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

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Summary

Background Previous studies indicate that isoflurane could be useful for the sedation of patients in the intensive care unit (ICU), but prospective studies evaluating isoflurane's efficacy have been small. The aim of this study was to test whether the sedation with isoflurane was non-inferior to sedation with propofol.

Methods This phase 3, randomised, controlled, open-label non-inferiority trial evaluated the efficacy and safety of up to 54 h of isoflurane compared with propofol in adults (aged ≥18 years) who were invasively ventilated in ICUs in Germany (21 sites) and Slovenia (three sites). Patients were randomly assigned (1:1) to isoflurane inhalation via the Sedaconda anaesthetic conserving device (ACD; Sedana Medical AB, Danderyd, Sweden; ACD-L [dead space 100 mL] or ACD-S [dead space 50 mL]) or intravenous propofol infusion (20 mg/mL) for 48 h (range 42–54) using permuted block randomisation with a centralised electronic randomisation system. The primary endpoint was percentage of time in Richmond Agitation–Sedation Scale (RASS) range –1 to –4, assessed in eligible participants with at least 12 h sedation (the per-protocol population), five or more RASS measurements, and no major protocol violations, with a non-inferiority margin of 15%. Key secondary endpoints were opioid requirements, spontaneous breathing, time to wake-up and extubation, and adverse events. Safety was assessed in all patients who received at least one dose. The trial is complete and registered with EudraCT, 2016–004551–67.

Findings Between July 2, 2017, and Jan 12, 2020, 338 patients were enrolled and 301 (89%) were randomly assigned to isoflurane (n=150) or propofol (n=151). 146 patients (97%) in each group completed the 24-h follow-up. 146 (97%) patients in the isoflurane group and 148 (98%) of patients in the propofol group were included in the per-protocol analysis of the primary endpoint. Least-squares mean percentage of time in RASS target range was 90·7% (95% CI 86·8–94·6) for isoflurane and 91·1% (87·2–95·1) for propofol. With isoflurane sedation, opioid dose intensity was 29% lower than with propofol for the overall sedation period (0·22 [0·12–0·34] *vs* 0·32 [0·21–0·42] mg/kg per h morphine equivalent dose, p=0·0036) and spontaneous breathing was more frequent on day 1 (odds ratio [OR] 1·72 [1·12–2·64], generalised mixed linear model p=0·013, with estimated rates of 50% of observations with isoflurane *vs* 37% with propofol). Extubation times were short and median wake-up was significantly faster after isoflurane on day 2 (20 min [IQR 10–30] *vs* 30 min [11–120]; Cox regression p=0·0011). The most common adverse events by treatment group (isoflurane *vs* propofol) were: hypertension (ten [7%] of 150 *vs* two [1%] of 151), delirium (eight [5%] *vs* seven [5%]), oliguria (seven [5%] *vs* six [4%]), and atrial fibrillation (five [3%] *vs* four [3%]).

Interpretation These results support the use of isoflurane in invasively ventilated patients who have a clinical need for sedation.

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Introduction

Sedation is clinically indicated in a large proportion of patients who are invasively ventilated in intensive care units (ICUs) for their comfort and safety.[1–3] Concerns have been raised regarding the use of intravenous sedatives and opioids in patients in ICUs, in part due to the unpredictable pharmacodynamics and pharmacokinetics of these drugs in patients who are critically ill.[3] Recognised problems with the commonly used ICU sedatives propofol, benzodiazepines, and dexmedetomidine include long and unpredictable wake-up times, and the development of propofol infusion syndrome, delirium, and

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Research in context

Evidence before this study

Concerns regarding the use of common intravenous sedatives in patients who are critically ill in intensive care units (ICUs) have led to strategies aiming to reduce iatrogenic harm. The pharmacology of inhaled anaesthetics, in light of the organ dysfunction that many patients in the ICU have, indicates that they might be a good choice for ICU sedation; however, these drugs are not approved for this indication. At the time of designing the current study, a PubMed literature search was done on May 6,2016, identifying studies of isoflurane for ICU sedation, with or without the use of the anaesthetic conserving device (ACD), using the search terms "isoflurane sedation" and "intensive care" from Jan 1, 1985, (the approximate time of the introduction of isoflurane) onwards. The search included prospective randomised studies and retrospective cohort studies but did not include case reports. The search results were limited to those published in English. The identified studies indicated the potential benefit of the use of isoflurane; in subanaesthetic concentrations, isoflurane could be used for sedation of invasively ventilated ICU patients, with evidence indicating shorter time to emergence after end of sedation compared with intravenous sedation.

Added value of this study

This randomised controlled trial of 301 patients provides, to our knowledge, the largest prospective data source to date on inhaled sedation with isoflurane via the ACD. It confirms the efficacy and safety of this therapy for invasively ventilated patients and its non-inferiority to propofol. Sedation of patients who are invasively ventilated in the ICU with isoflurane via the ACD is efficacious and well tolerated. It facilitates opioid dose reduction, spontaneous breathing, and short and more predictable emergence times from sedation compared with intravenous sedatives.

Implications of all the available evidence

In line with previous data, the present study supports routine use of inhaled isoflurane. The results of this study and previous data support an application for a formal approval of isoflurane for ICU sedation and might affect sedation policies. Further research should address long-term effects during prolonged exposures such as ventilator time, length of ICU stay, and cognitive outcomes, as well as the effects of inhaled isoflurane in specific ICU subpopulations such as patients with acute respiratory distress.

life-threatening bradycardia.[1,3,4] Strategies have been developed to reduce the complications that sedatives and opioid infusions could cause.[5,6] Although non-sedation might be an appropriate strategy for some patients to avoid the iatrogenic harm of intravenous sedation, it could increase the risk of agitation and inadvertent removal of the endotracheal tube or lines, despite high staff density.[7]

A drug that sedates effectively but with minimal residual sedation after the end of administration, and without the aforementioned drawbacks of current agents, would be valuable. Evidence from a number of small studies indicates that isoflurane might fulfil this role.[8–10] There has been increasing interest in inhaled sedation in the past decade.[11,12] In parallel, the Sedaconda anaesthetic conserving device (ACD; Sedana Medical AB, Danderyd, Sweden), formerly known as AnaConDa, has been developed for the delivery of inhaled anaesthetics; this previously off-label therapy has now been endorsed in national and international guidelines (eg, German guidelines,[13] and guidelines from the Pan-American and Iberian Federation of Societies of Critical Medicine and Intensive Therapy[14]).

Although cohort studies and small prospective studies support the usefulness and safety of inhaled isoflurane for patients who are invasively ventilated in the ICU,[8,11,15] a larger prospective study is warranted to evaluate its safety and effectiveness in the ICU population. Our phase 3, randomised, controlled non-inferiority trial was done to evaluate the efficacy and safety of inhalation of isoflurane via the ACD compared with intravenous propofol as the sole sedative, combined with opioid administration, for up to 54 h in patients who were invasively ventilated in the ICU. Our primary hypothesis was that sedation with isoflurane would be non-inferior to sedation with propofol, assessed with the proportion of time within a predefined target sedation range.

Methods

Study design

This was a phase 3, randomised, controlled, open-label, multicentre, parallel-group, non-inferiority trial with up to 54 h of study sedation and 30 days of follow-up. Patients were recruited from 13 medical or general ICUs, ten surgical ICUs, and one neurological ICU in Germany (21 sites) and Slovenia (three sites).

The study was done in accordance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP) standards and the Declaration of Helsinki. Ethical approval for this study was provided by Ethikkommission der Ärztekammer des Saarlandes, Germany, during the ethics approval meeting on Feb 16, 2017, with final approval on April 18, 2017. Ethical approval was also provided by National Medical Ethics Committee Komisija republike Slovenije za medicinsko etiko, Slovenia on June 6, 2019. Approvals were also granted by the relevant authorities of Germany (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]) and Slovenia (Javna agencija republike Slovenije za zdravila in medicinske pripomočke). The study is registered in the European Medicines Agency's EU Clinical Trial register, 2016–004551–67.

Participants

Those assessed for inclusion in the study were adults aged at least 18 years, who were admitted to the ICU and were expected to require continuous invasive ventilation and sedation for at least 24 h, receiving propofol at the time of randomisation, and with a prescribed Richmond Agitation–Sedation Scale (RASS) target within the range of –1 to –4. Full inclusion and exclusion criteria are provided in the appendix (p 6). Informed, written patient consent complied with European and national laws and regulations; consent was obtained from the patient or patient's representative, as appropriate.

Randomisation and masking

Patients were randomly assigned (1:1) to isoflurane inhalation or propofol infusion, stratified by study site. Permuted block randomisation was used with block sizes of two, four, and six patients, using a centralised electronic randomisation system. Patients were enrolled by the local investigator or designee. Because of the difficulties of doing a blinded study involving both intravenous and inhaled sedatives, administering placebo via the ACD, the characteristic scent of isoflurane, and safety concerns when blinding gas monitoring, it was agreed with the relevant German competent authority (BfArM) that the study would be open label.

Procedures

Eligible patients were randomly assigned to receive 100% isoflurane via the ACD (ACD-L [dead space 100 mL] or ACD-S [dead space 50 mL]) or propofol administered intravenously (20 mg/mL) for 48 h (range 42–54) or until extubation, whichever occurred first. Patients were treated by the clinical team bedside, with study-related procedures supervised by the local investigator. Initially, all patients assigned to isoflurane received isoflurane via the ACD-L. After approximately half of the patients had been included and a protocol amendment had been approved on June 24, 2018, by Ethikkommission der Ärztekammer des Saarlandes, Germany, the smaller ACD-S was introduced and was used as standard except for in patients with exceptionally high tidal volumes (>800 mL).

The time course of study assessments and treatments is shown in the appendix (p 3). The ACD was set up according to the manufacturer's instructions, together with a gas monitor and a scavenging system (appendix p 4). Sedation was started after priming of the ACD with isoflurane. The syringe pump was started at an initial rate of 3·0 mL/h and any other sedatives were simultaneously turned off. During initiation and until the target sedation depth was achieved and considered stable, RASS was assessed every 15 min. Dosage was titrated by incremental adjustments of the pump rate by 0·5–1·0 mL/h as needed, up to a maximum 1·5 volume (%) to maintain the prescribed target sedation depth.

The need for sedation in the RASS range –1 to –4 is variable, but lighter levels are typically sufficient for most patients after a few days of mechanical ventilation.[1,2] The duration limit of 54 h was set by the sponsor of the study, in agreement with the German competent authority, as this duration was considered sufficient for regulatory approval of isoflurane for the new indication.

For patients in the propofol group, propofol 20 mg/mL was used. The dose was started at the same dose as the propofol dose before randomisation. As described previously, other sedatives were simultaneously turned off when the study sedative was started, and RASS was assessed every 15 min. Propofol dosage was titrated stepwise by approximately 0·5–0·8 mg/kg per h as needed to a dose range between 0·3 and 4·0 mg/kg per h. Doses above 4 mg/kg per h were not permitted.

See Online for appendix

RASS was scored every 2 h and before sedative dose changes. Whenever possible, only study sedatives were used, titrated as necessary or given in bolus doses (0·3–0·5 mL of isoflurane and 0·3–0·5 mg/kg of propofol) up to four times per h during planned procedures or if the patient was outside the target RASS range. In cases of inadequate sedation or acute agitation not controlled using the maximum study treatment and cotreatment with an analgesic agent, rescue sedation with bolus doses of midazolam (maximum of 20 µg/kg per h) was allowed. All patients received analgesia with sufentanil or fentanyl as the first-line opioid analgesic; other opioids could also be used as appropriate. All doses of sedatives, analgesics, inotropes, and vasoactive infusions, and other concomitant medications were recorded. The need for, and dosage adjustments of, analgesia were evaluated using the behavioural pain scale (BPS) every 4 h and before dose adjustments. Ketamine, α-2 agonists, muscle relaxants, and benzodiazepines (except for rescue sedation) were prohibited. Extubation time (time from stopping study drug to removal of the endotracheal tube) was recorded in patients extubated during study drug treatment.

After 48 h (range 42–54) of study sedation, if the patient was still invasively ventilated and in need of sedation, treatment was continued according to standard of care, at the discretion of the treating physician. Serious adverse events, adverse events, and concomitant medication from randomisation and up to 24 h after the end of study sedation were documented. A second follow-up by chart review or telephone contact was completed 30 days after randomisation to collect organ function parameters. Renal and hepatic laboratory test results, sequential organ failure assessment scores, and delirium and coma status for the 7 days after randomisation were collected from the medical charts. The use of renal replacement therapy, cardiac arrhythmias requiring treatment, time on the ventilator and in the ICU, mortality, and sedative agents used were recorded for the entire 30-day period.

During daily spontaneous awakening trials, study treatment and infusions of opioid analgesics were stopped, unless opioids were clinically indicated. A spontaneous breathing trial was done, and the Confusion Assessment

Method for the ICU and Glasgow Coma Scale were assessed. BPS was documented every 4 h, together with vital signs and ventilatory parameters.

Outcomes

The primary endpoint was sedation efficacy, assessed as the proportion of time within RASS –1 to –4 without rescue sedation for isoflurane compared with propofol, assessed in the per protocol population (defined as fulfilling study criteria: ≥12 h of study drug treatment, ≥5 RASS assessments, and no protocol violations impacting non-inferiority analysis or efficacy analysis; appendix p 7). Secondary efficacy endpoints were time to wrequirements during study sedation (and related BPS scores), and time to extubation. Secondary safety endpoints assessed the safety profile of isoflurane (adverse events, serious adverse events, biochemistry and laboratory values, vital signs, and organ function), number of ventilator-free days and number of ICU-free days (30-day follow-up), number of delirium-free days (7-day follow-up), and the ability to breathe spontaneously. All secondary efficacy and safety endpoints were assessed in the full analysis set (the intention-to-treat population for this trial), which comprised all randomised patients who had been treated with at least one dose of isoflurane or propofol and had post-baseline data collected. Exploratory efficacy endpoints were isoflurane and propofol dosing over time, sedation depth (assessed using RASS), and administration of rescue sedation. Exploratory safety endpoints were the number of coma-free days (7-day follow-up), inotropic or vasopressor agent administration, 30-day mortality, and the frequency of ACD deficiencies. All exploratory data was analysed in the full analysis set (appendix p 7).

Statistical analysis

The sample size calculation was based on non-inferiority testing of the primary endpoint. Given the unknown variance of the primary endpoint as defined for the study, a preliminary sample size with a non-inferiority margin of 15% and power of 80% was estimated as a first step before the study, with a conservative SD estimate (40%), indicating a sample size of 550 evaluable patients. A pre-planned, statistician-blinded, sample size re-estimation was done in the first 150 patients, without group separation, and showed a lower SD than initially estimated (15·6%), rendering a sample size of 300 patients, which was the minimum sample size required by BfArM for the study.

Continuous variables were summarised using descriptive statistics and categorical variables were summarised in frequency tables, both by treatment group. The primary efficacy endpoint was analysed using a fixed-sequence testing procedure consisting of a non-inferiority test followed by a superiority test if the non-inferiority test was positive. For the primary endpoint, the comparison between treatment groups was made using an ANOVA model with treatment group as fixed effect and centre or pseudocentre (sites with fewer than ten participants were merged into pseudocentres to avoid small strata in the analysis) as a categorical random effect. The primary endpoint mixed model ANOVA with additional pre-specified covariates and repeated measurement specifications (if applicable) was used for other continuous endpoints, and a mixed-effect model-based estimate of the difference between the treatment groups were calculated, along with 95% CIs. Non-inferiority (treatment relative difference less than 15%) of isoflurane versus propofol was evaluated on the basis of the one-sided 97·5% CI. This analysis was done in the per-protocol population (defined as patients who met all study criteria, who received study drug for >12 h, with a minimum of five RASS assessments, and with no major protocol deviation affecting analyses; appendix p 7). The full analysis set was used for the sensitivity analysis and test of superiority. This full analysis set (serving as the intention-to-treat population in this study) was defined as patients that had received any dose of study drug and had baseline data collected (appendix p 7). The primary endpoint and several other endpoints showed skewed distributions, and prespecified non-parametric Monte Carlo permutation tests as well as post-hoc bootstrap analysis methods and β-regression models were used to confirm the robustness of mixed-effect model results.

Differences between groups in time to extubation and wake-up time were analysed by Cox regression, adjusting for pseudocentre (time to extubation only), age, body-mass index (BMI; wake-up time only), and RASS at the start of the test. Sensitivity analyses were done for both time to wake up and time to extubation, using the log-rank test. Repeated measurements of binary outcomes were analysed in terms of the odds of a patient having the event of interest using a generalised linear mixed model with a logistic link function, allowing repeated assessments over time. Imputation of missing data was not done except for the primary outcome and for selected endpoints (SOFA score, coma-free and delirium-free days, ICU-free days, and delirium-free days) from the 7-day and 30-day follow-up periods. In the follow-up periods, missing data due to death or discharge were imputed according to prespecified rules, with attention to the reason for missing data. When assigning daily coma-free or delirium-free status during the 7 days after the end of study sedation, those who had died in the ICU were classified as having the adverse outcome for the remaining days of the 7-day period. Unknown daily status due to discharge categories other than death was replaced using a last observation carried forward approach. A p value equal to or less than 0·05 was taken to indicate statistical significance. Analyses of secondary endpoints were not adjusted for multiplicity, and hence p values should be interpreted as nominal.

A protocol amendment on June 24, 2018, led by investigators blinded to collected data at that time point (AM and PS), extended the follow-up period to 30 days,

together with the addition of the 7-day and 30-day secondary and exploratory endpoints. Retrospective consent from patients who were randomised before the amendment was sought for the extended follow-up. The amendment also permitted use of the ACD-S. The order of secondary and exploratory endpoints was finally determined in a protocol and analysis plan amendment on March 27, 2019. This amendment did not affect analyses as there was no hierarchy or fixed sequence for the analyses.

Role of the funding source

The funder of the study had no role in study design, data collection (except sponsor oversight of contract research organisation), or data analysis. One author (PS) was employed by Sedana Medical AB as the sponsor medical representative during patient recruitment and participated in data interpretation and writing of the report.

Results

2788 patients were assessed for eligibility, of whom 338 consented. Of these 338 patients, 301 (89%) were randomised between July 2, 2017, and Jan 12, 2020, from 21 sites in Germany and three sites in Slovenia (figure 1). Of the 301 patients, 150 (50%) were randomised to isoflurane and 151 (50%) to propofol. Of the patients in the isoflurane group, 86 (57%) received isoflurane via the ACD-L and 64 (43%) via the ACD-S.

292 (97%) randomised patients completed the 24 h follow-up visit, with 146 patients in each treatment group. Reasons for study discontinuation at this stage (n=9) were one adverse event in the isoflurane group, four deaths (two in each group), one loss to follow-up in the propofol group, two other reasons (one in each group), and one physician decision in the propofol group. In a blinded data review before database lock, all 301 randomised patients qualified for the safety analysis set and full analysis set populations (appendix p 7). Seven patients did not fulfill prespecified per-protocol analysis set criteria, making the per-protocol analysis set consist of 294 patients. Four patients randomised to isoflurane were excluded from the per-protocol analysis set because they received the study treatment for less than 12 h (2, 6·7, 8·8, and 9·5 h). Three patients randomised to propofol were excluded from the per-protocol analysis set: two patients because of major protocol violations regarding investigational product dispensing and one patient because of a non-fulfilled inclusion criterion regarding a maximum of 48 h of continuous

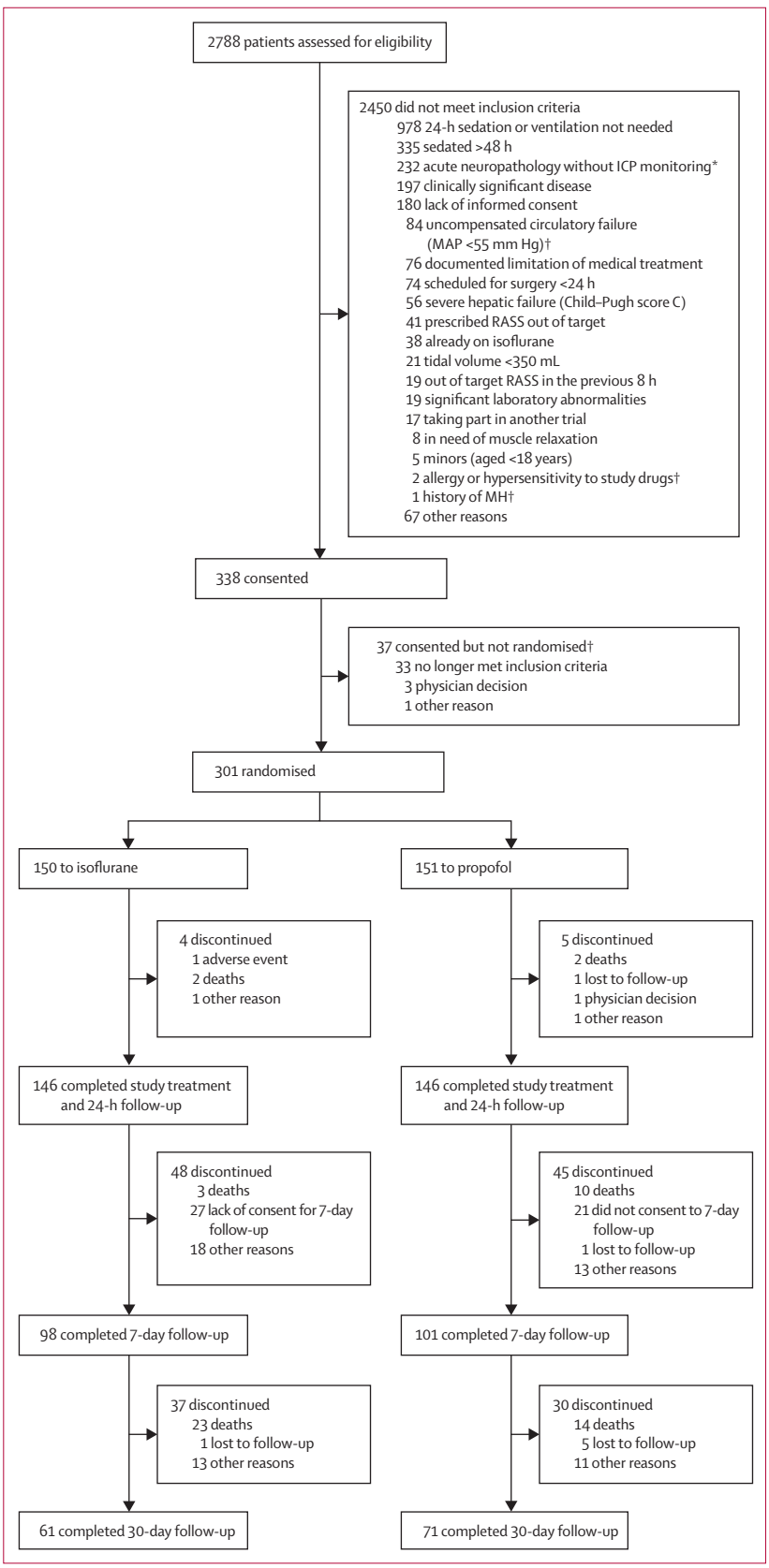

Figure 1: **Study profile**
ICP=intracranial pressure. MAP=mean arterial pressure. MH=malignant hyperthermia. RASS=Richmond Agitation–Sedation Scale.*Most of these patients gave informed consent for participation in the trial before a major operation, but after this were too unstable, critically ill, or did not need postoperative sedation and ventilation for an expected 24 h and were therefore not randomised. †Isoflurane was considered unsuitable for these patients.

	Isoflurane (n=150)	Propofol (n=151)
Age, years	65·8 (11·8)	64·3 (12·9)
Age group		
≥18–64 years	68 (45%)	70 (46%)
≥65–84 years	78 (52%)	74 (49%)
≥85 years	4 (3%)	7 (5%)
Sex		
Female	46 (31%)	53 (35%)
Male	104 (69%)	98 (65%)
BMI, kg/m²	28·0 (6·0)	28·3 (7·7)
Main reason for ICU admission		
Medical	59 (39%)	61 (40%)
Neurosurgical	1 (1%)	1 (1%)
Surgical	86 (57%)	82 (54%)
Trauma	4 (3%)	7 (5%)
Type of admission		
Emergency	98 (65%)	98 (65%)
Non-emergency	52 (35%)	53 (35%)
Any infection at admission		
Yes	72 (48%)	78 (52%)
No	78 (52%)	73 (48%)
SAPS II score	42·3 (16·9)	43·8 (18·5)

Values are n (%) or mean (SD). BMI=body mass index. ICU=intensive care unit. SAPS II=new simplified acute physiology score.

Table 1: **Baseline characteristics**

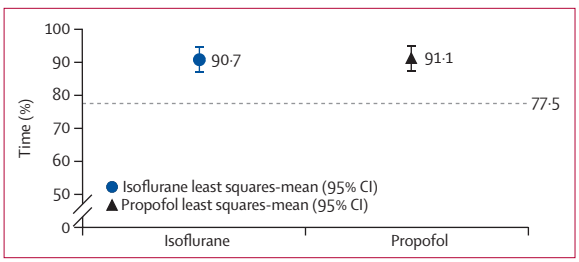

Figure 2: **Proportion of time within sedation target in the per-protocol population (primary endpoint)**
Sedation target was prespecified as RASS scores between –1 and –4. Dashed line indicates non-inferiority cutoff, 15% below propofol least squares-mean. RASS=Richmond Agitation–Sedation Scale.

invasive ventilation and sedation before the start of study sedation. All randomised patients fulfilled the full analysis set criteria, hence all randomised patients were in the safety and full analysis datasets. Patients in the two treatment groups had similar demographic and clinical characteristics at baseline (table 1).

The percentage of time patients spent in the target RASS range without rescue sedation (the primary endpoint) was similar for the per protocol isoflurane (n=146) and propofol (n=148) groups (figure 2); the least squares-mean time within the RASS target interval was 90·7% (95% CI 86·8–94·6) for isoflurane versus 91·1% (87·2–95·1) for propofol. Thus, the lower CI for isoflurane was well above the non-inferiority margin (15% below the least squares mean for propofol; 77·5%). Mean RASS scores for each day of the sedation are illustrated in the appendix (p 5). Six patients in each group received midazolam bolus as rescue medication throughout the study.

Table 2 shows a summary of treatment characteristics. Data on all sedative treatments in the 30-day follow-up after end of study sedation is provided in the appendix (p 7). Overall, 49 (40%) of 121 patients treated with isoflurane and 19 (15%) of 129 patients treated with propofol were switched to the other drug (ie, isoflurane to propofol and vice versa) during the course of the 30-day follow-up, at the treating physician's discretion.

Opioid dose intensity was significantly lower for isoflurane than for propofol on day 1 (least squares-mean 0·23 [95% CI 0·12–0·33] *vs* 0·32 [0·22–0·43] mg/kg per h morphine equivalent dose, p=0·0032) and for the overall sedation period (0·22 [0·12–0·34] *vs* 0·32 [0·21–0·42] mg/kg per h morphine equivalent dose, p=0·0036). BPS scores were similar between groups and remained low throughout the study (figure 3).

For the repeated measurements of spontaneous breathing (yes or no) every 4 h, the generalised linear mixed model estimated that the rate of spontaneous breathing was 50% in the isoflurane group on day 1 of sedation versus 37% in the propofol group (odds ratio [OR] 1·72 [95% CI 1·12–2·64], p=0·013). On day 2, the difference between the two treatment groups was not statistically significant (61% *vs* 51%, OR 1·51 [0·88–2·59], p=0·131).

The median time to wake-up on day 1 was 15 min (IQR 6–60) in the isoflurane group versus 19 min (10–94) in the propofol group (Cox regression adjusted for age, BMI, and RASS at sedation stop: p=0·099; log-rank test [sensitivity analysis] p=0·51). On day 2, at the end of the study treatment, wake-up was significantly faster with isoflurane with lower interindividual variability, at a median of 20 min (IQR 10–30) versus 30 min (11–120; Cox regression: p=0·0011; log rank test [sensitivity analysis] p=0·010; figure 4).

Median extubation time at sedation stop was 30 min (IQR 10–136) in the isoflurane group (n=60) and 40 min (18–125) in the propofol group (n=67). The difference between the two treatment groups was not statistically significant (Cox regression adjusted for pseudocentre, age, and RASS; hazard ratio [HR] 1·29 [95% CI 0·86–1·93], p=0·212).

Outcomes of safety assessments of laboratory parameters, sequential organ failure assessment scores, renal function, and vital signs were similar between the two treatment groups at baseline and throughout the course of the study (appendix p 7). Vasopressors were used in similar proportions between the study groups; 118 (79%) of 150 patients in the isoflurane group and 116 (77%) of 151 in the propofol group had vasopressors at baseline. During study sedation, 126 (84%) of 150 in the isoflurane group and 126 (83%) of 151 in the propofol group received vasopressors.

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	Isoflurane (n=150)	Propofol (n=151)
Pump rate, mL/h	3·5 (1·8)	..
Pump rate, mL/h per L min ventilation	0·39 (0·21)	..
Day 1 (n=150)	0·40 (0·21)	..
Day 2 (n=99)	0·33 (0·21)	..
Isoflurane end-tidal concentration (vol%)*	0·45 (0·19)	..
Day 1 (n=149)	0·45 (0·20)	..
Day 2 (n=74)	0·42 (0·21)	..
Propofol dosage, mg/h	..	191 (90.1)
Propofol dosage, mg/kg per h	..	2·4 (1·2)
Day 1 (n=149)	..	2·4 (1·2)
Day 2 (n=97)	..	2·1 (1·2)
Rescue sedation†		
Day 1	5 (3%)	4 (3%)
Day 2	2 (2%)	5 (5%)
Duration of study sedation		
≤12 h	4 (3%)	0
>12 h to ≤24 h	46 (31%)	51 (34%)
>24 h to ≤36 h	7 (5%)	8 (5%)
>36 h to ≤48 h	83 (55%)	77 (51%)
>48 h to ≤54 h	10 (7%)	15 (10%)

Values are n (%) or mean (SD), unless stated otherwise. *Only one patient in the isoflurane group had a mean end-tidal concentration above 1% (1·4% on day 1), and mean end-tidal concentration in the patient with the second highest mean exposure was 1·0%. †Midazolam boluses were allowed as rescue sedation.

Table 2: **Treatment characteristics**

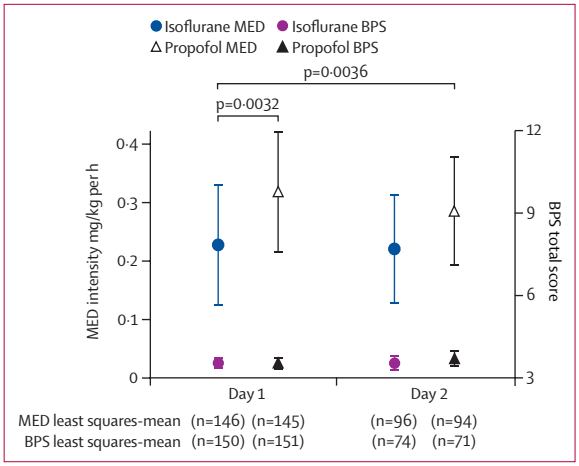

Figure 3: **Morphine equivalent dose intensity and BPS during study sedation in the full analysis set**

Data presented are least squares-means and 95% CIs. In cases in which a 24 h wake-up test was not done, a cutoff at 24 h was applied to separate day 1 and day 2. Three patients in the isoflurane group and two in the propofol group with ambiguous opioid infusion information were excluded from the analysis, as well as one patient in the isoflurane group and two in the propofol group with missing bodyweight information. Additionally, data for two patients receiving propofol with observed MED intensity greater than 10 mg/kg per h in 4 h periods were regarded implausible and excluded. BPS=behavioural pain scale. MED=morphine equivalent dose.

The most common vasopressor used in both treatment groups was norepinephrine. Renal replacement therapy was ongoing at baseline in six (4%) patients in the isoflurane group and seven (5%) patients in the propofol group. Renal replacement therapy was started on the day of randomisation or during the 30 days of follow-up from randomisation in 13 (9%) patients in the isoflurane group and 26 (17%) patients in the propofol group.

17 serious adverse events were reported in 15 patients (nine patients in the isoflurane group and six patients in the propofol group) from randomisation until 24 h after the end of treatment (appendix p 18). Three patients in each group died during treatment. None of the serious adverse events were judged by the responsible investigator or designee to be related to study treatment. The most common adverse events by preferred term (isoflurane *vs* propofol) were hypertension (ten [7%] of 150 *vs* two [1%] of 151), delirium (eight [5%] *vs* seven [5%]), oliguria (seven [5%] *vs* six [4%]), and atrial fibrillation (five [3%] *vs* four [3%]). Almost all events of hypertension, delirium, and agitation occurred shortly after stopping study sedation. A summary of all adverse events and serious adverse events is provided in the appendix (p 18–20).

The median number of delirium-free days was 7 (IQR 6–7) in the isoflurane group and 7 (5–7) in propofol group (p=0·431). The median number of coma-free days was 7 (IQR 5–7) in the isoflurane group and 7 (3–7) in the propofol group (p=0·145). The median number of ventilator-free days in the first 30 days after randomisation was 24 days (IQR 2–27) for isoflurane and 26 days (2–27) for propofol (least squares-mean 1·50 [95% CI –7·81 to 10·82; p=0·751]). The median number of ICU-free days in the first 30 days after randomisation was 17 (IQR 0–24) for isoflurane and 13 (0–24) for propofol (least squares-mean 4·14 [95% CI –4·46 to 12·73; p=0·344]).

29 patients in the isoflurane group and 22 patients in the propofol group did not provide consent to be monitored for 30-day mortality or were lost to follow-up. 28 (23%) of 121 patients in the isoflurane group died in the 30 days after randomisation versus 26 (20%) of 129 patients in the propofol group.

Drug dosing is reported in table 2, with data for the two days for both groups. More detailed dosing information was not in the scope of this publication; a prespecified substudy will address interactions between dosing, bodyweight, minute ventilation, endtidal concentration, and sedation depth. Administration of rescue sedation was included in the primary endpoint estimation. Vasopressor use was similar in groups and the numbers of events of hypotension as an indirect measure of haemodynamic effects are reported in the adverse events list in the appendix (pp 21–23). No ACD deficiencies were reported in the trial; there was one case of secretions in the device, leading to an earlier replacement of the ACD than planned, but no related adverse event occurred.

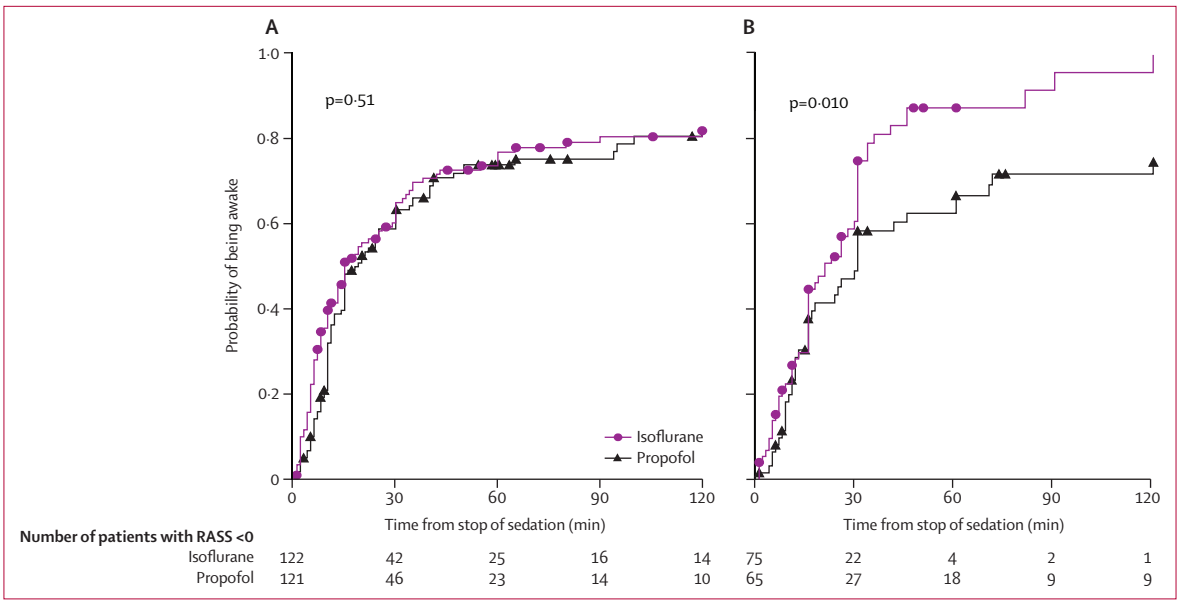

Figure 4: **Time to wake-up during spontaneous awakening trials on day 1 (A) and day 2 (B) in the full analysis set**
Analyses include only patients for whom a spontaneous awakening trial was done. Wake-up was classified as RASS score of ≥0. On day 1, two patients receiving propofol, and on day 2, three patients recieving propofol, were excluded because the registered RASS score was ≥0 at the start of the spontaneous awakening trial. Only the first 120 min of the test are presented. RASS=Richmond Agitation–Sedation Scale.

Discussion

This is, to our knowledge, the largest prospective, randomised, controlled trial of inhaled sedation to date. The main findings were that isoflurane, administered via the ACD for the sedation of patients in the ICU for up to 54 h, was efficacious, non-inferior to propofol, and well tolerated. Sedation with isoflurane also resulted in a higher rate of spontaneous breathing, and a shorter wake-up time after 48 h of study sedation, compared with propofol. These results are in line with findings from earlier studies, showing good tolerability and a relatively short time to wake-up and cognitive recovery, even after several days of sedation.[8,15]

Inclusion criteria were intended to target patients with a clinical need for sedation deeper than RASS 0. The target RASS range in the current study was comprised of four RASS levels, from RASS –1 to RASS –4. This range is one or two steps lower than the ranges used in other sedation efficacy studies,[1,16] but is still clinically relevant given the actual RASS scores in recent clinical studies. In a study aiming for early light sedation with either dexmedetomidine or usual care intravenous sedation, for example, more than 50% of patients were considered in clinical need of sedation at RASS –3 or deeper in the first days of the study.[1] In another recent study comparing propofol with dexmedetomidine in patients with sepsis who were mechanically ventilated with primarily lighter sedation targets, the median RASS was –2 (IQR –3 to –1) in the first days of sedation.[2]

Wake-up times with isoflurane were shorter than with propofol in our study. Furthermore, interindividual variation in wake-up times was smaller, implying greater predictability with isoflurane than propofol. Extubation times favoured isoflurane but these differences were not significant. Rapid emergence after inhaled sedation is a consistent finding in previous studies,[8,10,17] and inter-individual differences are typically small—a potentially valuable feature for planning extubation or reliable neurological evaluation.

The findings of this study and earlier studies examining wake-up times for isoflurane and for different intravenous sedatives after prolonged exposure[8,10,17] suggest that differences in emergence between isoflurane and intravenous sedation might be greater with increasing duration of exposure (>24 h).

Opioid dose requirements were lower in the isoflurane group than the propofol group, without any indications of increased pain. Reduced opioid requirements have also been noted in other studies of isoflurane sedation.[9,18,19] Inhaled anaesthetics have antinociceptive effects on the spinal cord[20] that could explain the reduced opioid need. One potential clinical effect of reduced opioid dose is a shortened time to wake-up and extubation. Opioids decrease intestinal motility, which is a disadvantage in a patient population in which paralytic ileus is common. Opioids might also contribute to the development of delirium[21] and, correspondingly, opioid-sparing treatment could reduce delirium.[22] However, we did not find any significant differences in delirium-free days.

Patients receiving isoflurane in this study were more likely to show spontaneous breathing activity than those receiving propofol; this finding is similar to those of other studies.[12,18] It is unclear whether this effect is

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caused by the reduction in opioids alone or by different brainstem actions of subanaesthetic concentrations of isoflurane compared with propofol.[23] Preservation of spontaneous breathing during invasive ventilation could be considered an advantage. Complete diaphragmatic inactivity for as little as 18–69 h results in marked disuse atrophy of human diaphragm myofibres.[24] Spontaneous breathing activity during mechanical ventilation could lead to lower peak ventilatory pressures than absence of spontaneous breathing, improved oxygenation, and improved haemodynamics, presumably by progressive dorsobasal alveolar recruitment.[25]

No serious adverse events were deemed to be treatment-related. Overall, there was a slight trend to more reported adverse events in the isoflurane than the propofol group. The open-label design of the study, in a population with multiple medical problems and treatments, and in which novel treatments tend to be more scrutinised, could have affected the reporting of adverse events.[26] The most common adverse event was hypertension, which occurred after the termination of isoflurane and in the absence of other sedation; we interpret this as a consequence of the rapid washout that isoflurane sedation entails. In this study, no other drugs (such as α-2 agonists) were permitted during spontaneous awakening trials. In the clinical setting, blunting the stress response pharmacologically upon rapid emergence might be considered for patients who develop clinically significant hypertension, a well known clinical phenomenon during emergence after general anaesthesia.

Our adult medical and surgical patient cohort, with emergency and planned admissions, makes the results fairly generalisable to adults who are invasively ventilated. The inclusion of patients with tidal volumes above 350 mL was not changed after the introduction of the 50 mL dead space ACD-S, although the manufacturer's device specifications allow use with tidal volumes as low as 200 mL. We believe that the results, mainly driven by the pharmacologically active part of the combination therapy, isoflurane, are valid for patients with such tidal volumes, provided that CO_2 is monitored and dead space is considered, similar to the management of standard heat and moisture exchangers. Although this study was done before the emergence of the COVID-19 pandemic, and no patients with COVID-19 were included in the study, the pandemic has led to an increased focus on inhaled anaesthetics for ICU sedation in patients who are invasively ventilated.[19,27,28] Besides being proposed as a sedative during mechanical ventilation in general, publications recommend this strategy to manage sedation needs in the COVID-19 patient population,[29,30] and the role of isoflurane sedation in COVID-19 acute respiratory distress syndrome (ARDS) is promising.[27,28]

The study had an open-label study design; many procedures reveal the use of isoflurane (eg, suctioning or replacing specific parts of the ACD, monitoring, or scavenging setup), making blinding problematic. Study sedative duration was relatively short (≤54 h), precluding firm conclusions regarding the benefits or risks of prolonged treatment beyond 54 h. Some patients were still in need of sedation at the end of the maximum study drug administration time; of whom, one-third were switched to the other study drug during the course of the 30-day follow-up. Three centres in Slovenia switched some patients to sedation with sevoflurane after the 48 h study period as their standard of care. Conversion of opioid dose intensities of sufentanil and fentanyl, the main opioids used in the study, to morphine equivalents cannot be interpreted as the actual dose of morphine that would have been required in the groups. Opioid standardisation is based on relative potency and does not account for differences in drug pharmacokinetics between the opioids used in this study and morphine, which has a longer duration of action. We did not adjust for multiplicity in our secondary endpoints; hence presented p values are nominal and should be interpreted as such. There were very few patients who were admitted to the ICU for a neurosurgical reason, and this patient group requires further study to better understand the benefits and risks of the therapy. In the past decade, there has been interest in the potential pulmonary protective effect of inhaled sedation in ARDS;[29,30] we did not study such potential effects in our heterogenous study population but acknowledge the need for further research in this area.

Contributors

PS and AM designed the study and the data collection plan. They participated in the interpretation of data analyses, and the writing of the report in collaboration with the coauthors. The Sedaconda study group did the study and collected the data; individual coauthors had full access to their own study centre data and accept final responsibility to submit for publication. Access to raw data and subsequent analyses were restricted to an independent statistician team led by Jonas Nilsson. PS and MB contributed equally to the study. PS and AM verified the data and developed the manuscript. All authors provided input to drafts of the manuscript. All authors read and approved the final manuscript. The corresponding author had final responsibility for the decision to submit this article for publication.

Declaration of interests

AM reports consultancy fees from Sedana Medical. TV reports grant support from B Braun. UG reports lecture fees from MT Monitor Technik and Getinge and reimbursement of clinical study expenses from Bayer Healthcare. TB reports lecture fees and travel costs from Sedana, Löwenstein Medical, and Dräger Medical. PK reports personal fees from Sedana Medical. MD reports lecture fees and travel costs from Cytosorbents Europe. PS reports employment by Sedana Medical and shareholding in Sedana Medical. All other authors declare no competing interests.

Data sharing

All data will be made available to relevant authorities for regulatory purposes but will not be shared publicly until after a period following expected approvals for marketing authorisations. Results have been made publicly available in the European Clinical Trial Register (EudraCT), which is a WHO primary register.

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