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Post-hoc analysis of the Sedaconda study

ICU- and ventilator-free days with isoflurane or propofol as a primary sedative – A post-hoc analysis of a randomized controlled trial

Bracht H et al. J Crit Care 2023;78:154350.

Patients who received isoflurane via the Sedaconda ACD as the primary sedative in the 30 days from randomization in the Sedaconda study had on average a 3.5-days shorter stay in the ICU and needed significantly less additional sedatives in comparison to those receiving propofol as the main sedative. Fewer isoflurane patients required renal replacement therapy compared to those in the propofol group. No statistically significant differences were found on ventilator-free days between the two groups. The results further support the efficacy of isoflurane as a primary sedative for invasively ventilated patients and show that its use is associated with an earlier discharge from the ICU.

BACKGROUND

This was a post-hoc analysis of a subset of patients from the pivotal Sedaconda study, the largest randomised controlled clinical trial on inhaled sedation in intensive care[1]. The Sedaconda study included 301 mechanically ventilated adult patients and demonstrated that isoflurane delivered via the Sedaconda ACD was safe and effective, reduced the need of opioids, enabled a faster and more predictable awakening, and facilitated spontaneous breathing compared to intravenous propofol. In this post-hoc analysis, isoflurane was associated with more ICU-free days. This is in line with earlier retrospective studies[2,3] and might be explained by the elimination of isoflurane which is minimally impacted by non-pulmonary organ dysfunctions[4], and by the reduced use of concomitant sedatives.

STUDY OBJECTIVES, DESIGN, ENDPOINTS & INCLUSION CRITERIA

- The aim of the post-hoc analysis was to compare ICU-free (ICU-FD) and ventilator-free days (VFD) in patients who received only isoflurane or only propofol as the main sedative in the 30 days after randomization.
- Patients were eligible if they had 30-day follow-up data available and if during the first 30 days from randomization they
    a) were extubated during the study and not re-sedated after the end of study treatment (which was 48 (+/-6) hours or until extubation), or
    b) received further sedation with the same drug they were randomized to and were never sedated with the other drug (with the exception of single bolus doses of propofol to facilitate e.g. airway procedures such as bronchoscopy).
- 69 of 150 patients randomized to isoflurane and 109 of 151 patients randomized to propofol were eligible.
- Primary endpoint:
    - ICU-FD in the 30 days after randomization
    - VFD in the 30 days after randomization
- Secondary endpoints
    - Use of other sedatives
    - Delirium-free days in the first week
    - Use of renal replacement therapy (RRT)
    - Mortality

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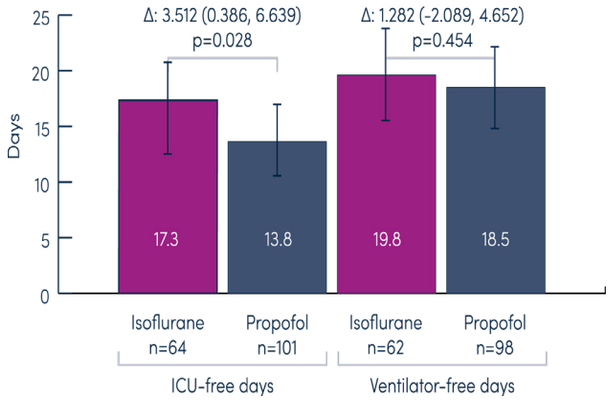
PRIMARY ENDPOINT
ICU-FREE DAYS AND VENTILATOR-FREE DAYS

- Patients in the isoflurane group had 3.5 more ICU-FD during the 30-day follow-up period than those in the propofol group after accounting for confounders.
- VFD differences favoured isoflurane but were not statistically significant.
- ICU-FD and VFD differences favoured isoflurane to a larger extent in sensitivity analyses that only included patients continuing sedation beyond the study treatment period.



SECONDARY ENDPOINTS

- More patients in the propofol group received other sedatives and during significantly more days than patients in the isoflurane group.
- Delirium-free days in the first week of follow-up were not statistically different among groups.
- Significantly more patients in the propofol group required RRT than in the isoflurane group.
- 30-day mortality was not statistically different among groups.
- Patients in the isoflurane group continued sedation beyond study treatment for fewer days than those in the propofol group.

Secondary 30-day follow-up data	Isoflurane	Propofol	p value
Proportion of patients receiving other sedatives*	47.8%	74.3%	0.0003
Mean (SD) number of days with registered other sedatives*	2.0 (3.8)	6.9 (8.3)	<0.0001
30-day mortality	24.6%	19.3%	0.454
Proportion of patients starting renal replacement therapy in the 30 days after randomization	2.9%	18.3%	0.0019

*other sedatives: midazolam, lorazepam, diazepam, ketamine, clonidine, dexmedetomidine, temazepam, zolpidem, zopiclone

References: 1. Meiser A et al. Lancet Respir Med 2021;9:1231-1240. **2.** Bellgardt M et al. Eur J Anaesthesiol 2016;33(1):6-13. **3.** Krannich A et al. Crit Care Med 2017;45(4):e384-390. **4.** Holaday DA et al. Anesthesiology 1975;43(3):325-332.

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