

ORIGINAL ARTICLE

## Feasibility of dexmedetomidine in facilitating extubation in the intensive care unit

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### SUMMARY

**Background:** Spontaneous breathing trials (SBT) and intermittent mandatory ventilation (IMV) are common techniques utilized to expedite the ventilator weaning process. These techniques often require the reduction and/or discontinuation of sedatives and analgesics. Reducing these medications can lead to agitation and the inability to conduct SBTs or weaning by IMV. Adding dexmedetomidine (dex), a potent alpha-2-adrenergic receptor agonist that possesses sedative, anxiolytic and analgesic effects without causing significant respiratory depression, may facilitate extubation in these patients.

**Objective:** To assess the feasibility of adding dex to facilitate extubation in a group of difficult-to-extubate patients secondary to agitation.

**Methods:** Mechanically ventilated patients who were deemed difficult to wean and extubate secondary to agitation were evaluated for dex therapy. Inclusion criteria were location in an intensive care unit, intubated and mechanically ventilated, required IV sedation, deemed suitable by unit criteria for weaning and extubation within 24 h of dex initiation, previous attempts at weaning sedation and/or analgesia resulted in agitation causing either severe patient ventilator dyssynchrony, prolong need for intubation, or an inability to conduct a successful SBT. Additional inclusion criteria were unsuccessful use of traditional intravenous agents to control agitation. Recommended dex dosing was a bolus of 1 µg/kg followed by an infusion of 0.2–0.7 µg/kg/h.

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**Results:** Twenty-five patients were evaluated for dex therapy with 20 meeting the criteria to treat. All had failed prior attempts at weaning. Fourteen of the 20 patients were successfully weaned and extubated and one patient was reintubated within 48 h, giving a 65% success rate. Heart rate trended down after dex initiation in most patients but did not result in the discontinuation of dex in any patient. The addition of dex was associated with minimal changes in mean arterial pressure. **Conclusions:** Dexmedetomidine was initiated in a group of mechanically ventilated patients who failed previous attempts at weaning and extubation secondary to agitation. After dex initiation, 65% of the patients was successfully extubated. Dexmedetomidine was associated with a reduction in concomitant sedative and analgesic use with minimal adverse effect.

**Keywords:** agitation, dexmedetomidine, extubation, intensive care unit

### BACKGROUND/OBJECTIVES

Critically ill mechanically ventilated patients frequently receive adjunctive sedatives and/or analgesics to prevent agitation and patient-ventilator dyssynchrony. Spontaneous breathing trials (SBT) and intermittent mandatory ventilation (IMV) are common techniques utilized to expedite the weaning process (1, 2). These techniques often require the reduction and/or discontinuation of sedatives and analgesics. In some patients, reducing these medications can lead to agitation and inability to conduct SBTs or weaning by IMV. In response to agitation, adding or resuming sedatives, anxiolytics, or analgesics that cause respiratory depression may lead to a prolonged need for

mechanical ventilation. Initiating medications that provide sedation, anxiolysis and/or analgesia without causing respiratory depression may allow for the reduction or discontinuation of agents that depress respiratory drive and subsequently facilitate extubation. Dexmedetomidine (dex) is a potent alpha-2-adrenergic receptor agonist that possesses sedative, anxiolytic and analgesic effects without causing significant respiratory depression (3–6). Infusions of dex reduce both opiate and propofol requirements and improve haemodynamic stability in the peri-operative and intensive care unit (ICU) settings. (7–10) Therefore, we sought to determine the utility of dex in facilitating extubation in a group of mechanically ventilated patients deemed to be difficult to wean and extubate secondary to agitation and continued need for sedation.

## METHODS

Mechanically ventilated patients who were considered difficult to wean and extubate secondary to agitation were referred to the unit-based pharmacist for dex therapy by the ICU team. The pharmacist then evaluated each patient using an institutional guideline. The patients were considered eligible for dex therapy if they met the following inclusion criteria: location in an ICU, intubated and mechanically ventilated, requiring IV sedation, deemed suitable by the unit Intensivist for weaning and extubation within 24 h of dex initiation, previous attempts at weaning sedation and/or analgesia resulted in agitation which was contributing to: severe patient ventilator dyssynchrony, prolonged need for intubation or an inability to conduct a successful SBT and traditional agents to control agitation were tried without success. The patients were considered not eligible for dex therapy, if they had a heart rate (HR) <50 or were in acute heart failure or had unstable angina or acute myocardial infarction in the last 30 days. The use of dex was discouraged but not contraindicated, if a patient was receiving vasopressors at the time of dex initiation. There were no predefined criteria for patient-ventilator dyssynchrony or prolonged need for intubation. These were based on the assessment of the Unit Intensivist. Our institutional ICU standard is to use the Richmond agitation-sedation scale (RASS) or the Sedation-Agitation Scale (SAS) to guide sedation and aid in

agitation assessments (11, 12). Based on each units criteria, a patient would be considered agitated with a RASS score of +2 (frequent non-purposeful movement or patient-ventilator dyssynchrony) or a SAS score of 'agitated' (anxious or mildly agitated, attempting to sit up, calms down to verbal instructions).

Dosing recommendations were based on those found in the product labelling: bolus of 1 µ/kg over 10 min followed by an infusion at 0.2–0.7 µg/kg/h. Dosing and titration were not per protocol and left to the discretion of the ICU team and nurse responsible for the patient. After dex initiation, attempts at weaning and extubation commenced at the discretion of the ICU team caring for the patient. Although each ICU unit utilizes standard subjective sedation scales (i.e. SAS), the goal sedation level after dex initiation was not prespecified and was set by each ICU team caring for the patient.

Main outcome variables included rate of extubation at 24 and 48 h post-dex initiation, mean time to extubation after dex initiation and the mean rate of propofol, midazolam and morphine equivalent infusions before and after dex initiation. Heart rate, mean arterial pressure (MAP) and oxygen saturations were measured at the time of dex initiation (baseline) and serially at the following time points: 1, 2, 4, 6, 12 and 24 h. Data are presented as mean ± standard deviation (SD). Changes in haemodynamic variables before and 6, 12 and 24 h after dex administration were tested with repeated measures one-way ANOVA utilizing a Tukey *post-hoc* analysis when appropriate. Paired *t*-tests were performed on all other variables obtained before and after dex administration. A two-tailed *P*-value of <0.05 was considered statistically significant. Institutional review board approval was obtained prior to data collection and analysis.

## RESULTS

Twenty-five patients were evaluated for dex therapy with 20 meeting the meeting criteria to treat. Of the five patients not qualifying for dex, the most common reasons were not requiring IV sedation ( $n = 3$ ) and absence of agitation while weaning sedation and/or analgesia ( $n = 3$ ). The 20 patients, who were treated with dex, were predominately male (75%) with a mean age of  $50 \pm 15$  years and a weight of  $83 \pm 21$  kg. The most common form of IV

sedation was propofol or midazolam  $\pm$  an opiate (Table 1). Six patients treated with propofol, two with midazolam and two with an opiate were weaned to off within 12 h of dex initiation (Table 1). The most common intermittent IV adjuncts before dex initiation were haldol (45%) and lorazepam (40%). Fourteen of the 20 patients initiated were successfully extubated (70%), most within 24 h (Table 2). One of these patients was reintubated within 48 h of extubation resulting in

**Table 1.** Dexmedetomidine and additional sedative and analgesic use

Medication	Dose		
Duration of dex infusion <sup>a</sup> (hours) ( <i>n</i> = 20)	29 $\pm$ 27		
Dex ( $\mu\text{g}/\text{kg}/\text{h}$ ) ( <i>n</i> = 20)	0.53 $\pm$ 0.2		
Dex at extubation ( $\mu\text{g}/\text{kg}/\text{min}$ ) ( <i>n</i> = 14)	0.43 $\pm$ 0.23		
	Prior to dex <sup>e</sup>	Post-dex <sup>f</sup>	<i>P</i> -value
Propofol <sup>b</sup> (mg/h) ( <i>n</i> = 15)	146 $\pm$ 90	70 $\pm$ 77	<0.001
Morphine equivalent <sup>c</sup> (mg/h) ( <i>n</i> = 12)	20 $\pm$ 27	13 $\pm$ 22	0.008
Midazolam <sup>d</sup> (mg/h) ( <i>n</i> = 5)	5 $\pm$ 4	1.7 $\pm$ 1.7	0.19

Dex, dexmedetomidine.

Data expressed as mean  $\pm$  SD.

<sup>a</sup>One patient received a standard bolus before initiation of maintenance infusion.

<sup>b</sup>Six of the 15 patients were weaned to off after dex initiation.

<sup>c</sup>Two of the 12 patients were weaned to off after dex initiation.

<sup>d</sup>Two of the 5 patients were weaned to off after dex initiation.

<sup>e</sup>Measured for 12 h before dex initiation.

<sup>f</sup>Measured for 12 h after dex initiation

**Table 2.** Results: rate of extubation after dex initiation

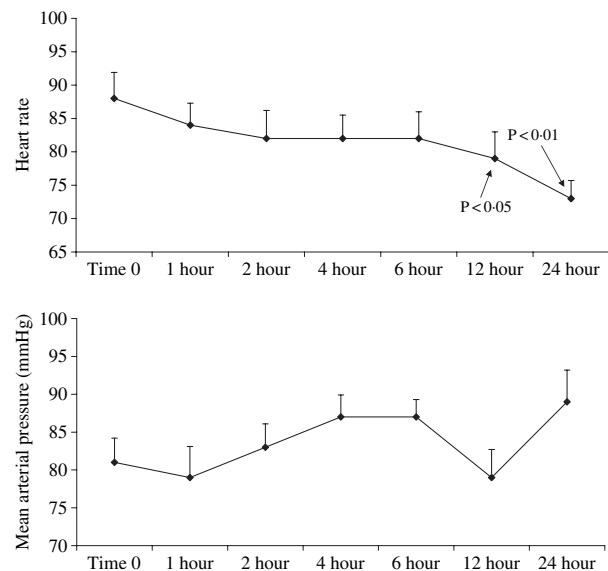
Extubation after dex initiation	<i>n</i> = 20
$\leq 24$ h	13 (65)
$>24$ h	1 (5)
Total	14 (70)
Time after dex initiation (hours)	11 $\pm$ 11

Data expressed as number and percentage or mean  $\pm$  SD.

an overall success rate of 65%. Heart rate trended downward at every time point after dex initiation but did not result in the discontinuation of dex in any patient or symptomatic bradycardia (Fig. 1). Heart rate at both 12 and 24 h after dex initiation was significantly lower than HR prior to dex initiation ( $P < 0.05$  and  $P < 0.01$  respectively) (Fig. 1). The addition of dex was associated with minimal changes in MAP ( $P = \text{NS}$ ) (Fig. 1). However, four patients received a vasopressor while on dex therapy. Phenylephrine was initiated in one patient after dex was started and three patients were on the vasopressor prior to dex initiation (Table 3). For the 16 patients who remained off vasopressors during the dex infusion, MAP was unchanged (mean MAP was 84 before the infusion and varied between 81 and 95 during infusion,  $P = \text{NS}$ ). Mean oxygen saturation for all patients was 97% at dex initiation and 2 h after initiation. The oxygen saturation for patients who were successfully extubated was 97% 1 h before and after extubation.

## DISCUSSION

Dexmedetomidine is considered an effective adjunct for sedation and analgesia in the peri-operative period; however, its use in the ICU setting is less



**Fig. 1.** Average ( $\pm$ SE) heart rate and mean arterial pressure pre- (Time 0) and post-dexmedetomidine initiation for all 20 patients. Heart rate at the 12- and 24-h time intervals was significantly lower compared with Time 0.

	Patient 1	Patient 2	Patient 3	Patient 4
CVP <sup>a</sup> (mmHg)	5	8	ND	ND
Time (hours)	Norepinephrine (µg/min)	Norepinephrine (µg/min)	Phenylephrine (µg/min)	Phenylephrine (µg/min)
0	10	6	60	0
1	10	8	65	60
2	10	8	65	50
4	9	8	65	30
6	8	6	70	15
12	4	4	80	20
24	ND	2	20	ND

ND, no data.

<sup>a</sup>Central venous pressure at dex initiation.

clear. All of our patients had proven difficult to wean and extubate which were attributable to agitation by each attending intensivist despite the use of traditional agents. Seventy percent of our patients able to be extubated, most within 12 h of dex initiation. In most cases, the standard background sedatives/analgesics were weaned and in some cases discontinued. This finding is consistent with other reports of patients initiated on dex for sedation in the ICU (9, 10).

This analysis expands on the previous work done by Siobal *et al.* who initiated dex in five surgical ICU patients to facilitate extubation (13). All the patients had failed attempts at weaning and extubation secondary to agitation. Similar to our analysis, delirium was not evaluated as a cause of agitation. Shortly after dex initiation, four of the five patients were extubated with minimal adverse effect. The average time to extubation after dex initiation was longer in our analysis (11 vs. 2 h). In addition, propofol were discontinued in four of five patients within 30 min of dex initiation. One possible explanation for this difference could be that Siobal *et al.* (13) encouraged weaning background sedation and ventilatory support soon after dex initiation. Our protocol left both to the discretion of the caring for the patient. This difference can also be explained partially by the higher initiating dose of dex used by Siobal *et al.* (13) (0.5–0.7 µg/kg/h). The explanation for their ability to obtain such a rapid effect with dex without a bolus dose is unclear. The pharmacokinetics of dex would suggest that any significant anxiolytic/analgesic effect would take

**Table 3.** Vasopressor requirement before and after dexmedetomidine initiation

several hours to obtain without a bolus dose. Nonetheless, our findings are consistent with those of Siobal *et al.* in that many of our patients were able to discontinue background sedation sometime after dex initiation.

Dexmedetomidine initiation was associated with a decrease in HR, whereas blood pressure (BP) appeared to be unaffected in the majority of patients. One patient (5%) required a vasoactive agent after dex was initiated. However, the vasopressor doses were largely unchanged in the three patients already on vasopressors and BP did not fall in the remaining 15 patients. The overall apparent lack of effect that dex initiation had on BP is not readily explained and is not consistent with the other reports (10). One plausible explanation may be that propofol requirements were significantly reduced and in some cases discontinued after dex initiation. Propofol is considered a vasodilator; therefore, the net effect may be no change in BP. The effects of dex on HR are consistent with those reported in the literature but did not result in symptomatic bradycardia or the reduction and/or discontinuation of dex in any patient (10).

This was an observational analysis and has some limitations that should be considered when interpreting these results. Firstly, there was no control group and dex administration was open label. Therefore, we were unable to determine the direct impact that dex may have on rates and time to extubation. However, it is reasonable to postulate that the initiation of dex led to a decrease in the amount of sedatives and analgesics while at the same time maintaining a satisfactory level of

sedation for ventilator weaning and extubation. Second, there was no systematic collection of sedation scores prior to dex initiation. Grading agitation before dex initiation may have better defined the patient population that may have benefited from dex in this setting. However, we felt that categorizing patients as agitated or not based on standard ICU criteria (i.e. RASS or SAS) was sufficient to target the intended study population. Third, there was no standard definition for patient-ventilator dyssynchrony or prolonged need for intubation. Therefore, defining the population that may benefit from treatment with dex is less clear. Classifying each patient as dyssynchronous with the ventilator or requiring prolonged ventilation was left to each patient's Intensivist. This was primarily due to variations and lack of defined criteria for each in practice, but still may have introduced bias. Fourth, there was no target sedation score while on dex therapy. To our knowledge, there is no proven subjective sedation level (i.e. SAS or RASS) during the peri-extubation period or when dex is the primary agent utilized for sedation that is considered standard of care. Also, our intention was not to describe the level (i.e. SAS or RASS) of sedation or to determine the optimal level of sedation level while on dex during the peri-extubation period. Rather, we intended to describe the feasibility of using dex when other medical therapies targeting sedation and agitation had failed. Lastly, delirium was not systematically evaluated as a possible cause of agitation. If delirium was a significant contributor, medications to treat delirium could have been utilized in the place of dex. However, 45% of our patients received haloperidol before therapy with dex was considered and still were deemed to be agitated.

## CONCLUSIONS

Dexmedetomidine was initiated in a group of mechanically ventilated patients who failed previous attempts at weaning and extubation secondary to agitation. After dex initiation, 65% of patients were successfully extubated. In addition, dex was associated with a reduction in concomitant sedative and analgesic use with minimal adverse effects. Further studies are necessary to determine if dex improves important clinical outcomes or

reduces overall costs compared with usual sedation and analgesic practices or a more structured approach to the difficult to wean patient, including a systematic evaluation for delirium and the target use of neuroleptics.

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