Preemptive Acetaminophen: Quantification of Opioid-sparring Effects and Need for Further Research

To the Editor:

Xuan et al (1) conducted an important meta-analysis on the effect of preemptive acetaminophen on opioid consumption. In short, the authors included 6 randomized controlled studies (RCTs) and showed decreased opioid consumption and lower pain scores at 12 hours in patients receiving preemptive preoperative acetaminophen. Only pain scores at 24 hours were not different between groups, but the forest plot shows large confidence interval. We would like to make 2 points of discussion on the results of this meta-analysis.

First of all, regarding the analysis on opioid consumption, the authors correctly used the Standardized Mean Difference (SMD), since they compared data from different opioids. In particular, the 5 included RCTs described opioid consumption in terms of hydromorphone (n = 1) (2), tramadol (n = 2) (3,4), morphine (n = 1) (5), and morphine-equivalents (n = 1) (6). As suggested by the Cochrane handbook (7), SMD is preferable when studies assess the same outcome, but estimate it in different ways. Indeed, the SMD expresses effect size relative to the variability observed in each study. However, by choosing this approach, the authors were not able to provide readers with a practical understanding of the effect size (in other words, quantifying the opioid-sparring effect). In order to add such valuable information, we performed an analysis on opioid consumption after conversion into morphine-equivalents, using the Oregon Pain Guidance calculator (8). Our analysis confirms a significant opioid-sparring effect in patients receiving acetaminophen ($P = 0.02$), with a mean difference (MD) of 12.63 mg (morphine-equivalent - 95% confidence interval [-23.59, -1.68], Supp. Fig. 1).

A second point for discussion is the evaluation of the robustness of the meta-analysis findings, and the need for developing further research. We think the study benefits in this regards from trial-sequential analyses (TSAs), allowing to calculate the "information size" and estimating the power of the meta-analysis itself. We would like to offer such contribute and, by importing the data used by the authors in the TSA Software (Copenhagen Trial Unit's TSA Software®; Copenhagen, Denmark), we calculated the information size assuming a 5% alpha risk with a 80% power (beta). The estimated effects on opioid consumption and on pain scores were computed using weighted-averages from the included RCTs, with random-effect model, and MD as effect measure. Details on TSA and its interpretation are available elsewhere (9).

Therefore, we conducted 3 TSAs. While the analysis on pain scores at 12 hours (Supp. Fig. 2) showed robust results indicating no need for further research, the other analyses showed opposite findings, meaning that current evidence is grossly underpowered. Indeed, we found the following ratios of patients recruited/needed: a) opioid consumption 503/1035 (49%, Fig. 1), and b) pain score at 24 hours 448/1763 (25%, Fig. 2). Therefore, more research seems warranted on these outcomes as the "information size" required by the TSA has not been reached yet. Indeed, as shown in the Figs. 1 and 2, the Z-curves for these outcomes have not crossed the alpha-spending boundary of significance (according to O'Brien-Fleming) nor the futility boundary.

In summary, the authors conducted a very elegant investigation, but it is also important that meta-analyses provide readers with clinical information (quantification of the opioid-sparring effect in this case) and scientific community with need for further randomized research.

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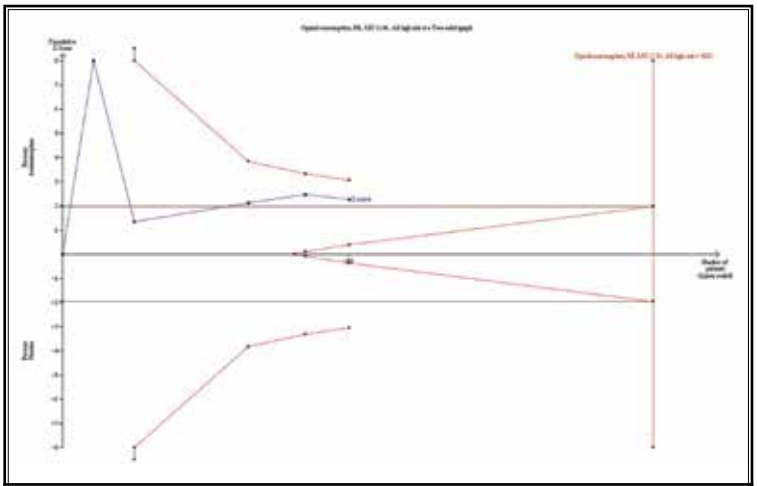

Fig. 1. *Trial Sequential Analysis on opioid consumption, between patients receiving preoperative acetaminophen or placebo. Analysis is performed with random effect (RE) model, with mean difference (MD) set at 11 mg of morphine-equivalents.*

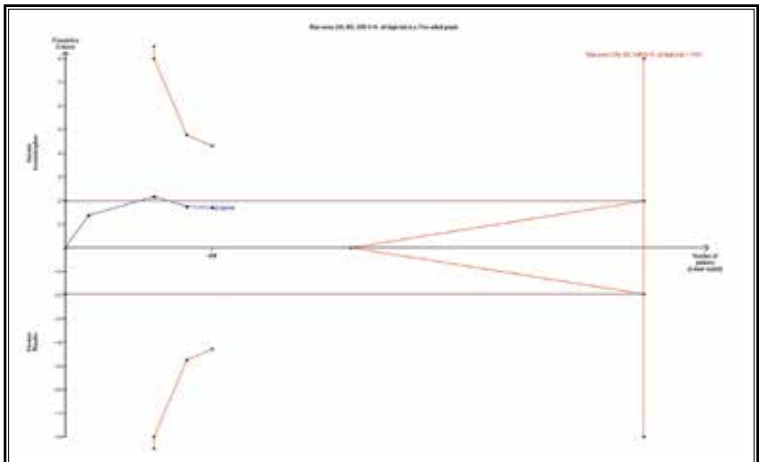

Fig. 2. *Trial Sequential Analysis on pain score at 24 hours, between patients receiving preoperative acetaminophen or placebo. Analysis is performed with random effect (RE) model, with mean difference (MD) set at 0.45.*

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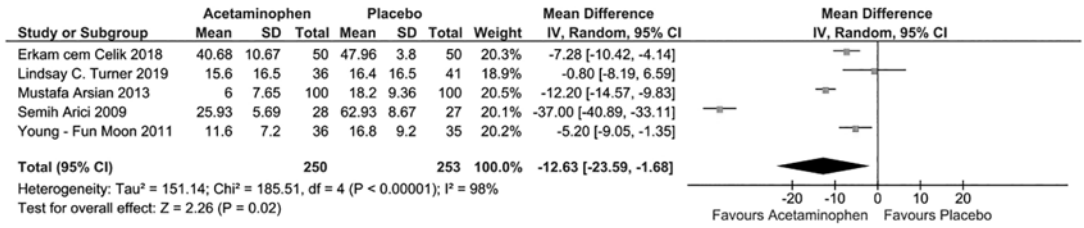
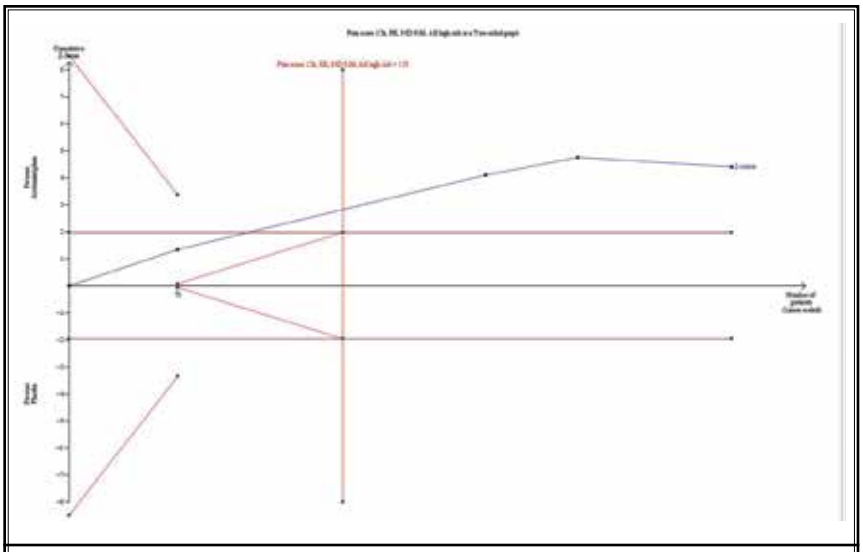


Supp. Fig. 1. *Forest plot of the opioid consumption (expressed as morphine-equivalents, milligrams) in the first 24 hours postoperatively, between patients receiving preoperative acetaminophen or placebo. Analysis is performed with random effect (RE) model with inverse variance (IV). Results are presented as Mean Difference (MD). SD= standard deviation.*



Supp. Fig. 2. *Trial Sequential Analysis on pain score at 12 hours, between patients receiving preoperative acetaminophen or placebo. Analysis is performed with random effect (RE) model, with mean difference (MD) set at 0.86.*