



Bone & Joint Research

Sabharwal S, Patel NK, Griffiths D, et al. Trials based on specific fracture configuration and surgical procedures likely to be more relevant for decision making in the management of fractures of the proximal humerus: findings of a meta-analysis. *Bone Joint Res* 2016;5:470-480.

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Authors' reply:

Comparing apples and oranges: a response to 'Going far beyond the evidence'

27 October 2016

Sir,

We welcome this letter from a research group at the forefront of clinical research evaluating the management of proximal humerus fractures. Their criticisms of our study¹ are mostly fair and not surprising. When reading our paper, Handoll and colleagues would have recognised the sizeable section on study limitations that we reported. Many of their comments overlap with what we have presented and we shall address each point specifically.

'Inadequate selection of outcomes and presentation of the evidence': A wide range of outcome measures has been reported among the existing randomized trials. Pooling each of these outcomes is challenging for the purpose of a meta-analysis presented as a paper in a journal compared with the expansive reporting that is feasible in a Cochrane Review. Furthermore, the four outcomes of interest (the Constant score, health utilities, additional surgery, and the defined adverse events) each have important applications to clinical decision making. The criticism of use of the Constant score as a single functional measure is valid, however, at the time our analysis was performed, the PROximal Fracture of the Humerus: Evaluation by Randomisation (PROFHER) trial² was the only study to have used the Oxford Shoulder Score. Health utilities are an important outcome, specifically as their application in economic evaluation informs health policy, and the existing research carries enough trials to include them in a meta-analysis. Secondary surgery is also an important outcome because of the impact it has on the patient. Our analysis of adverse events or complications was presented in a restrictive way because there is a distinct lack of agreement on what a complication is. The PROFHER trial reported 14 different types of complications (not including secondary surgery), whereas Stableforth's study from 1984 reported just one.³ Avascular necrosis, osteoarthritis and nonunions will all impact on a patient's life. Clinical decision making requires some knowledge of differences in functional and clinical outcomes to guide treatment. A young active patient with a shoulder fracture may value a slightly improved functional outcome with the risk of a treatment complication more than would a frail sedentary patient with ongoing medical illness. The outcomes we have presented are incomplete, and not inadequate, as Handoll and colleagues have suggested.

'Inappropriate subgroup analyses': Subgroup analysis is a commonly utilised tool in meta-analysis.⁴ Within our limitations section we asserted 'it is important to state that subgroup analysis is an observational method that identifies possible variables that drive heterogeneity.' We defined our subgroup variable *a priori* based on the biological plausibility that fracture morphology affects outcomes. The classification of subgroup variables is clearly defined in the Methods and an inability to perform meta-regression is also reported. We did not, as Handoll and colleagues correctly state, report on the subgroup analysis performed within the PROFHER trial. We did report on what the subgroups of fractures included (Table I), and it is worth pointing out that the debate on this subject would probably not exist if the subgroup of four-part fractures in the PROFHER trial were substantially greater than the 11 out of a total of 250 patients that were evaluated.

'Incorrect interpretation of results': Handoll and colleagues stated that caution is required in the interpretation of our results based on the limited sample size of our meta-analysis. We stated in our limitations that 'because the number of trials included was small, the sample size of subgroup analysis was also small, which probably resulted in large confidence intervals which are seen throughout this analysis. This suggests less than precise point estimates'. Their letter also states that, because the GRADE assessment found weak estimated effects, it was curious that we used our subgroup analysis to support our conclusions. Again, this point was presented to the readers in our limitations section. While the question is raised on the value of Olerud et al's study⁵ in relation to health utility data, it is worth noting that this study included 49 patients with a four-part proximal humeral fracture. This was, by far, the largest study in relation to four-part fractures. Furthermore, we have not advocated surgical treatment for four-part fractures as a result of our findings. We have simply suggested that the subgroup differences raise the question of whether an 'apples and oranges' approach is suitable for future research.

We were surprised that Handoll and colleagues considered our conclusion and study title to be bold, unsubstantiated and headline-grabbing. Our title is "Trials based on specific fracture configuration and surgical procedures likely to be more relevant for decision making in the management of fractures of the proximal humerus". This is a suggestion that different types of fractures and different management strategies may affect clinical decision making. There is no statement of superiority of treatments, nor is there a statement that the existing evidence base has no value. Selected outcomes of interest that our authorship viewed to be relevant to decision making in a clinical setting were evaluated, and statistical heterogeneity, as well as differences in treatment effects, were identified through subgroup and sensitivity analysis. Our conduct was fair, transparent and the numerous limitations are described in depth. Within our paper, we reported the PROFHER trial to be the most methodologically robust randomised controlled trial (RCT). We also commended its population size and its superiority with regard to external validity. Despite its excellence, the PROFHER trial is not the endpoint of research in this field. Murray et al⁶ quite elegantly depicted their approach for treatment as a triangle based on patient factors, fracture personality and surgical factors that converged on an apex of absolute indication for surgical treatment. Surgical decision making is complex, and pragmatic trial design has its limitations when applying its findings to clinical practice. Does the current evidence base offer a definitive answer to clinicians when dealing with the various fracture complexities, patient factors (particularly frailty) and surgical considerations? The answer is no. Future pragmatic trials that are sufficiently powered to guide treatment on individual subgroups are needed. At this point, neither the PROFHER trial nor any of the other RCTs has the strength to inform decision making for more complex fractures where surgical treatment and the type of surgical treatment are important factors that orthopaedic surgeons must consider. We have proposed a direction for future research in this field and we welcome a strong debate on the matter.

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1. **Sabharwal S, Patel NK, Griffiths D, et al.** Trials based on specific fracture configuration and surgical procedures likely to be more relevant for decision making in the management of fractures of the proximal humerus: findings of a meta-analysis. *Bone Joint Res* 2016;5:470-480.
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Conflict of Interest: None declared