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Letter to the editor

Comment on an article published in the December 2025 AAB issue concerning evidence from meta-analyses and subsequent large-scale randomized controlled trials in perioperative medicine

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To the Editor,

The study entitled “Exploring discordance in evidence from meta-analyses and subsequent large-scale randomized controlled trials in perioperative medicine”, published in Acta Anaesthesiologica Belgica was very interesting reading[1]. Congratulations to the authors for introducing the use of TSA (Trial Sequential Analysis), which may improve the applicability of meta-analyses and accelerate the translation of evidence into the daily anesthesia practice. Meta-analyses are a form of dialectical knowledge development that periodically synthesizes newly available and relevant evidence. TSA should reduce the chance capitalization of type I and II errors due to repeated testing, using boundaries on a TSA-graph to indicate whether a treatment effect is significant, biased, or futile. TSA would also determine when further research is needed[2].

Besides the authors’ critical, extensive discussion and emphasis on its strengths, limitations, complexities, and potential alternatives, the methodology of TSA may unintentionally give the impression that some kind of “ultimate truth” could be claimed about a given outcome once the required information volume (number of subjects) is reached and the cumulative Z-statistic can or cannot be considered “enough significant”[3]. In contrast, the famous philosopher Karl Popper (°1902-+1994) argued that science is never certain and does not advance by proving theories true (verification), but by trying to prove them false (falsification).

In concreto, what should a careful physician conclude from the article in question regarding the most striking discordance it reveals on such an important topic as survival: should we reject the “old” evidence that a combination of epidural and general anesthesia results in a better survival, and argue the opposite? In this case, nuanced reasoning is required, avoiding too straight-lined “Popperazzi” reflexes, so that a single falsifying experiment, such as one contradictory study, does not necessarily and automatically must undermine the current evidence.

Therefore, I focused on the discrepancy with respect to survival, which is shown in the forest plot (Fig. 3) of the article. The issue is whether combined epidural-general anesthesia favors a better survival or not. The OR (Odds Ratio) from the previous meta-analysis and the recent RCT (Randomized Controlled Trial) are both clearly statistically significant, with respective 95% confidence intervals that do not overlap and neither contains the number 1. According to the forest plot legend, the lack of overlap indicates inconsistency between meta-analysis and RCT[4,5]. Thus, they point statistically significant in opposite directions: one in favor of combined epidural-general and the other in favor of general anesthesia only. For this specific meta-analysis, no TSA-graph is shown, nor the TSA zone to which it was assigned by the authors, as only the frequency counts of the respective classifications are reported in the Tables I, II and III. A TSA-graph of an updated version of this meta-analysis with the inclusion of the recent RCT, would be a kind of sensitivity analysis to test whether the consistency and robustness of the previous evidence holds or changes. Moreover, Table V, summarizing the data extracted by the authors from the selected meta-analyses, displays an inappropriate OR of 0.96 for the survival meta-analysis, which is outside the boundaries of the reported 95% confidence interval: 0.51-0.92. This must be a clerical error: it does not correspond to the OR depiction in the forest plot and a statistic always lies within its own confidence interval and never outside it. Table V further reports that 80 effect cases (mortality) were recorded in the intervention group (combined epidural-general) out of a total of 3911, and 122 effect cases out of a total of 3855 patients in the control group (general anesthesia only), which represents estimated mortality rates of circa 2% versus 3%, respectively. The post-hoc RCT on survival by Du et al. demonstrated an effect (mortality) in 355 cases of the intervention group (combined epidural-general) out of a total of 853 and an effect in 326 cases out of a total of 859 in the control group (general anesthesia only), representing mortality rates of 42% versus 38%, respectively[5]. Why do these percentages differ so much between the meta-analysis and the later RCT,

regardless the differences caused by the type of anesthesia? The lemons and lemonade metaphor the authors cited to model meta-analyses obviously needs to be supplemented with apples and oranges. No doubt that the definitions used for survival should differ consistently between the meta-analysis and the RCT, a point that must be scrutinized. A hypothetical explanation could be that the meta-analysis likely only recorded perioperative mortality, while the RCT assessed long-term survival after (cancer) surgery[5].

Finally, it is reassuring that the authors still consider (large) RCTs as the golden standard to fuel meta-analyses and update their conclusions, rather than overanalyzing existing data with the associated risks of bias. Furthermore, RCTs are generally accepted to be the only experimental research design suitable for demonstrating causality. The authors' conclusion that meta-analyses should be viewed as "hypothesis-generating" therefore feels somewhat counterintuitive, especially if it were for those based solely on RCTs. Nevertheless, evidence must be continually critically assessed to avoid dogmatic thinking, and perhaps meta-analyses using TSA or another similar statistical tool could help to refine or modify some hypotheses and also unravel incomparable composite endpoints. It may therefore be expected that clearer and more unambiguous outcome definitions can be "generated" for RCTs and subsequent meta-analyses.

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