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Editorial

EDITORIAL

Volatile sedation in sepsis: a promising therapeutic approach or a venture doomed to fail?

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Summary

Preclinical strategies targeting sepsis often had a single target and could not be translated into the clinical setting. Volatile sedation modulates multiple aspects of inflammation and improves sepsis-related survival in animal models. Whether a similar effect can be achieved in humans is unclear. Only a prospective clinical trial will be able to answer this question. The implementation of such a study in times when volatile anaesthetics are the focus of attention because of their greenhouse effect and their carbon dioxide emission will be a challenge, even though the alternative, i.v. sedation, is still insufficiently investigated in this respect.

Keywords: isoflurane; long-term sedation; propofol; sepsis; sex differences; short-term sedation; survival; volatile sedation

Sepsis is a challenge. The 30 day mortality for sepsis, although declining, is still 24%, and for septic shock, even 35%.[1] A contributor to the lack of progress is the unsuccessful translation of promising therapeutic approaches from animals into humans.[2] Preclinical treatment strategies for sepsis have been targeted at the inflammatory response, the coagulation pathway, or vascular regulation,[2] but so far promising drugs or therapies from *in vivo* studies could not be translated into a clinical scenario.

Volatile anaesthetics are well known to modulate inflammatory processes, such as by attenuating the production of various mediators, thereby positively impacting the orchestration of inflammation and the outcome.[3,4] In their recent work published in *BJA Open*, Ikeda and colleagues[5] tackle two crucial questions, which have not been addressed so far in animal models of sepsis. The first concerns the duration of sedation with a volatile anaesthetic in individuals with sepsis to achieve a survival benefit. Interestingly, sedation for 72 h with a volatile anaesthetic exerts a similar effect as exposure to isoflurane limited to the intraoperative phase.[5] The median survival in the extended isoflurane exposure group was only marginally longer (1.44 *vs* 1.37 days). The second question addressed by Ikeda and colleagues[5] was the impact of volatile sedation on survival in both male and female animals. In the extended sedation group, isoflurane improved survival in both male and female animals. In animals subjected to intraoperative isoflurane only, survival was significantly longer in females but not in males compared with intraoperative propofol.[5] This apparent sex-dependent difference with intraoperative isoflurane exposure could indicate a true sex-related effect, but it is possibly a false-positive finding in a study with small sample sizes.

Whilst data in animals with sepsis treated with volatile anaesthetics look promising, a new debate has started. The scientific community has suggested carefully considering using TIVA in preference to volatile anaesthetics whenever possible,[6–8] as volatile anaesthetics are greenhouse gases with a global warming potential.[9] Approximately 50% of the greenhouse gas emissions from the entire healthcare system come from perioperative patient care.[10] Such ecological concerns should not be downplayed. Measures to reduce the ecological footprint in the perioperative setting, such as minimal fresh gas flow when using volatile anaesthetics, must be implemented without fail. However, volatile anaesthetics

should be considered in the context of the available alternatives. Whilst propofol does not emit greenhouse gases directly, its indirect carbon footprint is poorly described.[11] The use of propofol contributes to significant waste production. Moreover, the environmental impact of bioaccumulation, water pollution, and toxicity must be considered.[12] As long as the environmental impact of the two most common anaesthesia techniques is inadequately evaluated and compared, the preference should be based on patient, surgical, and anaesthetic factors, and the benefits and risks for the individual patient and the entire population should be considered.[13]

Recent evidence highlights that short- and long-term volatile sedation is feasible in the ICU using the AnaConDa™ (Sedana Medical, Danderyd, Sweden) and MIRUS™ (Medcaptain, Guangdong, China) systems.[14] Despite growing evidence that volatile anaesthetics can favourably influence the course of sepsis in animal models,[3,15] its impact on sepsis in humans has not been studied to date. Retrospective data in critically ill patients undergoing surgery showed a survival benefit[16] when volatile anaesthetics were used. Whilst such a result does not necessarily mean that this also applies to patients with sepsis, it can at least be taken as a favourable sign. The stigma of possible selection bias will never disappear from retrospective data analyses, and extrapolation to other syndromes, such as sepsis, may or may not be possible. We hope that prospective clinical studies will soon shed some light on this. Only rigorous prospective clinical trials can show whether the promising approach of volatile sedation in sepsis described by Ikeda and colleagues[5] should be further pursued or whether this research chapter—because of the lack of its transferability to humans—should be closed.

A positive effect in patients that mirrored *in vivo* data from Ikeda and colleagues[5] would have a tremendous impact on our patients and also healthcare costs. Ecological issues would have to be considered and intelligent solutions implemented to reduce greenhouse gas emissions. Taken together, the study by Ikeda and colleagues[5] is encouraging and adds one piece to a giant puzzle.

Authors' contributions

Editorial conception: all authors.
Writing/editing of article: all authors.

Declarations of interest

MS and BBS have received unrestricted research funds from Sedana Medical (Danderyd, Sweden) and Roche Diagnostics International (Rotkreuz, Switzerland) for an investigator-initiated clinical trial (principal investigator [PI]: MS). BBS and MS have submitted a patent to mitigate the negative effects of surgery and anaesthesia for patients using medical gases, particularly oxygen and carbon dioxide. BBS has received a research grant for an investigator-initiated clinical trial from Baxter Healthcare Corporation (Deerfield, IL, USA) (PI: BBS). BBS submitted US and European patent applications for an injectable formulation for treatment and protection of patients having an inflammatory reaction or an ischaemia/reperfusion event.

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