# Original Contributions

# Use of Dexmedetomidine to Facilitate Extubation in Surgical Intensive-Care-Unit Patients Who Failed Previous Weaning Attempts Following Prolonged Mechanical Ventilation: A Pilot Study

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INTRODUCTION: Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that exhibits sedative, analgesic, anxiolytic, and sympatholytic effects without respiratory-drive depression. We prospectively evaluated the use of dexmedetomidine to facilitate the withdrawal of mechanical ventilation and extubation in 5 trauma/surgical intensive-care-unit patients who had failed previous weaning attempts due to agitation and hyperdynamic cardiopulmonary response. METHODS: Intravenous infusion of dexmedetomidine commenced at 0.5 or 0.7 $\mu$g/kg/h without a loading dose. Background sedation and analgesia with propofol, benzodiazepines, and opiates was discontinued or reduced as tolerated. Dexmedetomidine infusion was titrated between 0.2 and 0.7 $\mu$g/kg/h to maintain a stable cardiopulmonary response and modified Ramsay Sedation Score between 2 and 4. RESULTS: Following dexmedetomidine administration, propofol infusion was weaned and discontinued in 4 patients. In the fifth patient, benzodiazepine and opiate infusions were reduced. Ventilatory support in all patients could be weaned to continuous positive airway pressure of 5 cm $H_2O$ without agitation, hemodynamic instability, or respiratory decompensation. All patients were extubated while receiving dexmedetomidine infusion (mean dose of 0.32 $\pm$ 0.08 $\mu$g/kg/h). One patient required reintubation for upper-airway obstruction. CONCLUSION: Dexmedetomidine appears to maintain adequate sedation without hemodynamic instability or respiratory-drive depression, and thus may facilitate extubation in agitated difficult-to-wean patients; it therefore deserves further investigation toward this novel use. *Key words: dexmedetomidine, ventilator weaning, extubation, sedation, agitation.* [Respir Care 2006;51(5):492–496. © 2006 Daedalus Enterprises]

## Introduction

Mechanical ventilation is often associated with patient agitation requiring sedation to alleviate discomfort, prevent self-destructive behavior, decrease excessive central respiratory drive, and improve patient-ventilator synchrony.[1]

Agitation is a common management problem in the intensive care unit (ICU),[2] and is often caused by delirium.[1–3] Agitation caused by disturbances of consciousness, attention, cognition, and perception, once referred to as ICU psychosis,[4] is currently recognized as the hyperactive subtype of delirium,[5] and has been referred to as agitated delirium.[6,7]

Upon recovery from critical illness, sedation is reduced to facilitate the withdrawal of ventilatory support. Reduction in sedation can provoke a stress response, catecholamine release, and agitation, resulting in tachypnea, tachycardia, and hypertension.[8] This response often requires increased or resumed sedation and therefore may prolong

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mechanical ventilation in patients who should otherwise tolerate unassisted breathing and extubation.

Dexmedetomidine hydrochloride (Precedex, Hospira, Lake Forest, Illinois) is an alpha-2 receptor agonist with both sedative and analgesic properties that reduce the sedation, anxiolytic, and analgesic requirements in the perioperative setting.[9–12] In addition to its sedative effects, alpha-2 receptor stimulation in the central nervous system inhibits sympathetic activity[13] and reduces plasma epinephrine and norepinephrine levels.[14,15] Dexmedetomidine has been reported useful in attenuating hemodynamic stress secondary to hyperadrenergic over-reactivity[16] and agitation associated with delirium.[17] Because alpha-2 receptor stimulation does not cause respiratory depression,[18,19] sedation with dexmedetomidine may facilitate the transition to unassisted breathing in agitated patients.

We evaluated the use of dexmedetomidine to facilitate the withdrawal of mechanical ventilation and extubation in 5 trauma/surgical ICU patients who failed weaning attempts due to agitation and hyperdynamic cardiopulmonary response.

## Methods

Five patients in the surgical ICU were referred to the investigators by the critical care service. The study was approved by our institutional review board, and informed consent was obtained. Each patient was considered by the critical care service to be a suitable candidate for weaning from mechanical ventilation and extubation, based on the standardized institutional criteria. Each study patient had failed at least one trial of continuous positive airway pressure (CPAP), or had failed to tolerate low levels (5–10 cm $H_2O$) of pressure support over several days because of respiratory and hemodynamic changes associated with agitation.

Dexmedetomidine infusion was started at 0.5 or 0.7 $\mu$g/kg/h. The infusion rate was calculated based on an average between the patient's measured and predicted body weight, using a standard formula. After starting dexmedetomidine, background sedation (with lorazepam, midazolam, or propofol) and analgesia (with either fentanyl or hydromorphone) were titrated down or discontinued if possible. Dexmedetomidine dose was titrated according to blood pressure and heart-rate response. Aerosolized lidocaine (30 mg) was administered prior to the weaning trial, to prevent excessive coughing.

Soon after the dexmedetomidine infusion was started, pressure support was commenced at 5 cm $H_2O$ above 5 cm $H_2O$ of CPAP. Patients were weaned to CPAP and evaluated for extubation. Arterial blood gases were obtained at 3 points in time: (1) just prior to dexmedetomidine infusion, (2) during the CPAP trial, and (3) approximately 30 min after extubation. Heart rate, mean arterial blood pressure, respiratory rate, and oxygen saturation (measured via pulse oximetry) were collected prior to the beginning of dexmedetomidine infusion, and at the following time points: 5, 15, 30, 45, 60, 75, 90, 120, 150, and 180 min, 30 min after extubation, and 30 min after discontinuation of dexmedetomidine infusion.

The data were evaluated with the Kolmogorov-Smirnov test and found to be consistent with a normal distribution ($p > 0.10$). The data were compared with repeated-measures analysis of variance, and the threshold for performing Tukey-Kramer post-tests was a $p < 0.05$. InStat version 3.0 (GraphPad Software, San Diego, California) was used for statistical analysis.

## Results

The study patients had failed to tolerate daily weaning trials for $7.9 \pm 5.1$ d prior to enrollment. Baseline minute ventilation of $10.1 \pm 2.6$ L/min was associated with eucapnia and a normal pH. The ratio of $P_{aO_2}$ to fraction of inspired oxygen ($F_{IO_2}$) was $256 \pm 63$ mm Hg, and the static respiratory-system compliance was $31 \pm 5$ mL/cm $H_2O$ at the time of enrollment. Weaning failures on low levels of pressure support following baseline sedation-reduction were associated with agitation, hypertension, and varying degrees of tachycardia and tachypnea. In each patient, delirium was not explicitly ruled-out as the cause of agitation. Individual patient characteristics are summarized in Table 1.

After starting treatment with dexmedetomidine, background sedation was reduced or discontinued while analgesic levels were either reduced or maintained at the baseline level. Propofol was discontinued in all patients within 30 min. All patients tolerated a spontaneous breathing trial with CPAP and were extubated after an average of $120 \pm 43$ min. One patient developed upper-airway obstruction and required reintubation after 45 min. The patients received dexmedetomidine infusion for an average of $211 \pm 39$ min. The mean initial dose of dexmedetomidine was $0.58 \pm 0.11$ $\mu$g/kg/h. At 1 hour the mean dose of dexmedetomidine was reduced by 28%, to $0.42 \pm 0.18$ $\mu$g/kg/h. During dexmedetomidine infusion, patients would open their eyes spontaneously or with mild stimulation, and they had an average Ramsay Sedation Score of 3.4, without signs of agitation. Patients were extubated on a mean dexmedetomidine dose of $0.32 \pm 0.08$ $\mu$g/kg/h and continued to receive dexmedetomidine infusion for an average of $91 \pm 38$ min following extubation.

Heart rate, mean arterial blood pressure, respiratory rate, oxygen saturation, pH, $P_{aCO_2}$, and $P_{aO_2}$ at all time points were not different. A nonsignificant, transient increase in heart rate and mean arterial blood pressure occurred within 5 min of starting the dexmedetomidine infusion, but quickly subsided. Patients 1 and 4 required a 25-$\mu$g bolus of fen-

Table 1.    Characteristics and Outcomes of Patients Treated With Dexmedetomidine for Failure to Tolerate Spontaneous Breathing Trial

| Patient | Age | Sex | Diagnosis | Weaning Started (days after intubation) | Weaning Days Before Dexmedetomidine Trial | Reasons for Failing Prior Weaning/SBT | Outcome of Dexmedetomidine Weaning/SBT |
|---|---|---|---|---|---|---|---|
| 1 | 68 | F | Motor vehicle accident, epidural hematoma, subdural hematoma, medical history of hypertension | 0.5 | 4.0 | Agitation, hypertension | Extubated, reintubated for upper-airway obstruction |
| 2 | 29 | M | Multiple gun-shot wounds to the abdomen | 9.3 | 5.3 | Agitation, hypertension, tachypnea | Extubated |
| 3 | 32 | M | Motor vehicle accident, diffuse axonal brain injury, pulmonary contusions | 3.5 | 3.2 | Agitation, hypertension, tachypnea | Extubated |
| 4 | 61 | F | Motor vehicle accident, subdural hematoma, acute respiratory failure, pneumonia | 0.8 | 13.1 | Agitation, hypertension, tachycardia, tachypnea | Extubated |
| 5 | 38 | M | Pancreatitis, pneumonia, ARDS | 6.0 | 13.8 | Agitation, hypertension, tachycardia, tachypnea | Extubated |

SBT = spontaneous breathing trial
ARDS = acute respiratory distress syndrome

tanyl. Patient 3 required an increase in supplemental oxygen after extubation, which resolved within several hours. Patient 4 had 2 transient episodes of bradycardia, to a heart rate of 55 beats/min, which resolved after the dexmedetomidine dose was reduced by 0.1 $\mu$g/kg/h, following each event. Patient 4 also required a one-time 2-mg bolus of haloperidol at the end of the study.

## Discussion

In this small, uncontrolled study of trauma/surgical ICU patients, the infusion of dexmedetomidine allowed downward titration of baseline sedation and successful extubation without the cardiopulmonary instability or signs of agitation that had been noted during prior weaning attempts.

Our study differed from previous reports in 2 respects. First, we did not use a loading dose, but rather began with the infusion rate of 0.5 or 0.7 $\mu$g/kg/h. This was done to assess whether a loading dose is necessary in the presence of other sedative agents and to avoid potential hypertension, reflex bradycardia, and hypotension, which is sometimes encountered during loading-dose administration.[11,12] Effective analgesic-sparing sedation with minimal hemodynamic change has been reported without a loading dose prior to dexmedetomidine infusion,[9] and with dose-infusion rates of 0.2 or 0.6 $\mu$g/kg/h.[20] Second, our patients differed from previous reports in that three were recovering from traumatic brain injury, which is a cause of severe agitation. To our knowledge, use of dexmedetomidine to facilitate unassisted breathing and extubation in this subgroup of patients has not been previously reported.

A limitation of this small study is that it was an unblinded, single-arm trial and therefore subject to bias. In addition, the aerosolized lidocaine given to suppress cough reflexes introduced a confounding variable, as reduced airway reflexes may be the reason the patients could tolerate weaning of sedation without agitation and consequent cardiopulmonary stress response. Furthermore, the dosing method in this study used an average between the patient's measured and predicted body weight, which may have resulted in under-dosing, as the recommended dose range is based on measured body weight.

The sedative, analgesic, and anxiolytic-sparing effects, and sympatholytic properties of dexmedetomidine occur with minimal respiratory-drive suppression.[13,18,19] These characteristics may have important clinical implications in the sedation and care of critically ill ICU patients.

The ICU environment predisposes patients to develop agitation and delirium associated with noradrenergic hyperfunction.[6] The sympatholytic property of dexmedetomidine causes a reduction in plasma epinephrine and norepinephrine levels.[14,15] This effect attenuates the hyperdynamic physiologic response to stress[13,16,17] and may explain

why our study patients could be extubated during dexmedetomidine infusion after failing previous attempts.

Current practice usually entails reducing or discontinuing sedation prior to extubation. Because of the lack of respiratory depression, use of dexmedetomidine allows continued sedation during the entire weaning process and the subsequent extubation and post-extubation period. Dexmedetomidine may inhibit the hemodynamic stress response during weaning from mechanical ventilation and may help eliminate emergence agitation when sedation is being tapered, and it therefore may help to facilitate earlier extubation in some patients.

Sedation with dexmedetomidine may also reduce or eliminate the need for continuous intravenous sedation with opiates and benzodiazepines in some patients. Continuous intravenous sedation with opiates and benzodiazepines are associated with prolonged duration of mechanical ventilation.[21] Use of opiates and benzodiazepines is also a risk factor associated with the development of agitation[7] and delirium.[22,23] In adult ICU patients, sedative and analgesic withdrawal is also associated with prolonged stay and duration of mechanical ventilation.[3,24] Dexmedetomidine has been reported to be useful in maintaining sedation and attenuating withdrawal symptoms while reducing opiate and benzodiazepine requirements without delaying weaning and extubation.[25]

Although dexmedetomidine use for extended periods[26] (up to 7 days[9,25]) has been reported, it is approved by the Food-and-Drug-Administration only for use of < 24 hours duration in postoperative patients. Lack of addictive properties, cumulative effects, or clinical signs or symptoms of withdrawal,[9,13] make dexmedetomidine an attractive potential alternative to current ICU sedation regimens.

## Conclusions

Infusion of dexmedetomidine without a loading dose appears to be adequate in maintaining sedation without hemodynamic instability or respiratory compromise and may facilitate weaning and extubation in trauma/surgical ICU patients who have failed previous attempts at weaning because of agitation and hyperdynamic cardiopulmonary response. Before dexmedetomidine can be recommended as a means to facilitate extubation under these circumstances, it must be tested and properly validated in prospective randomized controlled studies. Further investigation of long-term ICU sedation with dexmedetomidine is necessary to establish sedation guidelines and the safety profile of this promising new agent.
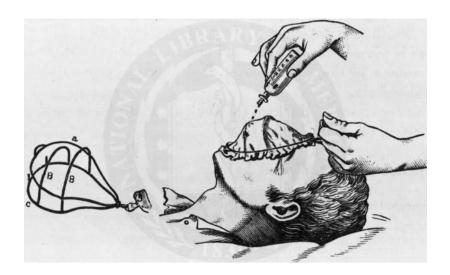
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Turnbull's modification of Skinner and Charrière's chloroform inhaler.
The inhaler's wire frame without its cover is shown at left.
From Laurence Turnbull, *Artificial Anesthesia*, 4th edition
Philadelphia: Blakiston; 1896
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