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Intraoperative High Inspired Oxygen Fraction: Are There Real Benefits?

To the Editor:

We read with interest the meta-analysis by Hovaguimian *et al.*[1] on the effects of a high perioperative inspiratory oxygen fraction. The positive conclusions in terms of decreased risk of surgical site infection (SSI), weak prophylactic effect on nausea, and no increased risk of atelectasis raise several methodological concerns.

First, the preventive effect on SSI was reported for patients receiving prophylactic antibiotics although the observed difference was not statistically significant (upper 95% CI, 1.00). Moreover, the actual rates of patients receiving antibiotics were only reported in four of the nine trials,[2–5] leaving the conclusion to be based on protocol information from five trials, and a separate analysis of antibiotics *versus* no antibiotics was omitted. The large body of evidence demonstrating no significant effect on SSI from perioperative hyperoxia to 1,966 patients for caesarean section was excluded from the current meta-analysis, because the intervention was delivered through nonrebreathing masks during neuraxial anesthesia,[6] although such face masks are able to deliver a fraction of inspired oxygen (F_{IO_2}) greater than 0.60 inducing an adequate high-to-normal F_{IO_2} ratio. The Evaluation of Nitrous Oxide In the Gas Mixture for Anaesthesia (ENIGMA) trial, favoring hyperoxia *versus* nitrous oxide to prevent SSI, was included without restrictions in the meta-analysis, suggesting that there is no difference between nitrous oxide and nitrogen in this context.[5] However, a randomized trial of 197 patients[7] receiving five different interventions, including a perioperative F_{IO_2} of 0.80, was excluded because data could not be extracted. Data seem to be available, and the significantly increased risk of SSI in the intervention group in that study would further have challenged the primary conclusion of this meta-analysis.

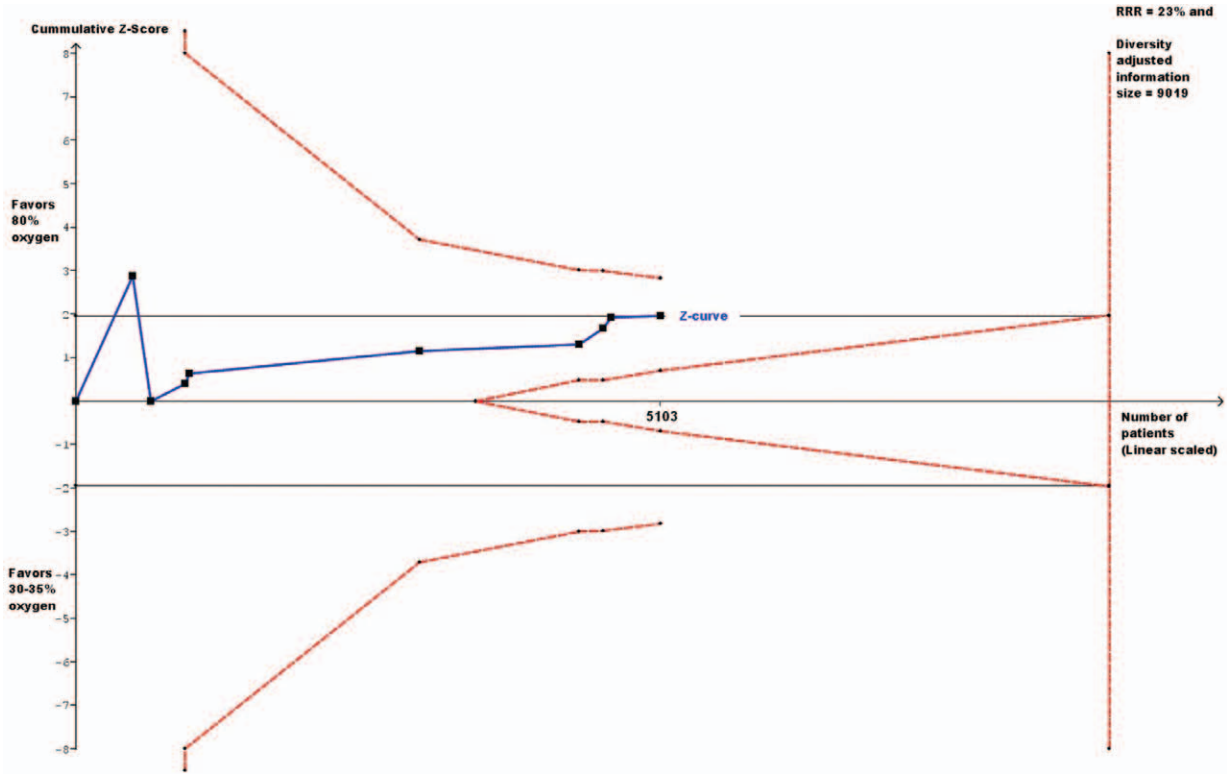

Fig. 1. Trial sequential analysis of the nine trials included in the meta-analysis of hyperoxia to prevent surgical site infection by Hovaguimian *et al.*[1] *Solid line* = cumulative Z-curve. *Dashed line* = trial sequential monitoring boundary. RRR = relative risk reduction.

Second, the mild beneficial effect of perioperative inspiratory hyperoxia on postoperative late nausea was the only one of six secondary outcomes that was statistically significant, suggesting that this finding may be due to chance rather than the intervention.

Third, although no significant differences were found as to the rates of pulmonary side effects, that outcome was not accurately defined and the adverse effects may be greatly underdiagnosed, because routine pulmonary examinations have not been performed in any of the large trials. Other harms were not assessed, but recently published data suggest increased long-term mortality with 80% oxygen.[8] A positive risk–benefit ratio along with the administration of a high perioperative inspiratory oxygen fraction is therefore not evident.

The meta-analysis included trials at low as well as high risk of bias, and finally, the authors did not consider the risk of finding the nearly significant result by chance because of too few randomized patients, which might have tempered their conclusion. The meta-analysis presented by the authors—following the previously published meta-analyses—may only be regarded as an interim-analysis toward a conclusive answer. In a trial sequential analysis,[9] it can be calculated that the diversity-adjusted required information size is 9,019 randomized patients for showing a 23% relative risk reduction (fig. 1), and there are thus no conclusive answer so far, as only 5,103 patients have actually been randomized.

Competing Interests

All authors of this letter were members of the PROXI trial steering committee investigating 80% oxygen to prevent surgical site infection (JAMA 2009; 302:1543–50) and are also authors of an upcoming Cochrane review about the effects of high perioperative inspiratory oxygen fraction for adult surgical patients (Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD008884. DOI:10.1002/14651858.CD008884).

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In Reply:

We would like to thank Drs. Hedenstierna, Belda, Meyhoff and colleagues for their interest in our meta-analysis.[1] We attempted to provide a comprehensive quantitative summary on the effects of perioperative high inspired oxygen fraction—definitely an on-going and passionate issue.

The main concern of Drs. Hedenstierna and Edmark is that we considered studies in which nitrous oxide was used as carrier gas, and that the variation in nitrous oxide concentrations among study groups may not have been properly controlled in all trials. Whether studies using nitrous oxide should be considered is, indeed, a relevant question in situations where nitrous oxide has been recognized as a confounding factor. For that reason, we did not consider data on postoperative nausea and vomiting from studies that were using nitrous oxide (because nitrous oxide has emetogenic properties). However, there is no evidence suggesting that nitrous oxide plays any role in the incidence of surgical site infection.[2] Nitrous oxide was administrated in one trial only that reported data on pulmonary outcome.[3] In that trial, the incidence of atelectasis was significantly higher ($P < 0.001$) in the group receiving 70% of nitrous oxide (*i.e.*, 30% F_{IO_2} [fraction of inspired oxygen]), suggesting either a detrimental effect of nitrous oxide or a protective effect of high F_{IO_2}, or both. In any case, the result tends to support our conclusions. We cannot exclude that, in trials that were using nitrous oxide, some variability in the concentration