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Research Article

Assessment of Dexmedetomidie for Ventilatory Weaning After Prolonged Sedation: About a Retrospective Analysis of 112 Patients

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- Dexmedetomidine
- Cooperative sedation
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Abstract

Background: Weaning from mechanical ventilation (MV) is a major challenge in the intensive care unit (ICU). We evaluated the use of dexmedetomidine to reduce the duration of weaning, compared standard sedation protocols.

Methods: Single-centre, retrospective, observational study in a mixed ICU from April 2018 to April 2020. All patients aged ≥18 years, requiring MV for at least 5 days before initiation of a weaning protocol, were eligible for inclusion. Patients were grouped retrospectively according to whether they received dexmedetomidine or standard sedation for weaning.

The primary endpoint was the average duration (in hours) of weaning from MV. Secondary endpoints were the frequency of self-extubation, and occurrence of re-intubation within 48 hours. A propensity score was used for the analysis of the primary endpoint.

Results: Among 1132 patients admitted during the study period, 112 were included: 66 in the standard care group, and 46 in the dexmedetomidine group. The duration of weaning did not differ significantly between groups (104.8 hours in the standard care group versus 127.1 hours in the dexmedetomidine group, p=0.1552). Self-extubations were numerically albeit non-statistically significantly more frequent in the standard care group (n=6 (9.09%) vs n=2 (4.54%)) with dexmedetomidine, p=0.3481). Similarly, re-intubation was also numerically more frequent in the standard care group, albeit without reaching statistical significance (n=5 (8,20%) vs n=1 (2.22%) with dexmedetomidine, p=0.1234).

Conclusion: The duration of weaning from MV is numerically, but not statistically significantly shorter with standard care as compared to weaning facilitated by dexmedetomidine.

INTRODUCTION

Sedation-analgesia is a cornerstone of management in patients on mechanical ventilation (MV) in the intensive care unit (ICU). It is only used after careful evaluation of the risk-benefit ratio, taking account of the patient's needs. Sedation-analgesia requires the involvement of trained healthcare professionals, following standardized written protocols and algorithms to adapt the depth of sedation to the patient's needs (1-2). Although there is currently no consensus regarding the choice of sedatives, the revised guidelines of the Society for Critical Care Medicine recommend light sedation with regular assessment of pain, depth of sedation and delirium (3).

Dexmedetomidine is an alpha-2 agonist that was approved in France in 2011 for sedation in the ICU in adults requiring a level of sedation that enables response to verbal stimulation (4-5). Several studies have demonstrated the safety and efficacy of dexmedetomidine for light to moderate sedation, with efficacy equivalent to that of propofol or midazolam (6-8). Dexmedetomidine exerts a sedative, anxiolytic, analgesic effect without impairing respiratory function, thus enabling spontaneous breathing to remain unaffected (4). It facilitates light sedation, enabling the patient to remain participative and communicative, while simultaneously reducing the risk of delirium (9-10).

Finally, from the public health and economic perspective, the use of light sedation would help to reduce the overall cost of management, through a reduction in the length of stay and the duration of MV (11-12).

To date, no single hypnotic or opioid agent has been shown to be superior in sedation-analgesia (13). Therefore, we sought to evaluate the impact of dexmedetomidine on the duration of weaning from mechanical ventilation, compared to standard protocols.

METHODS

Study design and patients

We included all adult (>18 years) patients admitted to the ICU between April 2018 and April 2020 at the mixed ICU of Reims University Hospital, France, and requiring MV for at least 5 days before initiation of weaning. We excluded patients with bradycardia (<55 bpm), patients with high-grade atrioventricular block (2nd or 3rd degree) in the absence of an implantable pacemaker, patients with psychiatric agitation, patients with severe acute or chronic liver disease (Child-Pugh class C), pregnant women and patients whose life expectancy at inclusion was estimated to be <72 hours.

Study outcome measures

The primary endpoint was the average duration of weaning from MV, expressed in hours. This duration was calculated from the time with the criteria for weaning were met, and the time extubation was achieved. Secondary endpoints were the number of self-extubations, and the occurrence of re-intubation within 48 hours.

Sedation algorithm

When patients met the criteria for weaning described below, the initiation sedation-analgesia was relayed by sedation at the discretion of the clinician (either standard sedation or sedation with dexmedetomidine). The weaning readiness criteria included respiratory parameters (SpO2 > 92% with FiO2 <50% and positive end-expiratory pressure (PEEP) <6 cm H20, presence of adequate cough reflex and excessive tracheobronchial secretion); hemodynamic stability; improvement of the acute disease for which the MV was required, achievement of a level of sedation between -2 and 0 as assessed by the Richmond Agitation-Sedation Scale (RASS); and a haemoglobin level > 8g/dL. Maintenance of a sedation level between -2 and 0 as assessed by the RASS was left at the clinician's discretion according to the clinical situation and the patient's potential contra-indications.

Standard sedation associated a hypnotic (midazolam or propofol) with an opioid agent (remifentanil or sufentanil). Sedation facilitated by dexmedetomidine could be initiated alone, or in combination with remifentanil or propofol to meet sedation and analgesia objectives.

The level of analgesia was evaluated by visual analog scale (VAS) with a target of <4. The level of sedation-analgesia was re-evaluated every 4 hours.

After the initial medical prescription, the protocol for dexmedetomidine use developed within the ICU was applied by the caregiving team. Dexmedetomidine was administered by infusion in a dedicated line, usually through a central venous catheter, and without administration of a bolus. The initial dose of 0.6 micrograms/kg/hour could be adjusted by increments of 0.2 micrograms/kg/hour, to reach a maximum dose of 1.4 micrograms/kg/hour to achieve the desired level of sedation. An infusion at a lower initial dose could be considered for frail patients. The maximum dose of 1.4 micrograms/kg/hour was not to be exceeded. In patients who did not achieve the desired level of sedation at the maximum dose of dexmedetomidine, an alternative sedative was used.

Data Collection and definitions

Data were extracted from the medical files (paper and electronic records). For each patient included in the study, we recorded the following data: age; sex; body mass index (BMI); context of ICU admission (medical or surgical); respiratory function (no history of respiratory disease, chronic obstructive pulmonary disease (COPD), asthma, restrictive pulmonary disease); date and time of intubation; indication for intubation (cardiac, respiratory, neurological, post-operative); duration of MV before start of weaning process; reasons for delay in weaning; date and time when criteria for weaning were met; Sequential Organ Failure Assessment (SOFA) score on the day when weaning criteria were met and on the day of extubation; reasons for delay in extubation. Regarding extubation, the following data were recorded: date and time; type of extubation (scheduled or self-extubation); need for re-intubation within 48 hours; cause of extubation failure (laryngeal oedema, or hemodynamic, respiratory or neurological reasons).

Statistical analysis

Quantitative data are described as mean± standard deviation (SD) and qualitative data as number (percentage). Groups were compared in bivariate analysis using the Student t, Chi 2 or Fisher's exact test as appropriate. To take account of indication bias in the use of dexmedetomidine, we calculated a propensity score (propensity to receive dexmedetomidine). To calculate the propensity score, we first performed a multivariate logistic regression analysis including the variables that could explain the choice of dexmedetomidine, to estimate for each patient the probability of receiving sedation by dexmedetomidine, given the characteristics of that patient at inclusion.

The variables in the model for the propensity score were pre-defined prior to analysis of outcomes, and included: age (≤ 60 or > 60 years); BMI (≤ 30 or > 30 kg/m^2); respiratory function status in two classes (no history of respiratory disease, or presence of the respiratory pathologies mentioned above); the indication for MV (respiratory causes, vs other causes (cardiac, neurological, post-operative)); the main indication for admission to ICU (medical vs surgical); duration of MV prior to weaning; SOFA score on the day when weaning criteria were met (≤ 5 or > 5); and reason for delay in extubation. Inverse probability of treatment weighting (IPTW) was used to mimic randomisation and balance differences in baseline characteristics between treatment groups.

The analysis of the primary outcome (quantitative variable) was performed using a generalized linear regression model

with adjustment for the inverse of the propensity score. For the secondary outcomes (qualitative variables), comparisons between treatment groups were performed by logistic regression, also adjusted for the inverse of the propensity score.

A p-value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary NC, USA).

RESULTS

Patients

Among 1132 patients admitted to the ICU during the study period, 183 met the study inclusion criteria, of whom 71 were excluded (13 had tracheotomy, 33 died, 25 were lost to follow-up). The flowchart of the study is presented in (Figure 1).

Among 112 patients eligible for the analysis, 46 (41%) received sedation with dexmedetomidine, and 66 (59%) according to the standard protocol. The characteristics of the study population according to treatment group are detailed in (Table 1). Average was 56.9±14.1 years in the standard protocol group, and 64.3±10.9 in the dexmedetomidine group (p<0.0033). BMI was significantly higher in the dexmedetomidine group (31.2 ± 9.57) compared to the standard protocol group (26.8 ± 6.61) (p<0.0089). The majority of patients had medical indications for admission in both groups. The mean duration of MV before inclusion was 9.5±9.4 days in the standard protocol group vs 9.4±7.3 days in the dexmedetomidine group (p<0.9493).

Propensity score

The standardized mean differences used to generate the propensity score are summarized in (Figure 2). In the dexmedetomidine group, the average propensity score was 0.48 ± 0.15 (range 0.11 – 0.78). In the standard protocol group, the average propensity score was 0.36 ± 0.17 (range 0.10-0.75) (Figure 3). Average IPTW scores were respectively 0.4060 ± 0.1802 in the dexmedetomidine group versus 0.4135 ± 0.1800 in the standard protocol group.

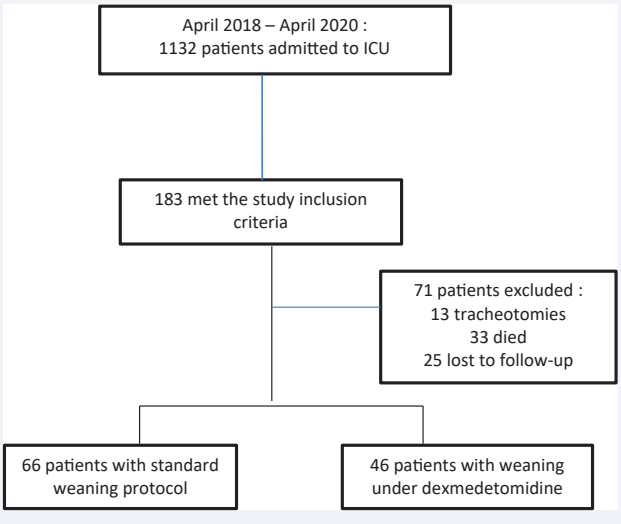

Figure 1 Flow Chart of the study population.

Table 1: Baseline characteristics of the study population.

Variable	Standard care group (n=66)	Dexmedeto-midine group (n=46)	p value
Age	56.9 (14.14)	64.3 (10.96)	<0.0033
Male sex	51 (77.27%)	35 (76.09%)	<0.8837
Weight (kg)	80.8 (20.71)	89.3 (21.15)	< 0.0357
BMI (kg/m^2)	26.8 (6.61)	31.2 (9.57)	< 0.0089
Indication for admission			
Medical	51 (77.27%)	36 (78.26%)	< 0.9017
Surgical	15 (22.73%)	10 (21.74%)	
Respiratory function history			< 0.4896
No respiratory disease	31 (46.97%)	17 (36.96%	
COPD	26 (39.39%)	19 (41.30%)	
Asthma	2 (3.03%)	4 (8.70%)	
Restrictive disease	7 (10.61%)	6 (13.04%)	
SOFA score (at day 1)	5.3 (2.56)	5.4 (2.72)	<0.7845

Primary and secondary outcomes

For the primary outcome, using IPTW, multivariate analysis adjusted for the inverse of the propensity score found a shorter average duration of weaning from MV in the standard protocol group, albeit without reaching statistical significance (104.9 ± 90.1 hours for standard protocol vs 127.1 ± 74.8 hours with dexmedetomidine, corresponding to an average difference of 23 hours, p<0.1552) (Table 2).

For the secondary outcomes, self-extubation appeared to occur more frequently in the standard protocol group (9.09%) than in the dexmedetomidine group (4.54%), but the difference was not statistically significant. Similarly, need for re-intubation within 48 hours was numerically, but not statistically significantly different between groups (8.2% in the standard protocol vs 2.22% in the dexmedetomidine group). In the standard protocol group, re-intubation was most often due to respiratory causes (40%) and laryngeal oedema (40%) (Table 3).

Complementary analyses

Patients in both groups received complementary sedatives and/or analgesics to achieve RASS and VAS score objectives. Weaning from MV was primarily delayed due to respiratory causes (n=34 (72.34%) in the dexmedetomidine group and n=35 (51.47%) in the standard protocol group, p<0.0247). Average SOFA score at extubation was 3.0 ± 1.62 in the standard protocol group vs 2.9 ± 1.67 in the dexmedetomidine group (p<0.6793).

DISCUSSION

We observed a numerical, albeit non statistically significant different in the average duration of weaning from MV in this study, with the standard group achieving successful weaning on average 23 hours earlier.

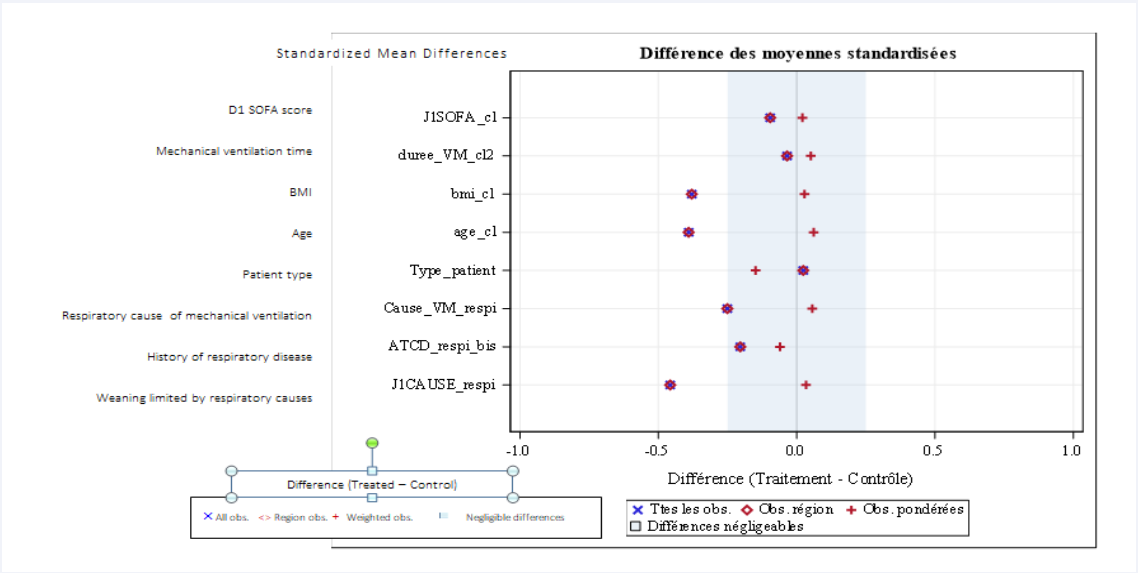

Figure 2 Differences in standardized averages used to generate the propensity score.

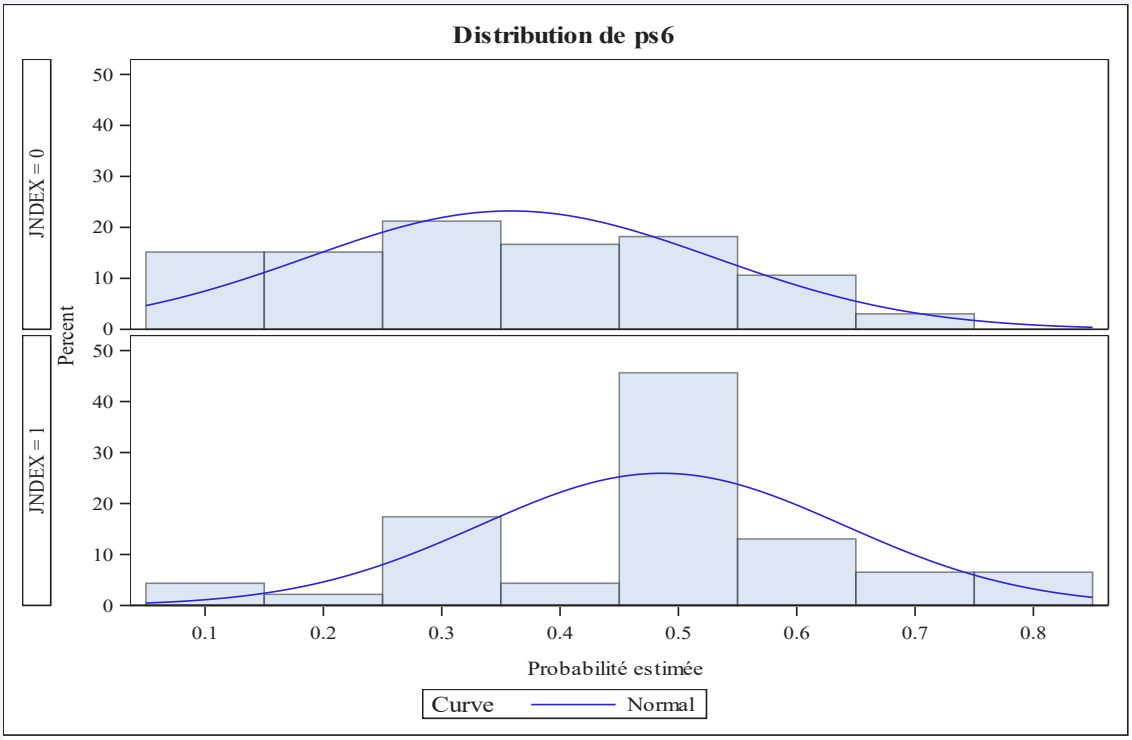

Figure 3 Distribution of the propensity score in the dexmedetomidine and standard protocol groups.

Two randomized, double-blind, multicentre, non-inferiority studies compared the use of dexmedetomidine vs midazolam (in the MIDEX study) or propofol (in the PRODEX study) (6). A reduction of the duration of MV was observed in the dexmedetomidine group compared to midazolam, but not compared to propofol. The SEDCOM study evaluated the efficacy and tolerance of dexmedetomidine compared to midazolam, and showed that patients were extubated significantly earlier with dexmedetomidine (on average, 1.9 days) (7).

In our study, patients were included after a minimum of 5 days of MV. The average duration of MV at inclusion was around 9 days in both groups, which is considerably higher than the duration reported in the MIDEX and PRODEX (72 hours) or SEDCOM studies (96 hours) (6,7). This duration of 5 days of MV prior to inclusion may have contributed to selecting a population of patients with pronounced respiratory comorbidities,

Table 2: Duration of weaning from mechanical ventilation in hours in both study groups.

	Standard care group (n=66)	Dexmedetomidine group (n=46)	p value
Unadjusted	105.51 ± 82.65	143.54 ± 79.05	p<0.0164
After adjustment for inverse of propensity score	104.88 ± 90.09	127.07 ± 74.83	p<0.1552

Table 3: Secondary endpoints.

	Standard care group (n=66)	Dexmedetomidine group (n=46)	OR [95% CI]	p	aOR [95% CI]	p
Extubation				0.3481		0.580
Scheduled	60 (90.91)	44 (95.46)	0.45 [0.88 ; 2.36]		0.61 [0.11; 3.51]	
Self-extubation	6 (9.09)	2 (4.54)				
Re-intubation within 48h				0.1234		0.149
No	61 (91.80)	45 (97,78)	0.19		0.19	
Yes	5 (8.20)	1 (2.22)	[0.022 ; 1.578]		[0.02 ; 1.81]	
Reintubation indication						
Laryngeal oedema	2 (40)	0				
Neurological	1 (20)	0				
Respiratory	2 (40)	1 (100%)				

consequently leading to difficult or prolonged weaning or requiring deep sedation. We did not investigate sedation during this period. Initial deep sedation (RASS between -4 and -5) or prolonged deep sedation may have generated deleterious effects and contributed to excess mortality (14-15).

It is noteworthy that our study included a majority of medical ICU patients, whereas the aforementioned studies included predominantly surgical patients. Compared to literature reports, the use of dexmedetomedine was thus evaluated here in conditions where weaning from ventilatory support is difficult, which may explain the failure to observed any significant difference between groups in our study.

Self-extubation and the need for re-intubation within 48 hours were more frequent in the standard protocol group, within re-intubations mainly due to laryngeal oedema. Few studies to date have investigated the incidence of self-extubation under dexmedetomidine. A meta-analysis by Tan et al reported an increased risk of self-extubation with dexmedetomidine, but without reaching statistical significance (5). This trend in favour of the use of dexmedetomidine may be explained by the greater comfort procured by dexmedetomidine in terms of both respiratory function and mental status, limiting the agitation that can lead to laryngeal oedema.

Our study has some limitations. Firstly, it was a retrospective, single-centre study, with a relatively small sample size. The patients included in this study were representative of a general population of adults in mainly medical intensive care, and thus, the results should not be extrapolated to other ICU populations. Secondly, the choice of sedation was not blinded in this study, which leaves room for selection bias. It is possible that dexmedetomidine was chosen by the investigators in patients in whom weaning was anticipated to be difficult. Third, the depth of sedation prior to the weaning phase was not recorded. The secondary effects of certain hypnotics (e.g. accumulation, metabolism, half-life) represent potential confounders that may affect the analysis of the impact of dexmedetomidine. Finally, sedation with dexmedetomidine was associated in all cases with an analgesic and/or an additional sedative. In certain cases, patients required complementary analgesics to achieve the target pain scores as evaluated by VAS, while in others, dexmedetomidine was insufficient to achieve the clinical grade of sedation required. The main strength of our study is the use of propensity score analysis to balance the differences in groups in terms of baseline characteristics.

CONCLUSION

In this observational study, we failed to demonstrate that cooperative sedation with dexmedetomidine was associated with a shorter duration of weaning from MV in patients ventilated for at least 5 days as compared to the standard protocol. Further randomized, controlled trials investigating the duration of weaning from MV as the primary endpoint are warranted to confirm these results.

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