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Opiod-free anesthesia: the importance of evidence synthesis despite heterogeneity

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Manuscript

We thank Dr. Tuhin Mistry [1], Dr. Abhijit Sukumaran Nair [1], and Dr. Mulier [2], and colleagues for their interest in our work and for their comments, which provided us with the opportunity to further discuss the methodology and implications of our network meta-analysis [3].

One of the most common definitions of opioid-free anesthesia (OFA) is "a practice that completely excludes the use of intraoperative systemic, neuraxial, or intracavitary opioids [4]." The OFA cultural paradigm is based on the idea that using opioids as intraoperative analgesics might increase adverse events such as respiratory depression, nausea and vomiting, acute tolerance, hyperalgesia, pain chronification, and subsequent chronic opioid use [5]. Although heterogeneous, the widespread use of this approach in clinical practice and research supports the rationale for conducting an evidence synthesis aimed at evaluating the existing body of evidence, describing its characteristics including heterogeneity. In our network meta-analysis, the selection of clinical outcomes was based on a preliminary scoping review performed at the protocol stage of the project to identify the most common and clinically relevant outcomes. Among these, we chose the 24-h timeframe for pain intensity as our primary outcome prioritizing clinical relevance, and in order to assess the effect of interventions on the processes of sensitization and hyperalgesia that the OFA paradigm aims to modulate [6]. Indeed, postoperative pain intensity and duration are widely recognized risk factors for the incidence of chronic post-surgical pain [7].

To assess the most direct effects of the OFA interventions, we also evaluated early perioperative outcomes, including pain at emergence up to 2 h after surgery, nausea and vomiting, and adverse events [3]. Due to the lack of systematic reporting of adverse events, we conducted a quantitative synthesis exclusively for those events that had a sufficient number of studies documenting them.

We recognized that the qualitative definition of the network nodes has limitations, but it surely represents a step forward compared to the pairwise technique, which represents an extreme simplification of the OFA interventions. Our work might serve to identify drug combinations that could be prioritized by future clinical research.

We analyzed the network using the component network met-analysis (CNMA) approach, and still, even under the less conservative common-effects approach, no component reached a clinically significant difference (Fig. 1).

We acknowledged heterogeneity in surgical settings, but a significant proportion of studies enrolled patients undergoing only endoscopic surgery (28/42, 66%). We have now performed a subgroup analysis of the studies

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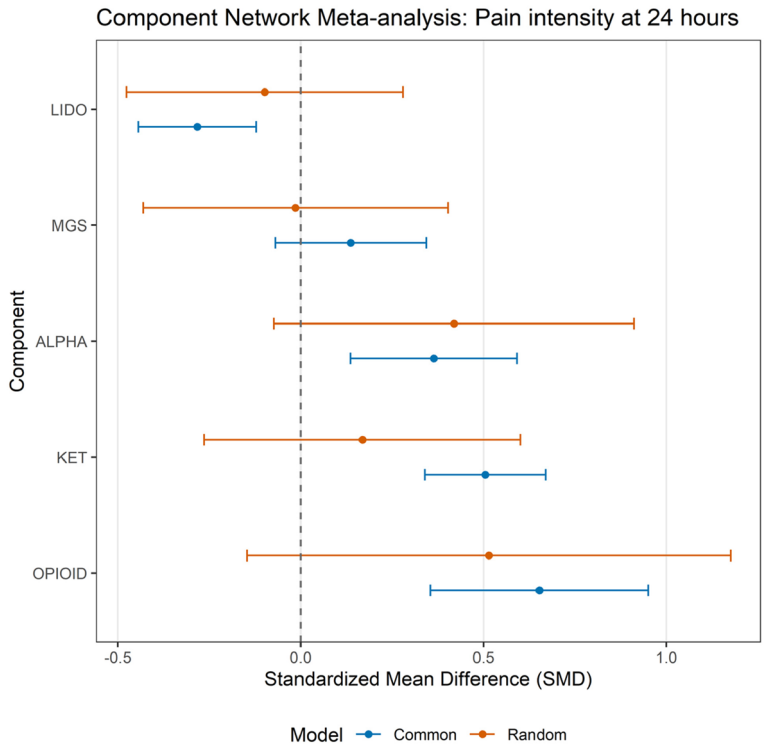

Fig. 1 Component network meta-analysis: pain intensity at 24 hours. CNMA of the primary outcome. Abbreviations: ALPHA: clonidine or dexmedetomidine, KET: ketamine, LIDO: lidocaine, MGS magnesium sulfate, OPIOID: opioid-based anesthesia.

involving only endoscopic surgeries and those without surgical wound infiltration and found no significant differences compared to our main analysis (Fig. 2C and D). We also report here the sensitivity analysis on the opioid consumption that excluded an extreme outlier in opioid consumption, and this analysis showed again no significant differences between OFA and opioid based anesthesia (Fig. 3).

We reported node-splitting analyses in Supplementary Figs. 5, 21, and 31 of our main publication; however, the star-shaped morphology of our graphs, resulting from the absence of cyclic sections in the evidence network, renders them uninformative. The global heterogeneity could be reduced from I^2 = 80.4% to I^2 = 57.6% and I^2 = 67.2% in the endoscopy surgery and wound infiltration sub-analyses, respectively. We expected a significant degree of heterogeneity, and we performed all our analyses under a random-effects model.

We believe that assessing the certainty of evidence according to current methodology is pivotal to understanding the knowledge about the current effectiveness and safety of OFA, and to inform its clinical application today, as well as guide future research directions. Specifically, we should move ahead from the "OFA" umbrella term, designing high-quality randomized trial testing reproducible strategies with well-defined pharmacological components, using outcomes that are clinically meaningful, and applying validated minimal clinically important differences for evaluating efficacy and safety [8]. The evaluation of the effects of a single intervention in multi-modal approaches is also pivotal for tailoring anesthesia to patients needs and to understand which patient benefits from which intervention. Not using opioids is not beneficial per se. The only way to evaluate superiority over a long-lasting clinical approach is to test it against reproducible, pathophysiological-sounding strategies in trials with high internal and external validity. Moreover, observational studies, although useful for hypothesis generation and external validity assessment, remain prone to confounding, information, and selection bias, which preclude causal inference [9]. Considering the high impact and prevalence of inadequate postoperative analgesia, more evidence is required to refute the role of opioids in anesthesia. As stated by Rathmell and Shafer [10], "Why would anyone administer an opioid to another human being? The reason, of course, is that opioids work. There is almost no acute pain that cannot be relieved by opioids [10]."

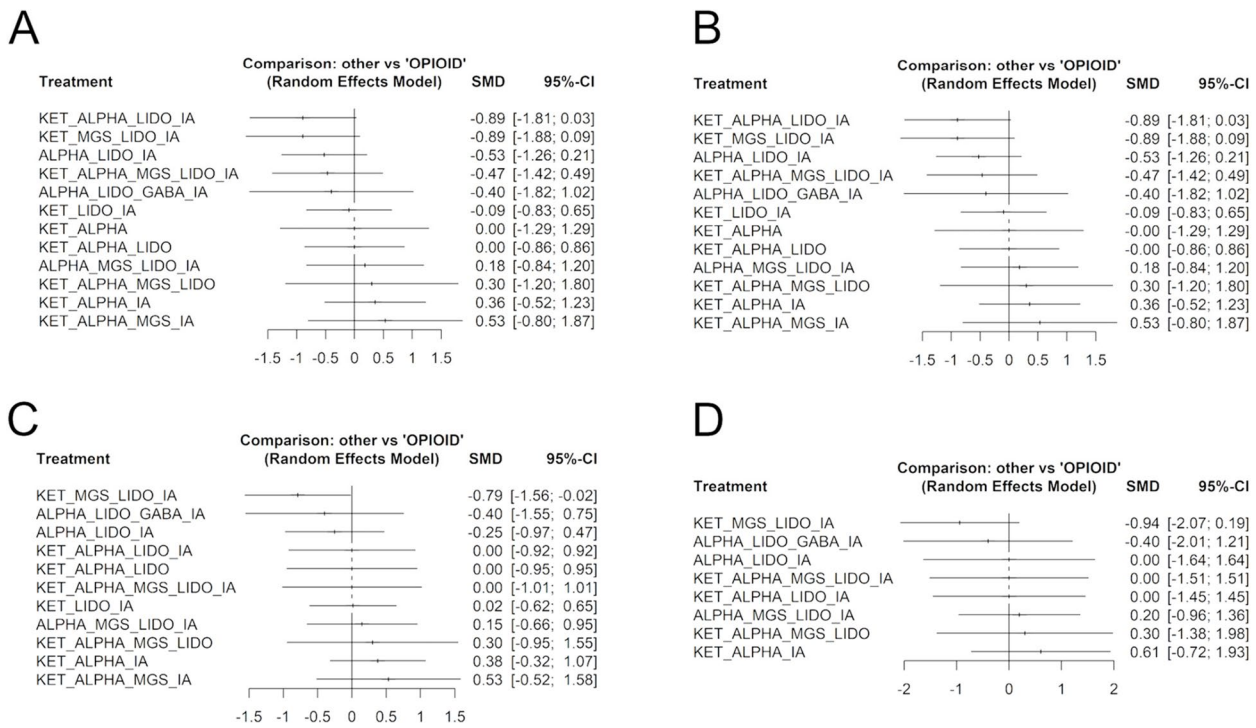

Fig. 2 Panel **A** main analysis **B** ROB-2 sub-analysis, as reported in the Supplementary Material of the main publication **C** sub-analyis on studies enrolling only patients undergoing endoscopic surgeries **D** sub-analyis on studies that described no infiltration of the surgical wound with local anesthetics. ALPHA: clonidine or dexmedetomidine, GABA: gabapentinoids, IA: inhaled anesthetics, KET: ketamine, LIDO: lidocaine, MGS magnesium sulfate.

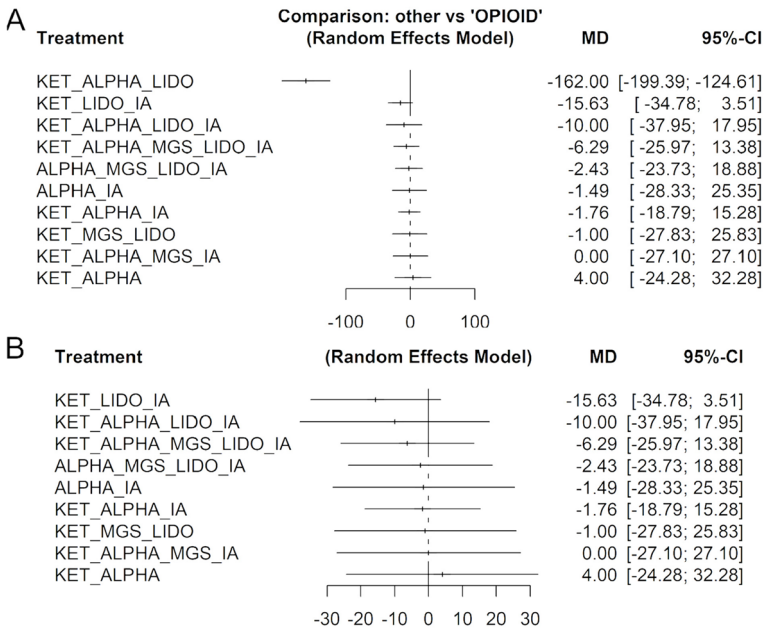

Fig. 3 Panel **A** main analysis on postoperative opioid consumption expressed as oral morphine mg equivalents **B** sensitivity analysis that excluded a single study featuring an extreme outlier in mean opioid consumption. ALPHA: clonidine or dexmedetomidine, GABA: gabapentinoids, IA: inhaled anesthetics, KET: ketamine, LIDO: lidocaine, MGS: magnesium sulfate

Finally, our conclusions are grounded in the evidence synthesis we conducted and should not be extrapolated beyond the intended scope of this type of analysis.

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None.

Authors' contributions
VFT, MI, SS and AC gave substantial contributions to the conception and design of the work and drafted the manuscript. AC also made an important contribution to the conceptualization and supervision of the manuscript.

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Data availability
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not obtained, this is a reply to matter arising.

Consent for publication
Not applicable; All authors approved for the submission of the manuscript.

Competing interests
The authors declare that they have no competing interests.The authors declare that they have no competing interests.

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