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ORIGINAL ARTICLE

Neuropsychological follow-up of isoflurane sedated intensive care patients: a substudy of a randomized trial

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ABSTRACT

BACKGROUND: Inhaled sedation of intensive care unit (ICU) patients ventilated >24 hours may have long term effects. We hypothesized that isoflurane has a better neuropsychological outcome in a one-year follow-up compared to propofol sedation.

METHODS: All 66 patients included by the coordinating center of the ISOCONDA study (EudraCT#: 2016-004551-67) took part in this substudy (DRKS00020240). A delirium test (CAM-ICU) was performed 24 hours after end of sedation. Sedation-, ventilator-, ICU- and delirium-free days within 30 days were calculated. Patients were sent five questionnaires one, three and twelve months after ICU discharge: ICU-Memory-tool (ICU-MT), Short-Form-36-Health-survey (SF-36), Posttraumatic-Stress-Scale-14 (PTSS-14), WHO-Five-Well-Being-Index (WHO-5) and Hospital-Anxiety-Depression-Scale (HADS).

RESULTS: CAM-ICU was positive in 17% of patients, however 68% showed signs of delirium during the ICU stay (no group differences). Mortality was lower after isoflurane (30-days: 1/33 *versus* 7/33, P=0.024; One-year: 9/33 *versus* 14/33, P=0.156). Isoflurane led to significantly more sedation- (median [IQR]: 28[25-29] *versus* 24[21-29], P=0.016), ventilator- (28[24-29] *versus* 22[4-28], P=0.011), ICU- (23[13-26] *versus* 11[0-25], P=0.044) and delirium-free days (25[21-29] *versus* 20[12-28], P=0.031). Return rate of questionnaires was high (87/128). In the ICU-MT, isoflurane patients recalled significantly more factual memories after one year. Generally, the psychological tests suggested a poor quality of life (SF-36), high rates of post-traumatic-stress-disorder (PTSS-14: 38%) and depression (WHO-5: 54%, HADS: 43%), without significant group differences.

CONCLUSIONS: Isoflurane sedation leads to more delirium free days during the ICU treatment and more factual memories of the ICU stay one year after the ICU stay. However long-term outcome of ventilated ICU patients is poor, and there were no differences between isoflurane and propofol sedation.

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KEY WORDS: Critical care; Isoflurane; Propofol; Delirium.

The occurrence of delirium is a frequently described phenomenon in patients in the intensive care unit (ICU)[1-4] and is associated with worse patient outcomes in the short and long term.[5] As ICU survivorship increases, reports of depression and posttraumatic stress disorder af-

ter critical illness and ICU treatment are also on the rise.[6, 7] While the majority of patients with invasive ventilation require analgesic and sedative therapy,[8] it is widely recognised that excessive doses and/or extensive duration of intravenous sedatives increase the incidence of negative psychological sequelae.[9] In contrast, several studies have established good efficacy and few side effects in patients treated with inhaled sedatives.[10-13] Faster wake-up times and better cognitive recovery could be achieved after long-term sedation with inhalational agents,[10, 12-14] which may imply lower incidence of delirium, more factual and less delusional memories since elements such as the ability to follow verbal commands are part of validated clinical tools to evaluate delirium. In this prospectively planned substudy of the Sedaconda study (a large randomized controlled trial evaluating the safety and efficacy of isoflurane compared to propofol), the neuropsychological follow-up of patients sedated with either isoflurane or propofol were examined in more detail to understand whether inhaled sedation might decrease the incidence of delirium and positively impact the long-term quality of life of ICU survivors.

Materials and methods

This trial is a substudy of a multi-center randomized trial assessing non-inferiority of isoflurane to propofol in 301 intensive care patients (Sedaconda study; European Medicines Agency's EU Clinical Trial register, 2016-004551-67).[15] The substudy was approved by the responsible Institutional Review Board (amendment of January 31, 2018; approval number 11/17, Ethikkommission der Aerztekammer des Saarlandes, Saarbruecken, Germany) and registered prior to data access in the German Clinical Trials Registry (registration number: DRKS00014030). Informed written consent complying with the German Medicinal Products Act was obtained from all included patients or their legal representatives. This substudy included patients of the Saarland University Hospital, the coordinating centre of the main trial. In the main Sedaconda trial, adult ICU patients with invasive ventilation for less than 24 hours, receiving propofol at the time of randomization and expected to require further continuous invasive ventilation for at least 24 hours, could be included. Sedation target, assessed with the Richmond Agitation and Sedation Scale (RASS), had to be within -1 to -4. Additional exclusion criteria for the long term-follow-up of the substudy were aphasia, no sufficient knowledge of the German language, and refusal of consent for sending questionnaires. The substudy consisted of a delirium assessment, a short-term- and a long-term follow-up. Delirium occurrence was assessed daily *via* the Intensive Care Delirium Screening Checklist (ICDSC). After 38 patients, Confusion Assessment Method in the ICU (CAM-ICU) was introduced additionally 24h after end of sedation. The short-term follow-up started with the end of the main trial, which was after 48 hours of study sedation or after extubation, whichever occurred first. Short-term follow-up lasted 30 days or until death, whichever occurred first. The charts of all patients were reviewed retrospectively and searched for objective criteria of delirium, *i.e.* documented scores of the ICDSC, or use of physical restraints. Patients discharged from the ICU were considered delirium-free. In addition, we analyzed mortality, the length of ICU stay, ventilator days (days with invasive ventilation for more than six hours) and days with deep sedation, defined as continuous administration of isoflurane or propofol for at least six hours. To calculate ICU-, ventilator- and sedation-free days, the length of ICU stay, ventilator days and days with deep sedation were subtracted from the length of short-term follow-up (30 days or days until death). The days awake without delirium were calculated by subtracting the days with delirium from the sedation-free days. For the long-term follow-up, surviving patients were contacted by phone call and asked permission to send the questionnaires. Questionnaires were sent four weeks, three months and one year after ICU discharge. The study algorithm is shown in Figure 1. Questionnaires included German versions of the Intensive Care Unit Memory Tool (ICU-MT),[16] the Short-Form-36 Health Survey (SF-36),[17] the Posttraumatic Stress Scale 14 (PTSS-14),[18] WHO-Five Well Being Index (WHO-5),[19] and Hospital Anxiety and Depression Scale (HADS).[20] Memories in the ICU-MT are examined *via* a checklist of 21 items. Items are divided

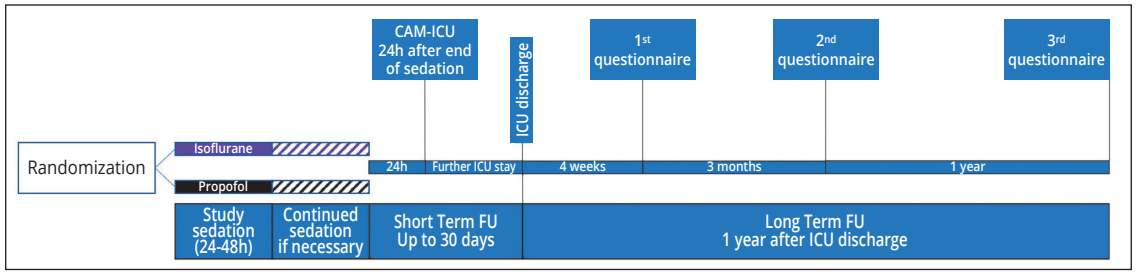

Figure 1.—Study algorithm with illustration of time frames observed in the study.
CAM-ICU: Confusion Assessment Method in the Intensive Care Unit; ICU: Intensive Care Unit; FU: follow-up.

into factual, emotional, and delusional memories. SF-36 investigates subjective health in patients by analyzing 36 items which are summarized into a Physical Health and a Mental Health Summary Score. PTSS-14 consists of two parts. The first part addresses memories of hospital stay, the second current symptoms indicating a post-traumatic stress disorder. WHO-5 consists of five statements regarding general wellbeing, which are evaluated by a point-system from zero to five. HADS examines symptoms of anxiety and depression. It consists of seven questions each.

Statistical analysis

As this substudy of a multicenter randomized clinical trial including was confined to a subgroup from one center, an a priori determination of the number of patients was not possible. In addition, effect sizes were unknown. Analysis of the questionnaires ICU-MT, and PTSS-14, WHO-5 and HADS was performed in Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA). Data was then transferred to IBM® SPSS® Statistics 25 (SPSS Inc., Chicago, IL, USA). SF-36 was analyzed with SPSS® using the syntax included in the corresponding manual.[17] Qualitative data are presented as absolute numbers and frequencies and compared between groups with χ^2 tests. Quantitative data, if normally distributed, are presented as means and standard deviations and compared with Student's *t*-test. Normality was assessed with the Shapiro-Wilk-Test. Not normally distributed data are presented as medians and interquartile ranges and compared with Mann-Whitney-U tests. For all comparisons, $P<0.05$ was considered significant. Data analysis was descriptive in nature; therefore, original P values are given and no corrections for multiple testing were performed,

Results

Informed consent was obtained in 74 patients, of which 66 were randomized on a 1:1 ratio to sedation with propofol or isoflurane (*i.e.* 33 patients in each group). Eight patients were not expected to require further continuous invasive ventilation for 24 hours and were not randomized. Table I shows the characteristics of each intervention group. CAM-ICU scores could be assessed in 24 patients. After one day from seda-

TABLE I.—*Patients' characteristics.*

	Isoflurane (N.=33)	Propofol (N.=33)	P value
Male sex	21 (63.6%)	22 (66.7%)	0.796
Age	64±12	65±14	0.842
Height, cm	173±9	173±8	0.928
Weight, kg	80 [72-85]	80 [74-100]	0.300
SAPS II	34±14	43±20	0.067
Emergency admission	16 (48,5%)	18 (54,5%)	0.563
ICU length of stay, days	9 [3-27]	11 [4-27]	0.508
Duration of ventilation, hour	45 [25-197]	67 [28-349]	0.357
MED, mg/kgBW/h	0.22±0.07	0.29±0.18	0.038

Data are patient numbers (percentage), mean ± SD, and median [1st quartile- 3rd quartile].
SAPS II: Simplified Acute Physiology Score II before randomization. MED: morphine equivalent dose.

tion stop, we did not find any difference in the CAM-ICU scores. Only two out of 11 patients in the isoflurane group and two out of 13 patients in the propofol group matched the criteria for delirium. During the short-term follow-up, 68% of patients suffered from delirium (23 out of 33 in the isoflurane group and 22 out of 33 in the propofol group) with no difference be-

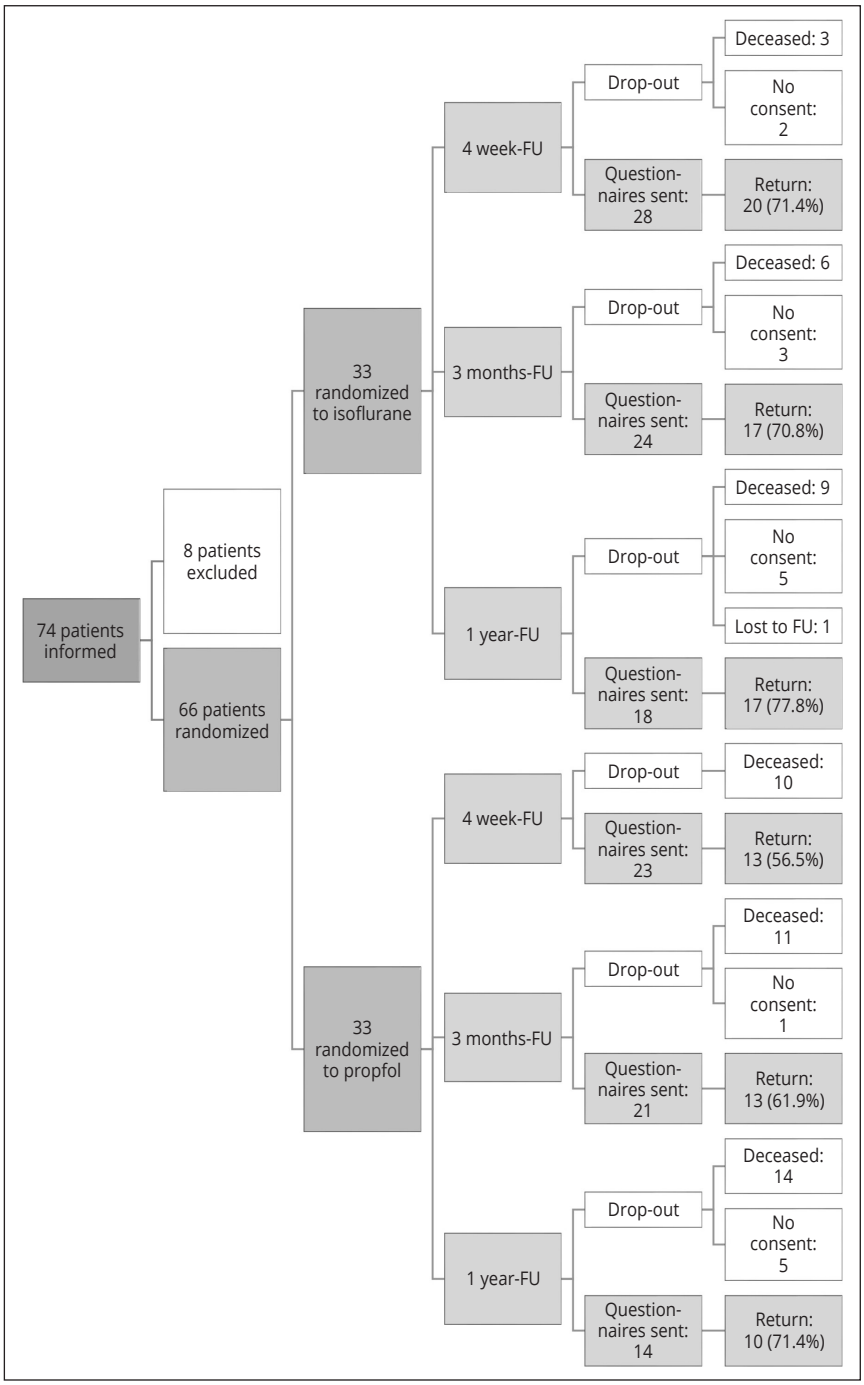

Figure 2.—Return of questionnaires in isoflurane and propofol patients after 4 weeks, 3 months and 1 year.

tween groups. Isoflurane patients showed significantly more sedation- (P=0.016), ventilator- (P=0.011), ICU- (P=0.044) and delirium-free days (P=0.031) compared to propofol patients (Figure 3). Thirty days after randomization, one patient in the isoflurane group died, compared to seven patients in the propofol group (3.0% *versus* 21.2%, P=0.024). After one year, no significant difference in mortality was found (isoflurane: 9 [27.3%] *vs*. propofol: 14 [42.4%]). In total, 128 questionnaires were sent out, of which 87 were returned yielding an overall return rate of 68%. Return of questionnaires is shown in Figure 2. Overall results are shown in Table II. In the ICU-MT, isoflurane patients recalled more factual memories compared to propofol patients after one year (5.4±2.4 *versus* 2.5±2.3, P=0.005), with a trend towards more factual memories after four weeks and three months. There were no significant differences in the number of emotional, and delusional memories between groups at any time point. PTSS-14 scores were not significantly different between groups at any time. However, the probability of PTSD increased over time and was highest after one year (isoflurane: 42.9% *vs*. propofol: 30.0%). Subjective health, general wellbeing and symptoms of anxiety and depression did not differ between groups at any time, as shown by the SF-36, WHO-5 and HADS scores, respectively. Compared to the general population, physical health according to SF-36 was below average and according to WHO-5 results, depression was likely in a majority of patients.

Discussion

The Sedaconda trial, a multicenter randomized controlled trial, showed that inhaled sedation with isoflurane was as effective as propofol for the sedation of invasively ventilated patients in intensive care. In this substudy of the Sedaconda trial, we prospectively investigated the neuropsychological status of 66 patients included at our institution with validated questionnaires at different follow-up times for up to one year after ICU discharge. In the studied population, outcome in general was poor, with high mortality and considerably decreased physical health

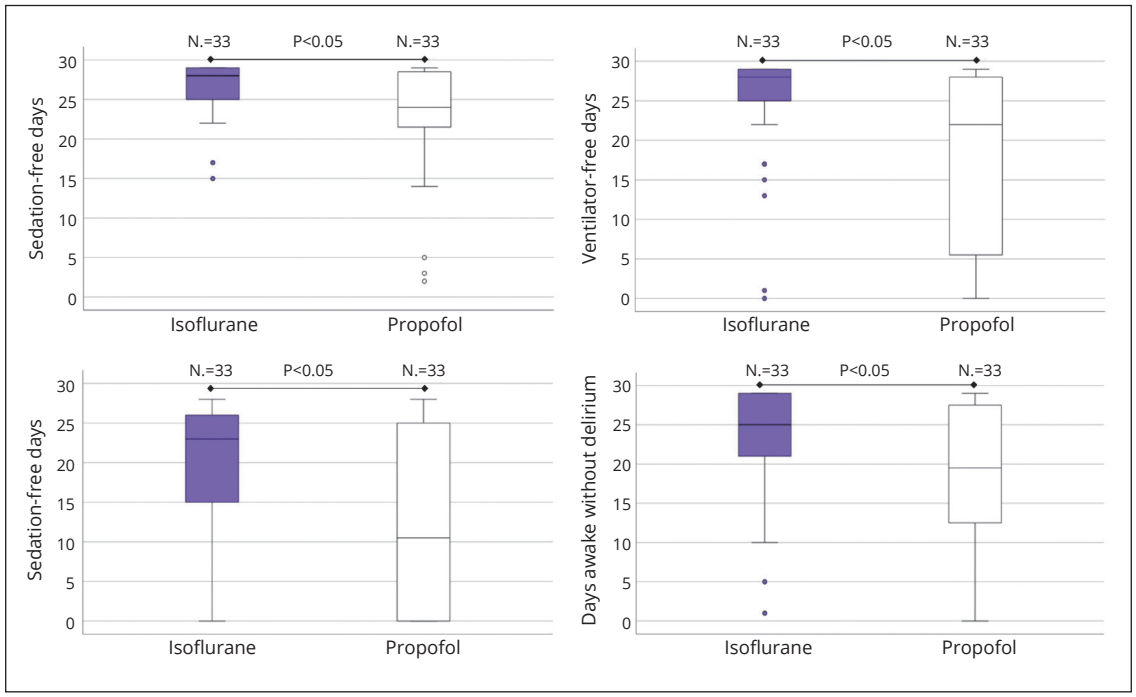

Figure 3.—Sedation-free days, ventilator-free days, intensive care-free days and days awake without delirium, shown as box plots for isoflurane and propofol patients respectively. Isoflurane patients showed significantly more sedation- (P=0.016), ventilator- (P=0.011), intensive care-free days (P=0.044) and days awake without delirium compared to propofol patients.

TABLE II.—*Results of the long-term follow-up.*

Study group	Four-week follow-up		Three-month follow-up		One-year follow-up	
	Isoflurane	Propofol	Isoflurane	Propofol	Isoflurane	Propofol
ICU-MT (N.)	20	13	16	11	14	11
Factual memories	18 (90%)	11 (84.6%)	16 (100%)	10 (90.9%)	14 (100%)	9 (81.8%)
Factual memories per patient	4.2±3.3	3.0±2.4	5.3±2.3	4.6±3.2	5.4±2.4*	2.5±2.3*
Emotional memories	11 (55%)	10 (76.9%)	13 (81.3%)	9 (81.8%)	10 (71.4%)	8 (72.7%)
Emotional memories per patient	2.4±1.9	1.25±1.25	1[1;7]	2[1;4.5]	3.57±2.5	2±2.16
Delusional memories	9 (45%)	8 (61.5%)	10 (62.5%)	8 (72.7%)	11 (78.6%)	9 (81.8%)
Delusional memories per patient	1.43±1.62	1.0±1.41	1.43±1.62	2.25±1.71	1.71±1.5	2.0±1.41
SF-36 (N.)	16	7	14	8	10	11
Physical Health Summary Score	32.2±10.1	31.4±5.5	34.4±11	37.4±14.4	42.4±9.7	42.4±9.7
Mental Health Summary Score	45.1±10.8	48.6±10.1	44.2±10.1	46.2±12.7	46±12.8	43.9±11.4
WHO 5 (N.)	16	11	16	11	14	10
General wellbeing	10.3±5.9	8.1±6.3	10.8±6.0	11.6±7.4	13.1±5.6	9.9±7.0
Depression likely (≤12 points)	11 (68.8%)	7 (63.6%)	9 (56.3%)	6 (54.5%)	6 (42.9%)	7 (70%)
PTSS-14 (N.)	19	11	16	10	14	10
PTSS-14 score	35±12.9	30.6±11.9	33.7±15,8	34.3±16.7	43.5±22.1	43.7±20.6
PTSD likely (≥40 points)	7 (36.8%)	1 (9.1%)	6 (37.5%)	2 (20%)	6 (42.9%)	3 (30%)
HADS Anxiety (N.)	19	11	16	12	14	10
Normal (≤7 points)	13 (68.4%)	7 (63.6%)	9 (56.3%)	9 (75%)	8 (57.1%)	6 (60%)
Borderline abnormal (8-10 points)	3 (15.8%)	1 (9.1%)	5 (31.3%)	1 (8.3%)	2 (14.3%)	2 (20%)
Abnormal (≥11 points)	3 (15.8%)	3 (27.3%)	2 (12.5%)	2 (16.7%)	4 (28.6%)	2 (20%)
HADS depression (N.)	19	12	16	12	14	9
Normal (≤7 points)	12 (63.2%)	5 (41.7%)	8 (50%)	5 (41.7%)	8 (57.1%)	5 (55.6%)
Borderline abnormal (8-10 points)	4 (21.1%)	4 (33.3%)	3 (18.8%)	1 (8.3%)	3 (21.4%)	2 (22.2%)
Abnormal (≥11 points)	3 (15.8%)	3 (25%)	5 (31.3%)	6 (50%)	3 (21.4%)	2 (22.2%)

Data are patient numbers (percentage) or mean ± SD.
ICU-MT: Intensive Care Unit-Memory Tool; SF36: Short Form-36 Health Survey; WHO 5: World Health Organisation-Five Well Being Index; PTSS-14: Post-traumatic Stress Scale-14, HADS: Hospital Anxiety and Depression Scale.
*Significant differences at a significance level of <0.05.

and general wellbeing compared to the general population. Patients sedated with isoflurane had significantly more sedation-, ventilator-, ICU- and delirium-free days compared to patients sedated with propofol. Similar results were found by Bracht *et al*. in a *post-hoc* analysis including all patients of the Sedaconda trial, with significantly more ICU-free days and a trend to more ventilator-free days.[21]

Delirium and short-term follow-up

When CAM-ICU was examined 24 hours after sedation stop, very few patients showed delirium. However during the 30 day short-term follow-up, 68% of patients were affected by delirium. This is in line with previous trials investigating delirium in intensive care, which reported between 30% and 80% of patients being affected by delirium.[1-4] Isoflurane patients had significantly more delirium-free days. This may be caused by several factors. Isoflurane patients woke up faster and showed a better cognitive recovery. They also received significantly less opioids.[14] Opioids have been associated with delirium in previous trials.[22-24] In one study, opioid usage led to 2.5-fold increase in delirium incidence. In addition, this same trial showed a strong relationship between propofol usage and development of delirium.[25] This could be an explanation for the poor results in the propofol patients of our trial.

Long-term follow-up

Many intensive care patients suffer from both physical and mental impairment even long after their hospital discharge.[6, 26-28] This is also represented in our patient cohort, where survival after one year was 63.6% and the results of the neuropsychological follow-up showed a poor quality of life in surviving patients. These results should not only be attributed to the choice of sedation agent, but to all aspects regarding intensive care. After discharge from the ICU, patients have a worse quality of life compared to age- and sex-matched groups.[29] Neuropsychological out-

come after inhaled sedation has only been investigated once by Sackey *et al*. in 2008. Patients were randomized to isoflurane and midazolam and after six months, questionnaires were sent to the surviving 29 of initially 40 included patients. Questionnaires included ICU-MT, HADS, IES (Impact of Event Scale), the Well-Being Index and several screening questions for PTSD.[7] While no differences were observed in long-term psychological morbidity, the results of the study indicated a trend towards fewer hallucinations or delusions with isoflurane compared to midazolam in the long-term follow-up. In our trial, the long-term follow-up was done in a larger patient cohort at three different points of time and the questionnaires used included ICU-MT, SF-36, WHO-5, HADS and PTSS-14. In summary, isoflurane patients had significantly more factual memories after one year, no further differences could be found.

Mortality

Mortality after inhaled sedation has been investigated in the past. Most trials had a short observation period, as opposed to our study where patients were followed for up to one year. Kong *et al*. reported a mortality of 3% in both groups in a 24-hour observation period,[12] Spencer and Williats reported a hospital mortality of 20% in isoflurane and 17% in midazolam patients.[30] Two trials investigated mortality after hospital discharge. Sackey *et al*. reported a six-month mortality in isoflurane patients of 20% (four out of 20 patients) compared to 35% (seven out of 20 patients) in midazolam.[7] Bellgardt *et al* analyzed a consecutive cohort of 369 critically ill surgical patients with sedation and invasive ventilation for more than 96 hours. Hospital and one year mortality after isoflurane sedation were considerably lower compared to propofol/midazolam sedation (40% *versus* 63% and 50% *versus* 70%, respectively).[31] Also in this substudy, the 30-day-mortality was significantly lower after isoflurane compared to propofol (3% *vs*. 21%), and mortality after one year also showed a trend in this direction (27% *versus* 42%). Lower mortality in isoflurane patients may be caused by several factors. Deep intravenous sedation can increase mortality, as Shehabi *et al*. showed in a prospective multicenter trial investigating the relationship between sedation depth and mortality.[4] It could be argued that isoflurane itself does not lead to lower mortality, but the prevention of adverse drug reactions in deep sedation does.[31] A recent meta analysis by Kotani *et al*. showed a significant mortality increase after propofol compared to other sedative agents.[32] In addition, isoflurane has many beneficial effects that may have contributed to a decreased mortality to some extent. Isoflurane has bronchodilatory[33] as well as vasodilatory effects in coronary arteries.[34] Organ-protective effects in the heart,[35-37] brain,[38] kidneys, liver, and the gastrointestinal tract[39] have also been suggested.

Limitations of the study

CAM-ICU was only introduced after 38 patients had been included. Short-term follow-up data were acquired retrospectively. In few cases, incomplete documentation made delirium assessment impossible, which may have lead to underestimation of delirium. Incidence of delirium is stated as delirium free days, where mortality could act as a confounder. Longer survival in isoflurane patients led to more opportunities to develop delirium. Nevertheless, isoflurane patients had significantly more delirium free days. In the long term follow-up, only relatively few patients could be evaluated. For instance after one year, data from little more than ten patients in both groups were available. Patients were contacted by phone and asked permission to send the questionnaires. Very few patients denied or were lost to follow-up, but many patients simply did not survive long enough to be assessed (mortality: four-weeks-FU 19.7%; three month-FU 25.8%; one-year-FU 34.8%). Overall return rate of the questionnaires was 68%, which was unexpectedly high and compares favorably with other studies.[7] However, some patients were reluctant to fill in the questionnaires and indicated their impaired physical status or recurring negative memories as a reason. This could have lead to a bias favouring better results, since patients with the greatest impairment may not have been assessed in the follow-up. Taken together, sample size of patients evaluated in the long term follow-up may preclude definite conclusions on differ-

ences in long term neuropsychological outcome in patients sedated with isoflurane or propofol. Therefore, larger studies are needed.

Conclusions

During 30 days after invasive ventilation and sedation, isoflurane sedation led to significantly more sedation-, ventilator-, ICU- and delirium-free days compared to propofol sedation. One year mortality was high and neuropsychological long term outcome was poor in both groups, with no significant group differences, likely because of high mortality and too few patients remaining for analysis.

What is known

• Incidence of delirium is high among patients sedated and ventilated in the ICU and is associated with poor patient outcomes.

What is new

• Sedation with isoflurane led to significantly more sedation-, ventilator-, ICU- and delirium-free days compared to propofol patients.

References

1. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, *et al.* Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703–10. [Internet]

2. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, *et al.* Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. J Trauma 2008;65:34–41.

3. Salluh JI, Soares M, Teles JM, Ceraso D, Raimondi N, Nava VS, *et al.*; Delirium Epidemiology in Critical Care Study Group. Delirium epidemiology in critical care (DECCA): an international study. Crit Care 2010;14:R210.

4. Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MA, *et al.*; Sedation Practice in Intensive Care Evaluation (SPICE) Study Group investigators. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med 2013;39:910–8.

5. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, *et al.* Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.

6. Kiekkas P, Theodorakopoulou G, Spyratos F, Baltopoulos GI. Psychological distress and delusional memories after critical care: a literature review. Int Nurs Rev 2010;57:288–96.

7. Sackey PV, Martling CR, Carlswärd C, Sundin O, Radell PJ. Short- and long-term follow-up of intensive care unit patients after sedation with isoflurane and midazolam—a pilot study. Crit Care Med 2008;36:801–6.

8. Soliman HM, Mélot C, Vincent JL. Sedative and analgesic practice in the intensive care unit: the results of a European survey. Br J Anaesth 2001;87:186–92.

9. Granberg Axèll AI, Malmros CW, Bergbom IL, Lundberg DB. Intensive care unit syndrome/delirium is associated with anemia, drug therapy and duration of ventilation treatment. Acta Anaesthesiol Scand 2002;46:726–31.

10. Sackey PV, Martling CR, Granath F, Radell PJ. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. Crit Care Med 2004;32:2241–6.

11. Meiser A, Laubenthal H. Inhalational anaesthetics in the ICU: theory and practice of inhalational sedation in the ICU, economics, risk-benefit. Best Pract Res Clin Anaesthesiol 2005;19:523–38.

12. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. BMJ 1989;298:1277–80.

13. Yassen KA, Jabaudon M, Alsultan HA, Almousa H, Shahwar DI, Alhejji FY, *et al.* Inhaled Sedation with Volatile Anesthetics for Mechanically Ventilated Patients in Intensive Care Units: A Narrative Review. J Clin Med 2023;12:1069.

14. Soldinger N. [Evaluation of wake-up and extubation times as part of the IsoConDa study]; 2020 [Internet]. Available from: https://publikationen.sulb.uni-saarland.de/bitstream/20.500.11880/31379/1/Dissertation_UdS_Soldinger.pdf [cited 2024, Feb 7]. [German].

15. Meiser A, Volk T, Wallenborn J, Guenther U, Becher T, Bracht H, *et al.*; Sedaconda study group. Inhaled isoflurane via the anaesthetic conserving device versus propofol for sedation of invasively ventilated patients in intensive care units in Germany and Slovenia: an open-label, phase 3, randomised controlled, non-inferiority trial. Lancet Respir Med 2021;9:1231–40.

16. Jones C, Humphris G, Griffiths R. Preliminary validation of the ICUM tool: A tool for assessing memory of the intensive care experience. Clin Intensive Care 2000;11:251–5.

17. Morfeld M, Kirchberger I, Bullinger M. [SF-36. M. SF-36. Health status questionnaire]. Göttingen: Hogrefe Publishing Corp.; 2011. [German].

18. Radtke FM, Franck M, Drews T, Weiss-Gerlach E, Twigg E, Harbeck-Seu A, *et al.* [The Post-Traumatic Stress Syndrome 14-Questions Inventory (PTSS-14) - Translation of the UK-PTSS-14 and validation of the German version]. Anasthesiol Intensivmed Notfallmed Schmerzther 2010;45:688–95. [German]

19. Bech P. The WHO-five Well-being Index (WHO-5); 1998 [Internet]. Available from: https://ogg.osu.edu/media/documents/MB%20Stream/who5.pdf [cited 2024, Feb 7].

20. Hermann-Lingen C, Buss U, Snaith RP. Hospital Anxiety and Depression Scale - Deutsche Version (HADS-D). Bern: Auflage; 2011. p.19–22.

21. Bracht H, Meiser A, Wallenborn J, Guenther U, Kogelmann KM, Faltlhauser A, *et al.*; Sedaconda Study Group. ICU- and ventilator-free days with isoflurane or propofol as a primary sedative - A post- hoc analysis of a randomized controlled trial. J Crit Care 2023;78:154350.

22. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing 2011;40:23–9.

23. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. Intensive Care Med 2001;27:1297–304.

24. Swart LM, van der Zanden V, Spies PE, de Rooij SE, van Munster BC. The Comparative Risk of Delirium with Different Opioids: A Systematic Review. Drugs Aging 2017;34:437–43.

25. Pavone KJ, Jablonski J, Cacchione PZ, Polomano RC, Compton P. Evaluating Pain, Opioids, and Delirium in Critically Ill Older Adults. Clin Nurs Res 2021;30:455–63.

26. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med 2001;29:573–80.

27. Samuelson KA, Lundberg D, Fridlund B. Stressful memories and psychological distress in adult mechanically ventilated intensive care patients - a 2-month follow-up study. Acta Anaesthesiol Scand 2007;51:671–8.

28. Granja C, Lopes A, Moreira S, Dias C, Costa-Pereira A, Carneiro A; JMIP Study Group. Patients' recollections of experiences in the intensive care unit may affect their quality of life. Crit Care 2005;9:R96–109.

29. Gerth AM, Hatch RA, Young JD, Watkinson PJ. Changes in health-related quality of life after discharge from an intensive care unit: a systematic review. Anaesthesia 2019;74:100–8.

30. Spencer EM, Willatts SM. Isoflurane for prolonged sedation in the intensive care unit; efficacy and safety. Intensive Care Med 1992;18:415–21.

31. Bellgardt M, Bomberg H, Herzog-Niescery J, Dasch B, Vogelsang H, Weber TP, *et al.* Survival after long-term isoflurane sedation as opposed to intravenous sedation in critically ill surgical patients: retrospective analysis. Eur J Anaesthesiol 2016;33:6–13.

32. Kotani Y, Pruna A, Turi S, Borghi G, Lee TC, Zangrillo A, *et al.* Propofol and survival: an updated meta-analysis of randomized clinical trials; 2023 [Internet]. Available from: http://creativecommons.org/licenses/by/4.0/ [cited 2024, Feb 7].

33. Brichant JF, Gunst SJ, Warner DO, Rehder K. Halothane, enflurane, and isoflurane depress the peripheral vagal motor pathway in isolated canine tracheal smooth muscle. Anesthesiology 1991;74:325–32.

34. Gamperl AK, Hein TW, Kuo L, Cason BA. Isoflurane-induced dilation of porcine coronary microvessels is endothelium dependent and inhibited by glibenclamide. Anesthesiology 2002;96:1465–71.

35. Asgeri M, Ahmadpour F, Negargar S, Khadra WZ, Porhomayon J, Nader ND. The comparative myocardial protection by propofol and isoflurane in an in vivo model of ischemia reperfusion. Semin Cardiothorac Vasc Anesth 2011;15:56–65.

36. Sepac A, Sedlic F, Si-Tayeb K, Lough J, Duncan SA, Bienengraeber M, *et al.* Isoflurane preconditioning elicits competent endogenous mechanisms of protection from oxidative stress in cardiomyocytes derived from human embryonic stem cells. Anesthesiology 2010;113:906–16.

37. Stadnicka A, Marinovic J, Ljubkovic M, Bienengraeber MW, Bosnjak ZJ. Volatile anesthetic-induced cardiac preconditioning. J Anesth 2007;21:212–9.

38. Khatibi NH, Ma Q, Rolland W, Ostrowski R, Fathali N, Martin R, *et al.* Isoflurane posttreatment reduces brain injury after an intracerebral hemorrhagic stroke in mice. Anesth Analg 2011;113:343–8.

39. Kim M, Park SW, Kim M, D'Agati VD, Lee HT. Isoflurane activates intestinal sphingosine kinase to protect against renal ischemia-reperfusion-induced liver and intestine injury. Anesthesiology 2011;114:363–73.

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Verena Fuchs and Henrik Simon have given substantial contributions to the study conception; Andreas Meiser, Verena Fuchs and Nina Soldinger contributed to the data acquisition, analysis and interpretation; all authors have participated to the manuscript draft, Thomas Volk contributed to data interpretation and revised the draft critically. All authors read and approved the final version of the manuscript.

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