THE AUTHORS RESPOND

Dr. Heeckt and colleagues have raised a number of potential issues with our systematic review and network meta-analysis on low-intensity pulsed ultrasound (LIPUS) versus electrical stimulation for fracture healing.[1]

Their first concern was that "fracture nonunion was improperly defined," specifically with respect to our definition of fracture union only including bridging at 4 cortices, and our decision to merge possible union (bridging at 3 cortices) and nonunion (bridging at ≤ 2 cortices) into 1 category (nonunion). To facilitate our standard meta-analyses and network meta-analysis, we dichotomized the outcome of fracture union to create a common outcome measure across trials. Our decision to merge possible union and nonunion into 1 category was informed by an experienced orthopedic surgeon who was blinded to the eligible studies in our review. This description was provided in the "Synthesis of results" subsection in the Methods section of our review.

Their second concern was that "reduced time to radiographic union was considered a surrogate end point." Dr. Heeckt and colleagues cited a survey,[2] led by one of us (M.B.), that found orthopedic surgeons consider radiographic outcomes to be more important than functional outcomes when designing clinical trials. Our systematic review specifically considered patient-important outcomes (Table 4, Question C in the systematic review). Return to functioning is a patient-important outcome, whereas radiographic outcomes are an indirect measure of functional recovery. This is an important distinction for readers, as improvements in surrogate outcomes may not translate to commensurate improvements in function. A systematic review by Busse and colleagues[3] on the effectiveness of LIPUS for fracture healing found that although there was low-quality evidence from 6 trials to suggest that LIPUS was effective in reducing time to radiographic healing, only 4 trials directly assessed functional recovery, with 3 showing no effect.

Their third concern was that "seminal LIPUS papers were omitted." Our extraction and analysis did include data from the trials they cited as being omitted,[4,5] but the cited references were incorrect. Thank you for bringing this to our attention; we have now provided the correct references to *CJS*.

Their fourth concern was that "the selection of studies for analysis was biased" and that studies with high risk of bias should have been excluded. Although these studies suffer from high risk of bias in multiple components on the Cochrane Risk of Bias tool, this does not warrant exclusion of the studies simply on the basis of risk of bias. It is inappropriate to exclude studies from meta-analyses based on arbitrary thresholds for study quality without first conducting subgroup analyses to explore whether or not treatment effect estimates differ among trials with low risk of bias and trials with high risk of bias.[6] We planned to perform such subgroup analyses to explore components of risk of bias as a factor to explain heterogeneity in treatment effect estimates, and we included this in our review as follows:

> We generated the following a priori hypothesis to explain variability between studies: studies with greater risk of bias will have larger effects than studies with lower risk of bias. This subgroup analysis was completed only on a risk of bias component × component basis if there was considerable variability within the risk of bias component. On consulting with a methodologist, we performed subgroup analyses only when there were at least 5 studies to avoid high risk of spurious subgroup findings.[1]

Given that each of our analyses consisted of fewer than 5 trials, we were underpowered to perform subgroup analyses to explore risk of bias as a factor to explain heterogeneity in effect estimates. To provide transparency to readers, we provided a risk of bias summary and a GRADE summary of findings table (Table 2 and 3 in the systematic review[1]). Additionally, the ESTIM studies (with multiple components of high risk of bias) were not excluded from our review because of risk of bias, but because they did not report the outcome of interest (union rates) for our analysis. This was described in our Results section as follows:

> Eight trials evaluating LIPUS (7 fresh fracture and 1 nonunion populations), and 7 trials evaluating ESTIM (3 fresh fracture and 5 nonunion populations), reported union rates as one of their outcomes and were used in the network meta-analyses.[1]

Their final concern was the claim that "whether fractures were fresh or nonunion prior to treatment was ignored." This distinction was not ignored in our review and we separated these 2 types of fractures in our analyses. This was stated in our objectives as follows:

> (...) to systematically review the LIPUS and ESTIM literature and perform a network meta-analysis of these 2 treatments for accelerating fracture healing in both fresh fracture and nonunion populations.[1]

We also provided the results separately for these 2 populations — we found that in patients with a fresh fracture, there was a nonsignificant benefit of LIPUS versus standard care and ESTIM on union rates at 6 months, and in patients with an existing nonunion or delayed union, we found a nonsignificant benefit of ESTIM over standard care on union rates at 3 months.

We thank Dr. Heeckt and colleagues for their interest in our paper and continue to believe our findings represent a careful and systematic review and analysis of the literature. Ultimately, the goal of our review was to shed light on knowledge gaps and we stand by our recommendation for large head-to-head trials with safeguards against bias that assess patient-important outcomes to confirm or refute the role of bone stimulation devices for fracture healing in either fresh fracture or nonunion populations.

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