Efficacy of postoperative buprenorphine in the first 12 hours after surgery

Dear Editor,

Albaqami *et al*.[1] are to be congratulated for their work suggesting that transdermal buprenorphine and sublingual buprenorphine have significant effects on pain relief, reducing also analgesic drug consumption. The effects of buprenorphine in the postoperative period seem promising as shown also by a randomized controlled study where increasing dosages of buprenorphine improved analgesia while not being associated with an increased incidence of side effects.[2]

However, a couple of issues in their analysis should be discussed.

First, the authors used a fixed-effects model, but this analysis should have been conducted in a random-effects model, which is recommended for several reasons. The fixed-effects model assumes that the "true effect" remains similar across studies. However, this is unlikely due to the substantial clinical variability in the included surgical populations, the differences in the study design, and the statistical heterogeneity (I^2). Indeed, the fixed-effects models should not be used when there is I^2 as in the meta-analysis by Albaqami *et al*.[1] where the heterogeneity was high both overall ($I^2 = 98\%$) and in the subgroup analyses (ranging from 97 to 99%). In such cases, it is strongly recommended to use a random-effects model, which better balances the weights

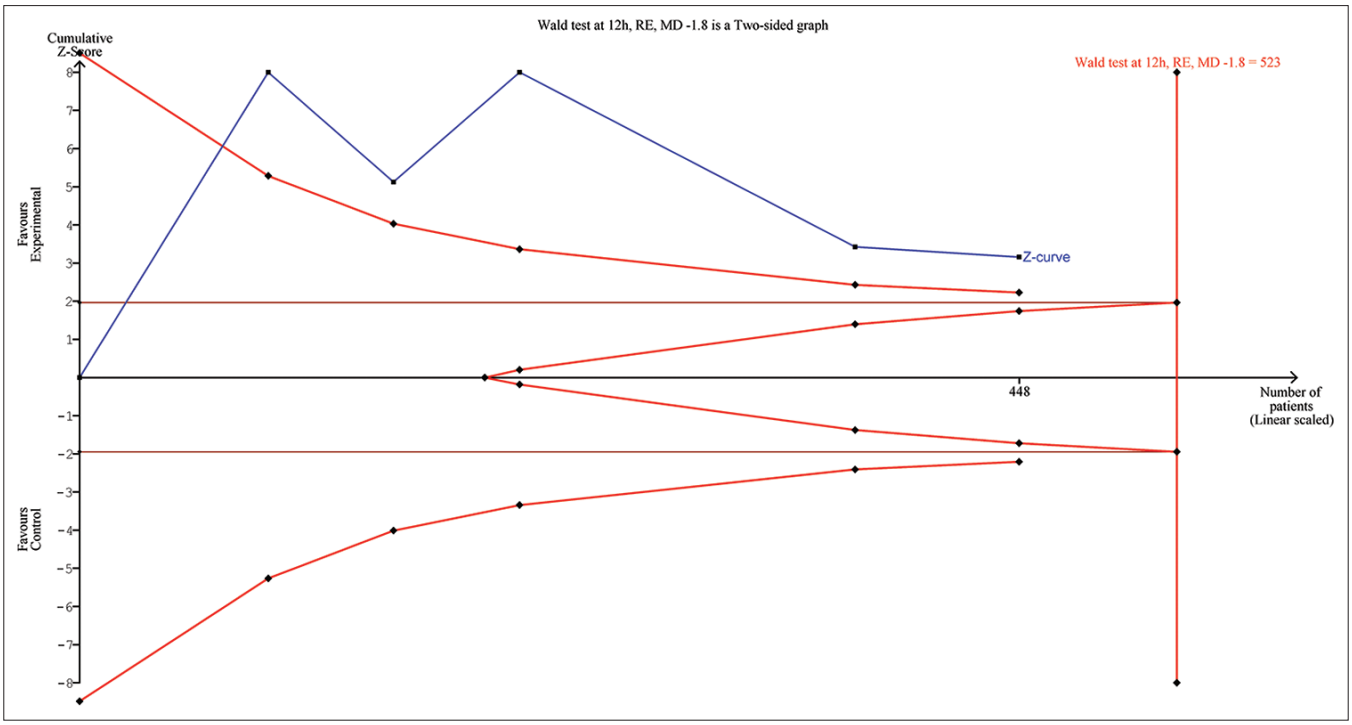

Figure 1: TSA on the Wald test score at 12 hours after surgery. RE: random effect; MD: mean difference

of the included studies.[3] Hence, we kindly ask the authors to report the standardized mean difference according to an analysis conducted in the random-effects model.

Second, considering the relatively low number of included studies, the differences in surgical population were included, and in the study design (ranging from randomized controlled studies to a retrospective cohort study), the robustness of the meta-analysis findings remains uncertain. Hence, we conducted trial sequential analyses (TSAs) based on the data provided by the authors, to provide such information. We inserted data in the dedicated software (Copenhagen Trial Unit's Software®), and the information size was computed assuming an alpha risk of 5% with a power of 80%. We used a random-effects model with the outcome analyzed as a mean difference. The estimated outcome effects were computed using a weighted average of the included studies. Further details on TSA and its interpretation are available elsewhere.[4,5]

We conducted four TSAs on the investigated outcomes, such as the Wald test of pain score at different time points. In our TSA conducted at 12 hours, the Z-curve crossed the alpha spending boundary (O'Brien–Fleming method), showing the robustness of the findings. Indeed, buprenorphine significantly reduced the Wald test of pain score at 12 hours, although the overall number of patients was slightly lower than the estimated "information size" [n = 448/523, Figure 1]. However, the other TSAs on day 1, day 2, and day 3 showed that more research is needed, since the ratios of patients recruited/needed were 358/8.661, 340/2.754, and 340/2.320, respectively.

In summary, the promising results of transdermal or sublingual buprenorphine shown by Albaqami *et al*.[1] should be confirmed by a reanalysis in the random-effects model. However, the TSAs suggest that more research is needed to determine the role of buprenorphine in reducing acute postsurgical pain beyond the first 12 hours.

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Conflicts of interest
There are no conflicts of interest.

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