Inappropriate Conclusion from Meta-analysis of Randomized Controlled Trials

To the Editor:
Paul et al.1 should be congratulated for examining the body of evidence on the comparison of patient-controlled analgesia opioid or epidural analgesia with femoral nerve blockade for analgesia after a common operation, total knee arthroplasty. A meta-analysis, by pooling and analyzing statistically the results from several combinable studies, can increase the statistical power to detect small but clinically important treatment harms and effects. Paul et al. clearly demonstrated that femoral nerve blockade improved analgesia and reduced opioid consumption compared with intravenous patient-controlled analgesia techniques.

The quality of the systematic review performed by Paul et al. is high, as evidenced by the comprehensive and systematic search of the literature and explanation of statistical tests and models used for their analyses. Furthermore, the authors (and the accompanying editorial2) clearly emphasize the limitations of their meta-analysis regarding comparison of single shot femoral nerve block (SSFNB) with continuous femoral nerve blockade (CFFFNB) with continuous femoral nerve block, including that:

1. Most of the data come from indirect comparisons, which are subject to the same biases as observational studies.
2. Only two trials with a total of 69 patients directly compared the two techniques, and they came to conflicting conclusions.3,4
3. The different conclusions may be explained by the different local anesthetics used in these two studies (ropivacaine vs. bupivacaine), so we question the appropriateness of combining these studies in a meta-analysis in which the type and dosage of local anesthetics are not considered a source of heterogeneity (as in this meta-analysis).
4. Other studies exist, not included in this meta-analysis (for correct reasons), that contribute to the evidence base comparing SSFNB with continuous femoral nerve block. These other studies support the use of continuous techniques.5

In reality there was only one study4 comparing SSFNB with continuous femoral nerve block that used a technique considered clinically appropriate in 2010. In view of this and the above points, we were somewhat mystified by the contents of the highlighted box on the first page of the article, which stated “these studies do not demonstrate further improvement with continuous compared with single-shot femoral nerve block.” This finding, one of only two key findings in the highlighted box, is based on data which, by the authors’ own admission, are “subject to the same biases as observational studies.” This is inconsistent with the subtitle of the article, “A Meta-analysis of Randomized Controlled Trials,” which suggests that the key results will be of the highest level of evidence.

We believe that this key message contained within the highlighted box is misleading and unsupported by the data, discussion, and accompanying editorial. This falls below the standard expected of a scientifically informed and scholarly process and does not do justice to the excellent meta-analysis and editorial.

On the issue of comparison of SSFNB and continuous femoral nerve block, the meta-analysis could come to only one conclusion: that there is conflicting evidence and more studies are required to determine which techniques are most appropriate for femoral nerve blockade for total knee arthroplasty. Anesthesia appears to be promoting SSFNB in preference to continuous techniques for total knee arthroplasty. This is not an accurate reflection of current evidence and may influence practitioners’ opinions, including those of surgeons, which may inhibit both appropriate clinical practice and innovation in this area.

We would strongly agree with the editorial2 that continuous catheter techniques provide the ability to control the dosage of local anesthetic used and are preferred to SSFNB, where the inevitable tendency is to increase the initial dose, potentially impairing motor function. Analgesia is not the only goal of femoral nerve blockade, and early mobilization is a realistic goal when dilute concentrations of local anesthetic are used in a controlled fashion. Readers should be reminded that lack of evidence is not the same as evidence of lack of effect, and the commonsense approach outlined in the editorial should be strongly considered.


References

This letter was also sent to the author of the referenced Editorial, who felt that a reply was not necessary.
In Reply:
We thank Drs. Barrington, Olive, and Kluger for their interest in our recent meta-analysis of femoral nerve block for total knee arthroplasty and for the opportunity to respond to their concerns. The concern raised is that the key message in the highlighted box on the first page of the article, “that these studies did not demonstrate further improvement with continuous compared with single-shot femoral nerve block alone,” was unsupported by the data.

Of the 23 randomized controlled trials that were included in our meta-analysis, only 2 trials (with a total of 69 patients) directly compared single shot femoral nerve block to continuous femoral nerve block, the trials by Hirst et al. and Salinas et al. The trial by Salinas et al. located the nerve with a nerve stimulator and used 30 ml ropivacaine, 0.375%, with epinephrine for the single shot femoral nerve block, and the continuous femoral nerve block group also received a continuous infusion of ropivacaine, 0.2%, at 10 ml/h. The trial by Hirst et al. also located the nerve using a nerve stimulator but used 20 ml bupivacaine, 0.5%, with epinephrine for the single shot block, and the continuous nerve block group received an infusion of bupivacaine, 0.125%, at 6 ml/h. The trial by Salinas et al. showed that a continuous femoral nerve block (in comparison with a single shot femoral nerve block alone) resulted in lower pain scores (during the first and second postoperative day and during physical therapy) and opioid consumption was also reduced; by contrast, the study by Hirst et al. found that there were no differences in pain scores or opioid consumption. We disagree with Barrington et al. that the trial by Hirst et al. was not clinically appropriate and the results do apply to current practice. Thus, the direct evidence is equivocal, with conflicting evidence for a continuous femoral nerve block.

In addition to the direct evidence, our Bayesian meta-analysis combined the indirect results from the 7 trials (with 136 patients) that investigated single shot femoral nerve block and the 13 trials (with 352 patients) that investigated continuous femoral nerve block. These results showed that there was no difference in analgesia outcome for these groups in terms of opioid consumption, pain scores, nausea, range of motion, or length of stay. The weakness of this approach, that these were not randomized comparisons and subject to the same biases as observational studies, was described in the original paper. We defend our inclusion of trials that used either bupivacaine or ropivacaine for their femoral nerve blocks because one local anesthetic has not been proven superior to the other in terms of block effectiveness. Thus, the evidence from the indirect comparisons does not support the use of continuous femoral nerve blocks.

Overall there is equivocal evidence for a continuous femoral nerve block from the direct evidence and no evidence from the additional indirect comparisons from the Bayesian analysis. Although these indirect comparisons were nonrandomized, the treatment groups were quite similar between studies. Given these results, we feel that the conclusion “that these studies did not demonstrate further improvement with continuous compared with single-shot femoral nerve block alone” was justified.

The fact that some of the evidence described in the studies does not come from randomized comparisons is a fair criticism and clearly stated in the article. This is a weakness of the literature, as opposed to the methods used in the meta-analysis. More authors need to study the head-to-head comparisons for single shot versus continuous femoral nerve block for total knee arthroplasty, and this was in fact the final conclusion of our study, as stated in the last sentence. Although the idea of a continuous femoral nerve block makes intuitive sense because it prolongs the duration of the nerve block while patients are still having significant pain, its advantages have not been proven in the literature to date. This message is important for investigators because most of the trials published (11 of the 13 trials of continuous femoral nerve block) ignore the comparison with a single shot nerve block group as if it can be taken for granted that continuous femoral nerve block is the superior approach.

References