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ORIGINAL RESEARCH ARTICLE

Effect of Sedation Regimen on Weaning from Mechanical Ventilation in the Intensive Care Unit

Silvia L. Nunes[1] · Sune Forsberg[2,3] · Hans Blomqvist[4] · Lars Berggren[5] · Mikael Sörberg[6] · Toni Sarapohja[7] · Carl-Johan Wickerts[1]

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Abstract

Background Intensive care unit patients undergoing mechanical ventilation have traditionally been sedated to make them comfortable and to avoid pain and anxiety. However, this may lead to prolonged mechanical ventilation and a longer length of stay.

Objective The aim of this retrospective study was to explore whether different sedation regimens influence the course and duration of the weaning process.

Patients and methods Intubated adult patients ($n = 152$) from 15 general intensive care units in Sweden were mechanically ventilated for ≥ 24 h. Patients were divided into three groups according to the sedative(s) received during the weaning period (i.e. from being assessed as 'fit for weaning' until extubation): dexmedetomidine alone (DEX group, $n = 32$); standard of care with midazolam and/or propofol (SOC group, $n = 67$); or SOC plus dexmedetomidine (SOCDEX group, $n = 53$).

Results Patients receiving dexmedetomidine alone were weaned more rapidly than those in the other groups despite spending longer time on mechanical ventilation prior to weaning. Anxiety during weaning was present in 0, 9 and 24% patients in the DEX, SOC and SOCDEX groups, respectively. Anxiety after extubation was present in 41, 20 and 34% in the DEX, SOC and SOCDEX groups, respectively. Delirium during weaning was present in 1, 2 and 1 patient in the DEX, SOC and SOCDEX groups, respectively. Delirium at ICU discharge was present in 1, 0 and 3 patients in the DEX, SOC and SOCDEX groups, respectively. Few patients fulfilled criteria for post-traumatic stress disorder.

Conclusion Dexmedetomidine, used as a single sedative, may have contributed to a shorter weaning period than SOC or SOCDEX. Patients who received dexmedetomidine-only sedation tended to report better health-related quality of life than those receiving other forms of sedation.

Key Points

Dexmedetomidine used as single sedative was associated with a shorter weaning period.

Patients sedated during the weaning period with only dexmedetomidine reported better health-related quality of life.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40261-018-0636-2) contains supplementary material, which is available to authorized users.

✉ Silvia L. Nunes
silvia.lindqvist-nunes@sll.se

1 Department of Anaesthesiology and Intensive Care, Danderyd Hospital, 18288 Stockholm, Sweden

2 Department of Anaesthesiology and Intensive Care, Norrtälje Hospital, Norrtälje, Sweden

3 Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

4 Department of Anaesthesiology and Intensive Care, Karolinska University Hospital, Stockholm, Sweden

5 Department of Anaesthesiology and Intensive Care, Örebro University Hospital, Örebro, Sweden

6 Orion Pharma AB, Stockholm, Sweden

7 Orion Pharma, Espoo, Finland

1 Introduction

Patients undergoing mechanical ventilation (MV) have traditionally been sedated with benzodiazepines and/or propofol to make them comfortable and to avoid pain and anxiety. However, sedation may have negative consequences, such as prolongation of MV and weaning period with consequent higher costs [1, 2]. The risk of complications such as ventilator-associated pneumonia may also be increased [3, 4].

Early deep sedation, however it is achieved, has been associated with longer time to extubation and increased mortality [5]. Conversely, it has been demonstrated that comfort during MV can be achieved with no or very light sedation, and this is associated with lower incidences of delirium, shorter length of stay (LOS) and other benefits for patients [6–9]. Recent guidelines [10] and commentaries [11] have advocated a revision of intensive care unit (ICU) sedation practices and the adoption of sedation strategies based on non-benzodiazepine sedatives [either propofol or dexmedetomidine (DEX)] to improve clinical outcomes in mechanically ventilated adult ICU patients.

DEX has been shown to provide good patient comfort during MV; it also has a satisfactory safety profile [2, 12–14] and reduces time to extubation [2].

This study aimed to investigate whether different choices of sedation regimen can influence the weaning process. Patients receiving DEX during the weaning period were compared with those receiving standard of care (SOC) sedation with propofol and/or midazolam. Patients receiving both DEX and SOC during the weaning period were analysed separately.

Our primary efficacy point was weaning time. Secondary endpoints were total duration of MV and intensive care LOS. Additional data were collected on whether the sedative drug affects the level of patient anxiety, occurrence of delirium and on the amount of analgesics and sedatives used during weaning from MV. Moreover, information on the total cost of ICU stay was recorded for health economy purposes, together with data on health-related quality of life (HRQoL) after ICU and the presence of Post-Traumatic Stress Disorder (PTSD).

2 Patients and Methods

2.1 Patients

Patients were eligible to participate in this study if they were: (i) admitted to a general ICU ward; (ii) intubated and mechanically ventilated for at least 24 h; (iii) lightly to moderately sedated [corresponding to Motor Activity Assessment Scale (MAAS) score 2–3 [15] or Richmond Agitation and Sedation Scale (RASS) score 0 to −3]; [16, 17] (iv) sedated with DEX, midazolam and/or propofol; (v) aged > 18 years; and (vi) able to communicate clearly in Swedish.

Patients were excluded if they: (i) did not comply with the prescribed sedation regimen; (ii) had an estimated mortality rate of > 80%; (iii) were tracheotomised; (iv) had their sedative drugs changed after reaching the 'fit for weaning' time point; (v) received other alpha-2 agonists (clonidine) during their ICU stay; (vi) had a positive pregnancy test or were lactating; (vii) participated in another study involving use of a pharmacologically active compound; (viii) had "do not resuscitate" and/or other decisions for limitations in therapy; or (ix) were otherwise unable to complete the study, in the investigator's opinion.

Patients who fulfilled the selection criteria were invited to participate in the study and gave their written informed consent. This was signed just prior to ICU discharge or when the patient had been discharged onto a general hospital ward; no study-related data were obtained before consent was provided.

The 152 enrolled patients were divided into the following groups: (i) patients who received DEX as the only sedative agent during the weaning period (DEX group, $n = 32$); (ii) patients who received propofol and/or midazolam during the weaning period (SOC group, $n = 67$); and (iii) patients who needed both propofol/midazolam and DEX during the weaning period (SOCDEX group, $n = 53$) to achieve their sedation target [propofol + DEX ($n = 49$); midazolam + DEX ($n = 2$); propofol + midazolam + DEX ($n = 2$)]. Inclusion and description of this third group was deemed relevant as it reveals the observed clinical practice.

2.2 Protocol

This was a non-interventional, retrospective study conducted in 15 Swedish ICUs between June 2012 and October 2015 (see Table 4 in Appendix). The centres were chosen based on the number of mechanically ventilated patients treated per year (data obtained from the Swedish Intensive Care registry) to ensure optimal enrolment. The study protocol was approved by Stockholm's regional ethical committee and additional permissions were issued for each of the remaining locations. Simulations based on previous data [2, 18] indicated that a sample size of 250 subjects would have ≈ 80% power to detect a 30% difference in weaning time. However, slower enrolment than anticipated restricted recruitment to 152 patients.

Patients were treated according to the judgement of their attending physician and the choice of sedation regimen followed normal clinical practice at each centre. According to guidelines for sedation in the ICU [11], all patients had opioids to ensure pain control. Data collection for endpoint measurements was done exclusively from medical records. The procedures and instruments used to measure the

clinical effect outcomes were part of general clinical practice at all centres. The study timeline is shown in Fig. 1.

Data from clinical records were collected regarding the Simplified Acute Physiology Score 3 (SAPS-3) at admission and the amounts of sedative and analgesic medications administered during the 24 h before the patient was considered 'fit for weaning' (Period 1) and during the weaning period (Period 2) (Fig. 1). 'Fit for weaning' was determined as the time point when: (i) fraction of inspired oxygen ≤ 0.5; (ii) end inspiratory pressure ≤ 25 cmH_2O; (iii) positive end-expiratory pressure ≤ 10 cmH_2O; (iv) existing respiratory drive at/without a wake-up test; (v) no major surgery planned; (vi) need for light-to-moderate sedation; and (vii) no medical/surgical indication for continued intubation. All seven criteria should be met but, in some cases, the local investigator could consider the patient fit for weaning even if a single criterium was not met.

The time points for the beginning and end of MV were recorded (intubation + extubation). LOS in the ICU was defined as the time in days (total number of hours divided by 24) from the time of admission to the ICU until ICU discharge. Assessment of anxiety and delirium was done using the MAAS/RASS and the Nursing Delirium Screening Scale (Nu-DESC) [19] /Confusion Assessment Method for the ICU (CAM-ICU) [20, 21], respectively, during ICU stay and at ICU discharge. Resource utilization (workload) in the ICU was calculated based on cumulative Vård Tyngd Sverige (VTS) score (cumulative number of points per patient, which is equivalent to the Therapeutic Intervention Scoring System score [22]) for each period as a surrogate for cost of care.

HRQoL was assessed using the 15D instrument during a follow-up visit at 2 to 4 months after ICU discharge. The 15D score is calculated on a scale ranging from zero to one, where 0 = dead and 1 = full health. A change of 0.03 is considered the minimum clinically relevant change [23, 24]. PTSD was also assessed at the post-ICU follow-up visit using the Post-Traumatic Symptom Scale (PTSS)-14 questionnaire, a validated 14-dimension instrument [25].

Adverse events (AEs) and serious AEs were recorded throughout the study.

2.3 Statistics

The primary efficacy endpoint, weaning time, was defined as the time in hours from a patient being considered 'fit for weaning' until actual extubation (Period 2). The total time on MV was defined as the time in hours from the start until the end of MV. The unadjusted comparison between the treatments was performed using the log-rank test. Pairwise log-rank tests were also performed. Adjusted comparisons were performed using Cox's proportional hazard regression model.

Kaplan–Meier curves and percentile estimates were used to describe LOS data and analysis was performed using the log-rank test. Mean sedative and analgesic doses per hour during Periods 1 and 2 were compared using analysis of variance (ANOVA) with all paired differences. Anxiety was defined as RASS score +1 to +4 or MAAS score 4–6. Delirium assessments were scored as either positive or negative. Comparisons between the treatment groups for anxiety and delirium were done using descriptive statistics.

HRQoL based on the overall 15D score was compared between the treatment groups using ANOVA. PTSS-14 questionnaire scores were analysed using ANOVA for sum score and the Chi squared test for binary response.

Statistical analyses, compilation of tables and subject data listings were performed using SAS® for Windows (SAS Institute Inc., Cary, NC, USA). A two-sided significance level of 0.05 was used throughout the efficacy and safety analyses.

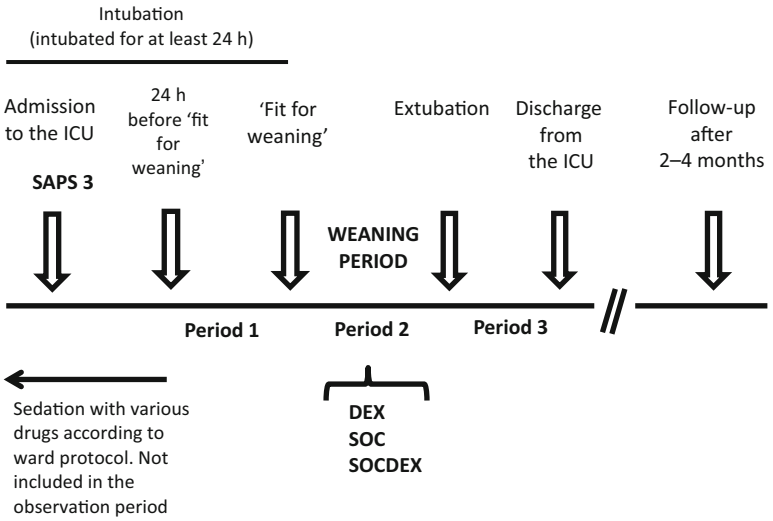

Fig. 1 Graphical depiction of study timeline. *DEX* dexmedetomidine, *SOC* standard of care, *SOCDEX* standard of care + dexmedetomidine, *ICU* intensive care unit, *SAPS* Simplified Acute Physiology Score

3 Results

The demographic details of the 152 patients are shown in Table 1. Most patients ($n = 95$) were male and in all three groups mean age, body mass index and SAPS-3 score on admission were similar. The reason for admission to the ICU was predominantly medical, although this was less so in the DEX group than in the other groups. Detailed information on reasons for admission is provided as supplementary material.

Sedation levels were measured predominantly using the RASS (MAAS, $n = 14$). According to the RASS, mean sedation levels during weaning were -0.5 ± 0.9 (median 0), -1.4 ± 1.5 (median -2.0) and -0.6 ± 2.1 (median -1.0) in the DEX, SOC and SOCDEX groups, respectively.

The median duration of intubation of patients in the SOC and SOCDEX groups before the start of the weaning period was significantly shorter than that in the DEX group (Table 2) ($p < 0.001$). On average, patients in the SOC group spent less time in the ICU before the start of the weaning period than those in the DEX ($p = 0.007$) or SOCDEX ($p = 0.025$) groups.

Patients in the DEX group were weaned in a significantly shorter median time than those in the SOC group ($p = 0.006$) or the SOCDEX group ($p < 0.001$) ($p = 0.213$ for SOC vs SOCDEX) (Table 2, Fig. 2). Across all study groups, medical patients tended to take longer to wean than surgical patients (20 vs 15 h). A greater percentage of DEX-only patients were admitted to the ICU for surgical reasons (Table 1) but adjusting for this did not change the results. No patient in the DEX group required re-intubation within 24 h, whereas there were three such extubation failures in the SOC group and one in the SOCDEX group.

DEX patients received less propofol prior to the weaning period compared with SOC ($p = 0.002$) and SOCDEX ($p < 0.001$) patients (Table 3). There were no statistically significant differences between groups regarding the use of other sedatives. All patients received opiates in accordance with the guidelines for sedation in the ICU [11] where pain management comes always prior to treatment for agitation. No differences were found among groups regarding the use of opiates (Table 3).

Anxiety was present during the weaning period in 0/23 DEX patients (0%), 5/55 SOC patients (9.1%) and 12/49 SOCDEX patients (24.5%). After extubation, the proportion of patients who experienced anxiety was higher in all groups: 40.9, 20.0 and 34.1%, respectively. Fifty patients were screened for delirium during weaning. One patient from DEX group, one from SOC group and two patients from SOCDEX group were diagnosed positive. Sixty-five patients were screened for delirium at ICU discharge. No patient from DEX group, one from SOC group and three patients from SOCDEX group were found positive.

HRQoL data 2–4 months after discharge from the ICU were obtained for 96 patients (63%). Mean [± standard deviation (SD)] score was higher in the DEX group (0.89 ± 0.10) than the SOC (0.84 ± 0.14) ($p = 0.147$) or SOCDEX (0.81 ± 0.14) ($p = 0.024$) groups. Data for each of the 15 contributing domains of the 15D are illustrated in Fig. 3.

PTSS-14 Part A data obtained at the same time point from 112 patients (74%) showed a tendency towards fewer patients with symptoms of nightmares, severe anxiety and panic, severe pain and breathing troubles in the DEX (40, 12, 16 and 29%, respectively) compared with the SOC (30, 13, 17 and 31%, respectively) and SOCDEX groups (45, 32, 26 and 32%, respectively), although there were no statistically significant differences.

Mean ± SD PTSS Part B scores were 22.9 ± 10.0, 25.2 ± 12.5 and 29.9 ± 14.6 for the DEX, SOC and SOCDEX groups, respectively. PTSD was diagnosed in 5/26 patients (19%) in the DEX group, 9/48 (19%) in the SOC group and 12/38 (32%) in the SOCDEX group, and these differences were not statistically significant.

Costs of care based on number of VTS points per day (24 h) during the weaning period were higher for the DEX group (204.2 ± 230.9) compared with the SOC (121.7 ± 170.3; $p = 0.031$) and SOCDEX (74.5 ± 47.0;

Table 1 Demographic details of the study participants

Characteristic	DEX ($n = 32$)	SOC ($n = 67$)	SOCDEX ($n = 53$)	Total ($n = 152$)
Percentage of females/males	34/66	43/57	32/68	37/63
Age (years); mean (range)	66 (27–81)	63 (23–85)	61 (19–86)	62 (19–86)
BMI (kg/m^2); mean (SD)	28.2 (7.3)	27.5 (6.6)	29.2 (7.0)	28.3 (6.9)
Percentage of patients admitted to the ICU for medical/surgical reasons	69/31	85/15	87/13	82/18
Percentage of patients admitted to the ICU for respiratory/sepsis reasons	50/13	31/37	53/25	43/28
SAPS-3 score; mean (SD) ($n = 144$)	60.8 (13.9)	60.6 (16.2)	60.0 (14.0)	60.5 (14.9)

DEX dexmedetomidine, *SOC* standard of care, *SOCDEX* standard of care + dexmedetomidine, *BMI* body mass index, *SD* standard deviation, *ICU* intensive care unit, *SAPS* Simplified Acute Physiology Score

Table 2 Median durations, with 25th to 75th percentiles in parentheses, of the study periods

Group	ICU admission until intubation (h)	Intubation until 'fit for weaning" (h)	Period 2: 'fit for weaning" until extubation (weaning) (h)	Period 3: extubation until ICU discharge (h)	Total length of ICU stay (days)
DEX	0.6 (−1.7–15.0)	79.1 (43.4–122.3)	5.4 (1.6–20.3)	56.6 (37.1–96.7)	7.1 (4.6–10.7)
SOC	1.1 (0.0–5.9)	37.0 (24.0–64.0)	17.8 (5.0–31.8)	49.7 (26.2–74.8)	4.9 (3.3–7.1)
SOCDEX	3.9 (0.3–19.0)	48.5 (30.6–77.8)	26.3 (16.8–38.1)	61.5 (35.1–122.2)	6.8 (5.1–9.3)

DEX dexmedetomidine, *SOC* standard of care, *SOCDEX* standard of care + dexmedetomidine, *ICU* intensive care unit

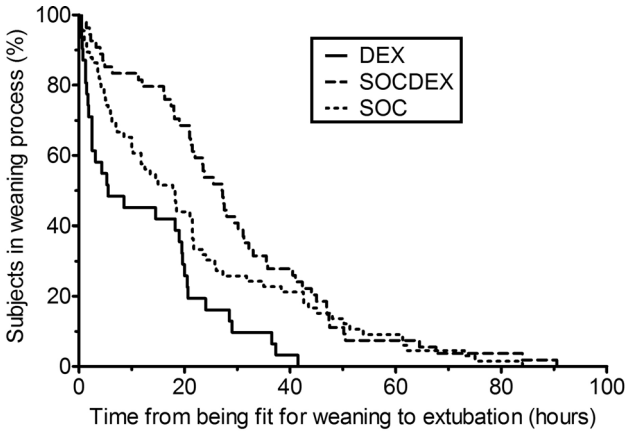

Fig. 2 Time from being fit for weaning until extubation for the different treatment groups. $p = 0.006$ DEX vs SOC; $p < 0.001$ DEX vs SOCDEX. *DEX* dexmedetomidine, *SOC* standard of care, *SOCDEX* standard of care + dexmedetomidine

$p = 0.001$) groups. However, the DEX group had a significantly lower number of VTS points per day (24 h) than the SOC and SOCDEX groups during the entire stay: 47.7 ± 15.3 versus 55.9 ± 22.0 or 53.3 ± 11.0, respectively; $p = 0.046$ versus SOC; $p = 0.198$ versus SOCDEX.

Fourteen patients died during the study and severe non-fatal AEs were registered in four. None of the registered deaths or AEs were considered related to the sedation used during weaning from MV.

4 Discussion

Our central finding was that patients sedated with DEX alone were more rapidly weaned despite a longer time on MV prior to weaning; however, patients receiving SOC sedation had a shorter time on MV as well as a shorter ICU stay.

Some of the limitations of this study must be acknowledged before offering any interpretation of the data. Firstly, we could not design a randomized study because Swedish legislation requires that patients must give consent before they can be enrolled. Mechanically ventilated ICU patients cannot therefore be included in a study before they improve to the point where they can provide informed consent. This contributed to a natural selection of our case-mix, with the most debilitated patients or those with severe complications after a long ICU stay tending to be excluded due to the legislative obstacles to obtaining consent. Those obstacles also contributed to very slow patient recruitment, which led to enrolment of additional centres. Several of these ended up by not recruiting as many patients as expected leading to the study being concluded before it had reached its planned enrolment target of 250 patients. Owing to the early termination of the study, we could not generate sufficient data to fulfil all secondary endpoints. The findings and conclusions of this research must therefore be viewed with caution until further studies have been conducted in this area, perhaps in jurisdictions that permit informed consent to be waived in ICU situations. This was, moreover, a retrospective investigation and may have been subject to record-based biases. Furthermore, our patients were sedated using various drug regimens and were grouped exclusively based on the drugs used during weaning. The effects of the different drugs used before and after weaning, might have exerted an influence on some of the results but probably not on the primary outcome.

DEX has been introduced for sedation in the ICU as a non-γ-aminobutyric acid-ergic agent with a distinct pharmacological profile but its role during the weaning period has not been fully elucidated. Previous reports in this area have indicated benefits from DEX in weaning ventilated patients affected by agitation and/or delirium [26–28]. Delirium was identified in very few of our patients and although anxiety was identified in a quarter of SOCDEX patients during weaning (and in 20–40% of patients in every group after extubation) it cannot be regarded as a robust proxy measure of pre-weaning agitation. To that extent, ours may have been a less acutely problematic ICU population than was examined in earlier studies. Nevertheless, in our investigation, as in the other studies, DEX appeared to facilitate weaning compared with conventional sedatives. Patients who can be sedated with DEX alone are expected to be more arousable and more able to communicate than those who receive SOC and that may have been one factor that contributed to a shorter weaning time in the DEX group [2].

Table 3 Doses of sedatives and opioids (mean ± standard deviation) administered per patient during Periods 1 and 2

Sedative/opioid	DEX ($n = 32$)		SOC ($n = 67$)		SOCDEX ($n = 53$)	
	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2
Dexmedetomidine (μg/h)	61.5 ± 38.1 ($n = 27$)	54.8 ± 31.3 ($n = 24$)	31.3 ± 18.0 ($n = 4$)	–	88.6 ± 221.5 ($n = 39$)	115.9 ± 206.5 ($n = 45$)
Propofol (mg/h)	45.6 ± 45.0 ($n = 17$)	–	119.2 ± 80.3 ($n = 54$)	102.9 ± 78.2 ($n = 49$)	134.7 ± 99.6 ($n = 47$)	76.6 ± 126 ($n = 44$)
Midazolam (mg/h)	0.6 ± 0.3 ($n = 2$)	–	6.9 ± 8.1 ($n = 12$)	1.6 ± 1.8 ($n = 6$)	6.3 ± 14.8 ($n = 7$)	19.0 ± 15.0 ($n = 3$)
Remifentanil (μg/h)	386.7 ± 302.2 ($n = 20$)	328.0 ± 197.7 ($n = 11$)	499.7 ± 383.4 ($n = 43$)	547.9 ± 723.1 ($n = 36$)	537.6 ± 614.1 ($n = 36$)	553.3 ± 482.9 ($n = 27$)
Ketobemidone (mg/h)	0.7 ± 1.0 ($n = 17$)	6.1 ± 16.5 ($n = 9$)	2.7 ± 6.9 ($n = 23$)	4.9 ± 10.3 ($n = 14$)	1.0 ± 1.1 ($n = 22$)	0.9 ± 0.7 ($n = 18$)

DEX dexmedetomidine, *SOC* standard of care, *SOCDEX* standard of care + dexmedetomidine

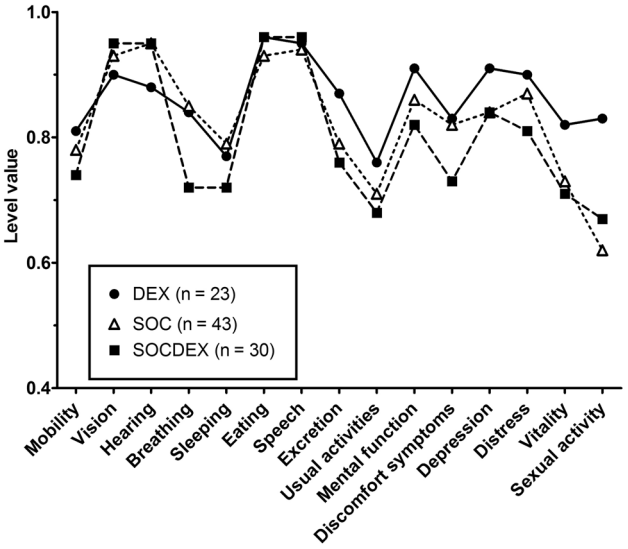

Fig. 3 15D scores for the different treatment groups, illustrated by domain. *DEX* dexmedetomidine, *SOC* standard of care, *SOCDEX* standard of care + dexmedetomidine

Our observations of total time on MV and LOS in the ICU are at variance with the results of randomized studies in which the duration of MV was shorter in patients who received DEX than in those sedated with conventional agents [2, 13]. By contrast, in this research the interval from intubation to 'fit for weaning' in patients treated with DEX was > 30 h longer than in either of the comparison groups. We are unable to say whether that difference is grounded in specific medical factors in the DEX group such as the greater prevalence of severe respiratory disease in the DEX group (Table 1 and electronic supplementary material), or whether it perhaps reflects caution among investigators using DEX. Given that the drug was newly available in Sweden at the start of our research it is plausible that weaning attempts were delayed in the DEX group until the investigators were fully satisfied of the prospects of success. Such measures could have contributed to the rapidity of weaning in the DEX group while producing no comparable reduction in the duration of MV.

A related possibility is that patients may have been switched to DEX some time prior to weaning to facilitate control of neurology and training of spontaneous ventilation. Those patients who tolerated a single sedative may thereafter have had fast and uneventful weaning. The increased use of DEX in the SOCDEX group and the continued widespread use of other sedatives in that group offer some indirect support to the conjecture that patients who can be maintained with a single sedative may have better prospects for rapid weaning.

HRQoL at follow-up, measured using the 15D, showed better aggregate scores in the DEX group than the SOCDEX group. These data may also be an indication that the

need for more than one sedative agent during weaning may anticipate less favourable outcomes. A direct impact of ICU sedation on HRQoL during long-term follow-up is hard to establish but there appear to be no longer-term detrimental effects to offset the early gains of lighter sedation and shorter duration of MV [29].

Few patients fulfilled criteria for a diagnosis of PTSD in this study and no treatment-related themes were identifiable. The reported prevalence of PTSD symptoms in ICU survivors is highly variable but several recent publications on this theme have cited higher rates than earlier research [25, 30–32]. The low rate of PTSD found among our patients may be a coincidence, the result of restricted statistical power or a reflection of the application in Sweden of modern principles of ICU sedation and nursing practice [33–35].

Costs of care based on the number of VTS points per day (24 h) were highest during the weaning period in the DEX group, but lowest in the same group for the entire ICU stay. Given the procedural difficulties that affected the conduct of this investigation the resilience of these data is unclear and further research into this aspect of DEX use is needed.

5 Conclusion

In conclusion, this retrospective investigation in patients in Swedish ICUs produced indications that use of DEX for sedation was associated with more rapid weaning from MV than sedation with SOC agents and with indications of better HRQoL during post-discharge follow-up. However, the obstacles to recruitment of patients mean that these findings are suggestive rather than conclusive and require further investigation in well-powered studies.

Compliance with Ethical Standards

Conflict of interest Carl-Johan Wickerts has received support for travel to a meeting and Lars Berggren has received consulting fees and honorarium as well as payment for lectures from Orion Pharma. Mikael Sörberg and Toni Sarapohja are employed by Orion Pharma. The remaining authors do not declare any conflicts of interest.

Ethical approval All procedures in this study were in accordance with the 1964 Helsinki declaration (and its amendments), as well as with the details of the Ethics Committee or institutional review board which approved the study.

Informed consent Written informed consent was obtained from all enrolled patients.

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Appendix

See Table 4.

Table 4 Details of the participating centres

Centre no.	Name of centre	No. of patients enrolled
1	Anaesthesia and Intensive Clinic, Danderyds Hospital, Stockholm	18
2	Anaesthesiology Clinic, St Görans Hospital, Stockholm	6
3	Anaesthesia and Intensive Care Clinic, University Hospital, Örebro	17
4	Anaesthesia and Intensive Care Clinic, Akademiska Hospital, Uppsala	9
5	Södersjukhuset MIVA, Stockholm	7
6	Intensive Care Unit, University Hospital, Linköping	10
7	Anaesthesia and Intensive Department, Gävle	8
8	Intensive Care Unit, Norra Älvsborgs Country Hospital, Trollhättan	22
9	Nyköpings Hospital, Nyköping	14
10	Intensive Care Unit, Centralsjukhuset, Karlstad	17
11	Intensive Care Unit, Västerviks Hospital, Västervik	9
12	Intensive Care Unit, Helsingsborgs Hospital, Helsingborg	1
13	Intensive Care Unit, Sundsvall-Härnösand Hospital, Sundsvall	7
14	Intensive Care Unit, Norrtälje Hospital, Norrtälje	3
15	ICU, Skellefteå Hospital, Skellefteå	4

References

1. Barrientos-Vega R, Mar Sánchez-Soria M, Morales-García C, Robas-Gómez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. Crit Care Med. 1997;25:33–40.
2. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J, Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012;307:1151–60.
3. Fagon JY, Chastre J, Domart Y, Trouillet JL, Pierre J, Darne C, Gibert C. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. Am Rev Respir Dis. 1989;139:877–84.
4. Lazarus HM, Fox J, Lloyd JF, Evans RS, Abouzelof R, Taylor C, Pombo DJ, Stevens MH, Mehta R, Burke JP. A six-year descriptive study of hospital-associated infection in trauma patients: demographics, injury features, and infection patterns. Surg Infect (Larchmt). 2007;8:463–73.
5. Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MA, Khoo TM, Ali SB, Saman MA, Shaltut A, Tan CC, Yong CY, Bailey M, 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.
6. Treggiari MM, Romand JA, Yanez ND, Deem SA, Goldberg J, Hudson L, Heidegger CP, Weiss NS. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med. 2009;37:2527–34.
7. Frontera JA. Delirium and sedation in the ICU. Neurocrit Care. 2011;14:463–74.
8. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010;375:475–80.
9. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, McArthur C, Murray L, Seppelt IM, Webb S, Weisbrodt L, Sedation Practice in Intensive Care Evaluation Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: a pilot study. Crit Care Med. 2013;41:1983–9.
10. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R, American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41:263–306.
11. Vincent JL, Shehabi Y, Walsh TS, Pandharipande PP, Ball JA, Spronk P, Longrois D, Strøm T, Conti G, Funk GC, Badenes R, Mantz J, Spies C, Takala J. Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med. 2016;42:962–71.
12. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG, SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301:489–99.
13. Ruokonen E, Parviainen I, Jakob SM, Nunes S, Kaukonen M, Shepherd ST, Sarapohja T, Bratty JR, Takala J, "Dexmedetomidine for Continuous Sedation" Investigators. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med. 2009;35:282–90.
14. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007;298:2644–53.
15. Devlin JW, Boleski G, Mlynarek M, Nerenz DR, Peterson E, Jankowski M, Horst HM, Zarowitz BJ. Motor activity assessment scale: a valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. Crit Care Med. 1999;27:1271–5.
16. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166:1338–44.
17. Almgren M, Lundmark M, Samuelson K. The Richmond Agitation-Sedation Scale: translation and reliability testing in a Swedish intensive care unit. Acta Anaesthesiol Scand. 2010;54:729–35.
18. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H, Stanchina M, Vieillard-Baron A, Welte T. Weaning from mechanical ventilation. Eur Resp J. 2007;29:1033–56.
19. Gaudreau JD, Gagnon P, Harel F, Tremblay A, Roy MA. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. J Pain Symptom Manage. 2005;29:368–75.
20. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29:1370–9.
21. Larsson C, Axell AG, Ersson A. Confusion assessment method for the intensive care unit (CAM-ICU): translation, retranslation and validation into Swedish intensive care settings. Acta Anaesthesiol Scand. 2007;51:888–92.
22. Miranda DR, Nap R, de Rijk A, Schaufeli W, Iapichino G, TISS Working Group. Therapeutic intervention scoring system. Nursing activities score. Crit Care Med. 2003;31:374–82.
23. Sintonen H. The 15D instrument of health-related quality of life: properties and applications. Ann Med. 2001;33:328–36.
24. Drummond M. Introducing economic and quality of life measurements into clinical studies. Ann Med. 2001;33:344–9.
25. Twigg E, Humphries G, Jones C, Bramwell R, Griffiths RD. Use of a screening questionnaire for post-traumatic stress disorder (PTSD) on a sample of UK ICU patients. Acta Anaesthesiol Scand. 2008;52:202–8.
26. Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, Davies A, Delaney A, Ghosh A, van Haren F, Harley N, Knight D, McGuiness S, Mulder J, O'Donoghue S, Simpson N, Young P, DahLIA Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA. 2016;315:1460–8.
27. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW, SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med. 2010;38:2311–8.
28. Siobal MS, Kallet RH, Kivett VA, Tang JF. Use of dexmedetomidine to facilitate extubation in surgical intensive-care-unit patients who failed previous weaning attempts following

prolonged mechanical ventilation: a pilot study. Respir Care. 2006;51:492–6.
29. Jackson JC, Girard TD, Gordon SM, Thompson JL, Shintani AK, Thomason JW, Pun BT, Canonico AE, Dunn JG, Bernard GR, Dittus RS, Ely EW. Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial. Am J Respir Crit Care Med. 2010;182:183–91.
30. Wade D, Hardy R, Howell D, Mythen M. Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. Minerva Anestesiol. 2013;79:944–63.
31. Wade DM, Howell DC, Weinman JA, Hardy RJ, Mythen MG, Brewin CR, Borja-Boluda S, Matejowsky CF, Raine RA. Investigating risk factors for psychological morbidity 3 months after intensive care: a prospective cohort study. Crit Care. 2012;16:R192.
32. Ratzer M, Brink O, Knudsen L, Elklit A. Posttraumatic stress in intensive care unit survivors—a prospective study. Health Psychol Behav Med. 2014;2:882–98.
33. Porhomayon J, El-Solh AA, Adlparvar G, Jaoude P, Nader ND. Impact of sedation on cognitive function in mechanically ventilated patients. Lung. 2016;194:43–52.
34. Nassar AP Jr, Zampieri FG, Ranzani OT, Park M. Protocolized sedation effect on post-ICU posttraumatic stress disorder prevalence: a systematic review and network meta-analysis. J Crit Care. 2015;30:1278–82.
35. Porhomayon J, Joude P, Adlparvar G, El-Solh AA, Nader ND. The impact of high versus low sedation dosing strategy on cognitive dysfunction in survivors of intensive care units: a systematic review and meta-analysis. J Cardiovasc Thorac Res. 2015;7:43–8.