Multimodal Analgesia for Spine Surgery: Does the intraoperative opioid dose matter?

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Sir,

We have read with great interest the work of Brinck *et al*.[1] The authors should be commended for this well-conducted and highly relevant trial. In our opinion, the authors have clearly answered a clinically relevant question and appropriately concluded that intraoperative S-ketamine effect is limited and not dose-dependent. However, we would like to highlight that the opioid-sparing effect was not specifically tested nor the effect of the intraoperative opioid dose.

Similarly to Brinck *et al*., Maheshwari *et al.* published recently a double-blinded study comparing multimodal analgesia (not only ketamine, but also lidocaine, gabapentin and paracetamol) *vs.* placebo in spine surgery.[2] The authors did not show any improvements on recovery after surgery.[2] As expected in adequately blinded trials, the clinicians delivering the anesthesia care to patients in the Maheshwari's work and Brink's study were not aware of the allocated groups of treatment. Notably, in both studies, the intraoperative opioid use was not affected by the intervention. In fact, the investigators added non-opioid analgesic(s) to the routinely used opioid, thus delivering to the intervention groups truly opioid-based multimodal analgesia regimens instead of opioid-sparing techniques.

Important interfering factors could have been the opioid types (between the Maheshwari's and the Brinck's studies) and doses (between the ketamine *vs.* placebo groups in the Brinck's study). However, these findings of both trials appear to point towards a lack of any significant intra and postoperative opioid-sparing effect of multimodal analgesia on spine surgery. Furthermore, these two studies are rare opportunities to dissect the specific impact of using an intraoperative multimodal opioid-based analgesic technique, independently from the

effects of opioid. Interestingly, in these two studies, the dosage of opioid administered intraoperatively should be considered moderate-to-high in all the groups.

Albrecht *et al.* published recently a meta-analysis on the use of low *vs.* high-dose intraoperative opioids.[3] They concluded that the use of low-dose of intraoperative opioids is one strategy that may be adopted to reduce post-operative pain, as it seems to have an independent effect according to the anesthetic management (i.e. other medications) and type of surgery (not revealing any differences in their analyses). More specifically, their conclusion was mostly based on the use of high-dose remifentanil, being associated with worse postoperative pain. In the Brinck's study, the intraoperative opioid regimen included remifentanil. Conversely in Maheshwari's study, nearly none of the patients received remifentanil and the dose of other opioids (mostly fentanyl) was similar between the groups.

Notably, it has been indicated that multimodal analgesia with ketamine is associated with significant improvements of pain-related outcomes. In a Cochrane Review also authored by Brinck, the conclusion was that ketamine is likely to reduces postoperative analgesic consumption and pain intensity. These results were consistent in different types of surgery, including spine surgery. But, again, the Brink *et al.* did not include, in this Cochrane Review, the intraoperative opioid type and dosages.[4]

While these studies clearly call to re-think the concept of systemic multimodal analgesia with the goal of reduce opioids perioperatively and accelerate recovery after major spine surgery, we would suggest that future trials should test the hypothesis that lowering the intraoperative opioid use could reduce postoperative analgesic requirements, improve in pain intensity and accelerate recovery. This call would permit the development of more robust ways

or means to provide multimodal opioid-sparing analgesia techniques including very simple measures like a decrease in unit dose of opioids presentations.

Consequently, we urged investigators to conduct randomized controlled trials assessing the impact of both multimodal analgesia and opioid-sparing techniques on recovery after different surgical procedures.[5]

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