, Wilson HA, Bouxsein ML. The Efficacy and Safety of Vertebral Augmentation: A Second ASBMR Task Force Report. *J Bone Miner Res*. 2019; 34:3-21.

2. Clark W, Bird P, Diamond T, Gonski P. Vertebroplasty for acute painful osteoporotic fractures (VAPOUR): study protocol for a randomized controlled trial. *Trials.* 2015; 16:159.

3. Rodriguez AJ, Fink HA, Mirigian L, Guañabens N, Eastell R, Akesson K, Bauer DC, Ebeling PR. Pain, Quality of Life, and Safety Outcomes of Kyphoplasty for Vertebral Compression Fractures: Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2017; 32:1935-1944.

4. Buchbinder R, Johnston R, Rischin KJ, Golmohammadi K, Jones A, Homik J, Kallmes DF. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture (Updated Review). *Cochrane Database of Systematic Reviews* 2018; Issue 11. Art. No.: CD006349. DOI:10.1002/14651858.CD006349.pub4.

5. Reply to Dr Clark complaint 3 June 2018. Available at https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006349.pub4/detailed-comment/en?messageId=167125591

6. Buchbinder R, Kallmes DF, Deyo R, Jarvik JJ. Commentary: Conduct and reporting of a vertebroplasty trial warrants critical examination. *Evidence Based Medicine* 2017; 22:106-7.

7. Firanescu CE, de Vries J, Lodder P, et al. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomised sham controlled clinical trial. *BMJ* 2018; 361.

8. Hansen EJ. A double-blind randomized clinical study comparing vertebroplasty with a SHAM procedure for acute osteoporotic vertebral compression fractures (VOPE). Thesis, University of Southern Denmark: Center for Spine Surgery and Research, Middelfart Hospital and Institute of Regional Health Research, University of Southern Denmark, Denmark 2015.

9. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009; 361:557-68.

10. Kallmes DF, Comstock BA, Heagerty PJ et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009; 361:569-579.

11. Staples MP, Kallmes DF, Comstock BA, et al. Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: meta-analysis. *BMJ* 2011; 342:d3952.

12. Yang EZ, Xu JG, Huang GZ, et al. Percutaneous vertebroplasty versus conservative treatment in aged patients with acute osteoporotic vertebral compression fractures. *Spine* 2016; 41:653–656.

13. Toy JO, Basques BA, Grauer JN. Morbidity, mortality, and readmission after vertebral augmentation: Analysis of 850 patients from the American College of Surgeons National Surgical Quality Improvement Program Database. *Spine* 2014; 39:1943–9.

14. Pugely AJ, Martin CT, Gao Y, Mendoza-Lattes S. Causes and risk factors for 30-day unplanned readmissions after lumbar spine surgery. *Spine* 2014; 39:761-8.