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The effect of dexmedetomidine on agitation during weaning of mechanical ventilation in critically ill patients

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SUMMARY

Ventilated patients receiving opioids and/or benzodiazepines are at high risk of developing agitation, particularly upon weaning towards extubation. This is often associated with an increased intubation time and length of stay in the intensive care unit and may cause long-term morbidity. Anxiety, fear and agitation are amongst the most common non-pulmonary causes of failure to liberate from mechanical ventilation. This prospective, open-label observational study examined 28 ventilated adult patients in the intensive care unit (30 episodes) requiring opioids and/or sedatives for >24 hours, who developed agitation and/or delirium upon weaning from sedation and failed to achieve successful extubation with conventional management. Patients were ventilated for a median (interquartile range) of 115 [87 to 263] hours prior to enrolment. Dexmedetomidine infusion was commenced at 0.4 μg/kg/hour for two hours, after which concurrent sedative therapy was preferentially weaned and titrated to obtain target Motor Activity Assessment Score score of 2 to 4. The median (range) maximum dose and infusion time of dexmedetomidine was 0.7 μg/kg/hour (0.4 to 1.0) and 62 hours (24 to 252) respectively. The number of episodes at target Motor Activity Assessment Score score at zero, six and 12 hours after commencement of dexmedetomidine were 7/30 (23.3%), 28/30 (93.3%) and 26/30 (86.7%), respectively (P <0.001 for 6 and 12 vs 0 hours). Excluding unrelated clinical deterioration, 22 episodes (73.3%) achieved successful weaning from ventilation with a median (interquartile range) ventilation time of 70 (28 to 96) hours after dexmedetomidine infusion. Dexmedetomidine achieved rapid resolution of agitation and facilitated ventilatory weaning after failure of conventional therapy. Its role as first-line therapy in ventilated, agitated patients warrants further investigation.

Key Words: dexmedetomidine, agitation, ventilation weaning, sedation, critical care

Mechanically ventilated patients frequently require sedation and analgesia to reduce anxiety and discomfort from endotracheal tubes and to facilitate other intensive care unit (ICU) procedures[1]. When mechanical ventilation is no longer required and sedation is weaned, patients can often develop agitation and/or delirium. In mechanically ventilated patients, the incidence of severe agitation has been reported at between 16[2] and 29%[3]. In the ICU setting, severe agitation can lead to traumatic self-extubation, extended duration of opioid and benzodiazepine treatment, longer length of stay and prolonged mechanical ventilation[2]. Longer-term effects can include prolonged cognitive dysfunction and increased risk of post-traumatic stress disorder. At six months post-discharge, post-traumatic stress disorder was present in 14% of patients who had been mechanically ventilated in an ICU[4].

Current evidence-based guidelines for weaning and discontinuing ventilatory support[5] identified non-respiratory causes and, in particular, psychological factors such as fear, anxiety, agitation and pain as the most important non-respiratory factors to consider during liberation from ventilatory support. A systematic review identified the paucity of trials of interventions to facilitate weaning from mechanical ventilation and called for more research into the non-pulmonary causes of weaning failure[6].

The 2002 clinical practice guidelines for sedation and analgesia in the critically ill[7] recommends the use of midazolam, diazepam, propofol or lorazepam for sedation of agitated ICU patients, and haloperidol as the agent of choice for delirium. However, the efficacy and safety profiles of these

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agents in this particular group of patients are not established[7-10]. Furthermore, different approaches have also been implemented to reduce over-sedation, including a nurse-directed protocol[11] and daily interruption of sedation[12] with reduction in ventilation time and intensive care length of stay.

A recent review[13] called for a systematic approach to implement a strategy to optimise analgesia and sedation in the critically ill. Such a strategy would focus on effective pain relief and include protocolised monitored sedation and co-ordinated care in an effort to alleviate problems inherited with conventional sedatives and analgesics.

An ideal agent for the ICU would provide effective pain control and sedation with a rapid onset of action, resulting in a calm patient who can be easily aroused for assessment. It should also allow for rapid recovery after discontinuation, with minimal systemic accumulation and an acceptable safety profile[14].

Dexmedetomidine is a highly selective alpha-2 agonist, producing sedation and anxiolysis due to a reduction in sympathetic central nervous system activity. A major advantage over other recommended sedatives is that it is associated with minimal respiratory depression[15], an important consideration when patients are ready to wean from mechanical ventilation. Moreover, its activation of alpha-2 receptors accentuates the action of opioids, reducing the doses needed to achieve adequate pain relief[14]. These analgesic and sedative effects make dexmedetomidine an attractive agent in the weaning of agitated ICU patients.

The aim of this prospective study was to evaluate the effects of dexmedetomidine on resolution of agitation during weaning from mechanical ventilation of critically ill patients who failed conventional therapy.

MATERIALS AND METHODS

Study type and site

This was a prospective, open-label, observational cohort study. It was performed in tertiary medical/surgical intensive care units at the Prince of Wales Hospital (a principal teaching hospital of the University of New South Wales) and the collocated Prince of Wales Private Hospital in Sydney, New South Wales. The South East Sydney Area Health Service Ethics Committee approved the study. Written informed consent was obtained from the person responsible prior to enrolment in the study. Furthermore, approval was obtained (Clinical Trial Notification Scheme) for the use of dexmedetomidine up to a dose of 1.0 μg/kg/hour and for longer than 24 hours – both higher than the current registered licence in Australia.

Patients

Inclusion criteria were: aged over 18 years, requiring invasive mechanical ventilation for longer than 24 hours, sedatives and/or opioids for longer than 24 hours, development of clinical agitation and/or delirium upon weaning from sedation and/or opioids and failure to achieve successful extubation with conventional therapy and weaning as assessed by the treating intensivist. In the ICUs included in this study, conventional first-line treatment for agitation consists of intravenous midazolam and/or propofol infusions, with the addition of intravenous haloperidol boluses as required. Nasogastric alprazolam is added if further anxiolytic therapy is required. Exclusion criteria were: allergy to dexmedetomidine, pregnancy or lactation, systolic blood pressure <90 mmHg and/or heart rate <55 beats per minute, likely to die within 24 hours and/or likely withdrawal of therapy, long-term α-2 agonist prescription, known opiate or benzodiazepine dependence or treatment for chronic pain or detoxification therapy within the preceding six months, chronic antipsychotic drug prescription, dementia, parkinsonism or chronic epilepsy, recent cerebrovascular surgery or severe traumatic brain injury, recent surgery involving a free arterial flap, hepatic encephalopathy within the last 14 days, recent drug overdose or carbon monoxide poisoning.

Ventilation strategy

Intubated patients were ventilated via pressure support ventilation and positive end-expiratory pressure with a low synchronised intermittent mandatory ventilation rate within 24 hours of intubation. Patients were considered for extubation after resolution of primary pathology when their fractional inspired oxygen (FiO_2) was <0.40 achieving a partial pressure of arterial oxygen (P_aO_2) >70 mmHg, pressure support ventilation and positive end-expiratory pressure ≤10 cmH_2O, and spontaneous tidal volume >5 ml/kg with a frequency of <30 /minute. Patients should have been within a Motor Activity Assessment Scale (MAAS) range of 2 to 4.

Intervention

While several instruments for assessing sedation and agitation have been validated, there is no accepted 'gold standard' scale. At our institution, the MAAS[16] was the current practice tool, the

staff were familiar with its use and it was thus utilised for sedation assessment.

Conventional therapy was running for up to 48 hours prior to enrolment. Dexmedetomidine infusion without a loading dose was commenced at 0.4 μg/kg/hour for two hours, after which it was titrated by 0.2 μg/kg/hour every 30 minutes up to a maximum dose of 1 μg/kg/hour, to obtain a target MAAS score of 2 to 4 ('responsive to touch or name', 'calm and co-operative' or 'restless but co-operative'). Concurrent sedative and/or opioid therapy was preferentially weaned two hours after initiating dexmedetomidine infusion. Rescue sedation (midazolam 1 mg and/or propofol) was given for MAAS scores of 5 to 6. Additional analgesia (morphine 1 to 2 mg or fentanyl 10 to 20 μg) was given if required. MAAS scores were re-evaluated at six and 12 hours and ventilator weaning continued as clinically appropriate. Dexmedetomidine infusion was discontinued once no longer required, at the discretion of the treating intensivist or when 14 days of dexmedetomidine infusion were completed.

Outcome measures

The main outcome was the percentage of patients achieving target MAAS score (2 to 4) assessed at six and 12 hours following the commencement of dexmedetomidine infusion. Other outcome measures included hours of ventilation, number of patients extubated and additional sedatives and analgesia after initiation of dexmedetomidine infusion.

Ventilation time included time of artificial airway such as tracheostomy tube. Successful extubation was documented when no re-intubation occurred within 48 hours.

Statistical analysis

Percentage and median were calculated for categorical and continuous variables, respectively. Interquartile range (IQR) was calculated for continuous variables. Fisher's exact test was used to compare the proportion of patients in the target MAAS category at baseline (zero hours) and at six and 12 hours after commencement of dexmedetomidine infusion. A P value of <0.05 was considered statistically significant and all analyses were done using Stata 9.2 software.

RESULTS

Twenty-eight patients were enrolled, with a total of 30 episodes recorded. Patients were ventilated for a median (IQR) ventilation time of 115 (87 to 263) hours before enrolment. These patients represented

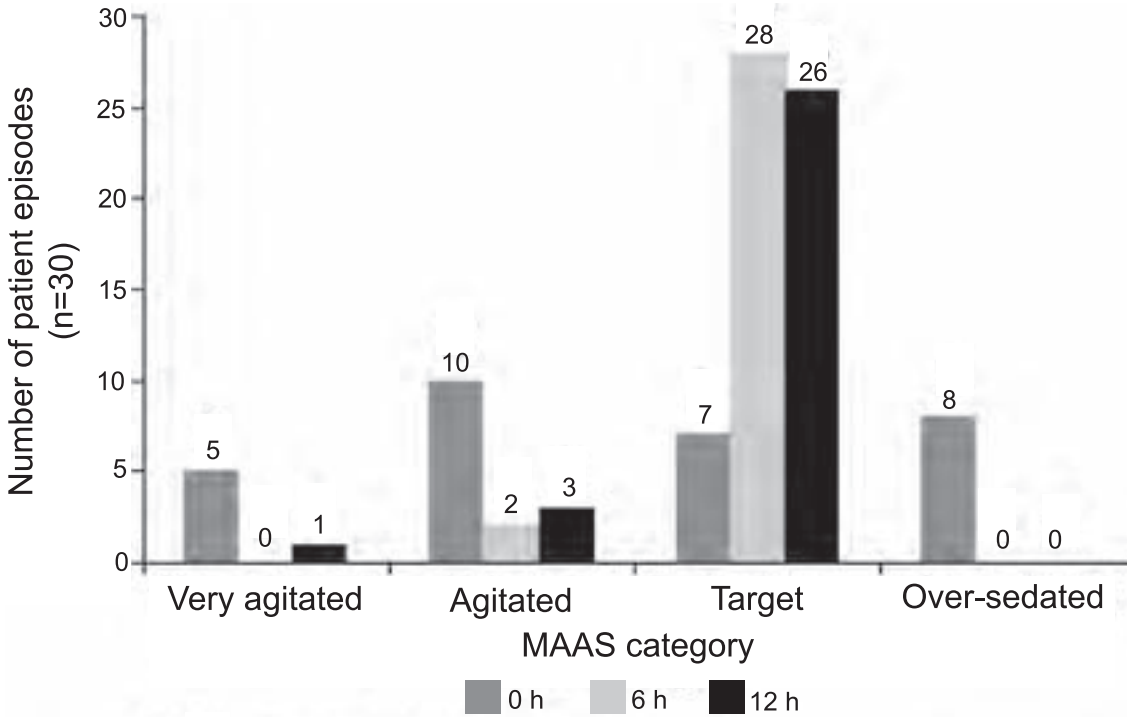

FIGURE 1: Sedation score categories at 0, 6 and 12 hours after commencing dexmedetomidine infusion. This histogram shows Motor Activity Assessment Scores (MAAS) at 0, 6 and 12 hours from dexmedetomidine infusion. At 0 hours, 23 (77%) patients were either agitated or over-sedated – within 6 hours of the infusion 28 (93%) patients were within target MAAS range of 2 to 4. Two-sided Fisher's exact test P <0.0001. This was maintained at 12 hours and at 24 hours (data not shown).

TABLE 1
*Individual patient characteristics**

Case no	Age (y)	Gender (M/F)	Admission APACHE II score	Admission diagnosis	Co-morbidities	Infusions during 48 hours preceding Dex†	Duration ventilation, total (h)	ICU LOS (days)	Maximum Dex dose (μg/kg/h)	Hours on Dex	Reason for cessation
1	76	M	21	Postoperative respiratory failure and aspiration pneumonia	Asthma, HT, COPD, thrombocytopenia, anaemia	Morphine 2 mg/h Midazolam 1 mg/h	126	7	0.6	36	Lack of efficacy, change to propofol
2	71	M	17	CABG	Type 2 diabetes, HT, IHD	Midazolam 3 mg/h Propofol 135 mg/h	52	4	0.7	66	Patient ready for ward
3	20	M	27	Rhabdomyolysis, acute renal failure	Developmental delay, recent seizures, encephalopathy	Propofol 95 mg/h	189	10	1.0	120	Clinical deterioration, seizures requiring midazolam and clonazepam
4	74	M	15	Thoracotomy	Paraplegia T3-T4, HT, moderate respiratory failure	Midazolam 2 mg/h Ketamine 10 mg/h	336	15	1.0	78	Sedation no longer required
5	78	M	29	Decreased level of consciousness and fever	HT, chronic renal failure (non-dialysis dependent)	Propofol 60 mg/h Fentanyl 20 μg/h	232	13	0.7	57	Prior to extubation at clinician discretion, clinically effective
6	70	F	16	Post CABG	HT, recent myocardial infarction, type 1 diabetes	Fentanyl 10 μg/h Midazolam 1 mg/h	106	9	0.4	70	Sedation no longer required
7	82	M	24	Self-inflicted stab wound to abdomen; small bowel perforation	Type 1 diabetes, GIT neoplasm, psychiatric illness	Fentanyl 40 μg/h Midazolam 5 mg/h	319	16	0.7	48	Clinician discretion
8	48	M	23	Aspiration pneumonia, necrotising fasciitis	Type 1 diabetes, morbid obesity, psychiatric illness	Fentanyl 50 μg/h Midazolam 5 mg/h Haloperidol 35 mg	191	16	1.0	48	Patient ready for ward
9	52	M	18	Mitral valve regurgitation, rapid AF	Hepatitis C	Morphine 1 mg/h Propofol 300 mg/h	27	1.7	0.7	27	Patient ready for ward
10	73	M	12	Continuous BIPAP, pneumonitis	Pacemaker, pneumonia	Haloperidol 20 mg	235	19	1.0	60	Clinical deterioration, respiratory failure requiring intubation
11	76	M	28	Recent jejunal perforation, worsening respiratory failure, ARDS	HT, pulmonary fibrosis	Propofol 100 mg/h Midazolam 2 mg/h Fentanyl 20 μg/h	599	25	1.0	83	Clinical deterioration, severe sepsis and haemodynamic instability
12	76	M	28	Recent jejunal perforation, worsening respiratory failure, ARDS	HT, pulmonary fibrosis	Midazolam 1 mg/h Fentanyl 10 μg/h	599	25	0.7	48	Clinical deterioration, required tracheostomy
13	61	M	16	Aortic and mitral valve replacement	Arrhythmias: AF	Propofol 150 mg/h Fentanyl 30 μg/h	24	25	1.0	144	Worsening of liver function
14	51	M	18	Atypical pneumonia, sepsis, liver abscess	COPD, prostatic hypertrophy	Propofol 60 mg/h Fentanyl 10 μg/h	167	5	0.7	48	Lack of efficacy
15	79	M	14	Severe mitral valve regurgitation	Previously well	Morphine 2 mg/h Midazolam 2 mg/h	138	7	0.7	27	Extubated; all sedation ceased
16	74	M	14	Repair thoracic aortic aneurysm	TIA, HT, left-sided weakness	Propofol 55 mg/h Midazolam 2 mg/h	456	24	0.7	63	Clinician decision

TABLE 1 CONTINUED

Case no	Age (y)	Gender (M/F)	Admission APACHE II score	Admission diagnosis	Co-morbidities	Infusions during 48 hours preceding Dex†	Duration ventilation, total (h)	ICU LOS (days)	Maximum Dex dose (μg/kg/h)	Hours on Dex	Reason for cessation
17	49	M	9	CABG, respiratory failure	AMI, HT	Propofol 150 mg/h Fentanyl 50 μg/h	169	3	0.7	51	Ready for extubation
18	53	M	31	Post-renal transplant	End-stage renal failure, AF, angina, gout	Propofol 40 mg/h	29	5	0.7	61	Patient ready for ward
19	26	M	6	Multiple trauma (chest fractures, closed head injury, spinal injury)	Transferred from another hospital	Missing data	60	6	0.7	30	Patient ready for ward
20	69	M	35	Sepsis, acute pancreatitis, acute renal failure	COPD, type 2 diabetes, AMI, CCF	Propofol 30 mg/h Fentanyl 20 μg/h	158	8	0.6	48	Patient ready for ward
21	74	M	47	Acute pancreatitis secondary to gallstone in common bile duct	Chronic renal failure, COPD, AMI, left ventricle dysfunction, AF, CVA, type 2 diabetes, HT, PVD	Propofol 60 mg/h Midazolam 3 mg/h Fentanyl 35 μg/h	133	5	0.7	67.5	Lack of efficacy, continued agitation
22	51	M	30	Subdural haematoma, fractured left neck of femur	Alcohol and recreational drug use	Propofol 70 mg/h Morphine 3 mg/h Midazolam 2.5 mg/h	220	11	0.7	72	Clinical deterioration requiring muscle relaxants and heavy sedation
23	75	M	15	Oesophageal rupture	IHD, AF, HT, high cholesterol, gout	Morphine 3 mg/h Midazolam 3 mg/h	360	26	0.6	43	Lack of efficacy, increasing doses of propofol and midazolam
24	75	M	15	Oesophageal rupture	IHD, AF, HT, high cholesterol, gout	Morphine 1.5 mg/h Midazolam 3 mg/h	360	26	0.7	24	Patient ready for ward
25	87	M	16	Leaking abdominal aortic aneurysm repair	HT, chronic renal failure	Fentanyl 15 μg/h	37	7	0.6	90	Haemodynamic instability requiring intubation, palliative therapy
26	35	M	22	Acute hepatitis continuous CVVHD	Systemic lupus erythematosus	None	316	24	0.6	72	No longer needed
27	62	M	25	Exacerbation of COPD	GORD; severe COPD on home oxygen	Midazolam 2 mg/h	123§	15	1.0	78	Severe respiratory failure, isofluorane for ventilation
28	33	M	26	Multiple trauma excluding head	Previously well	Propofol 140 mg/h Morphine 3 mg/h Midazolam 1 mg/h	142	27	1.0	142	No longer needed
29	62	M	16	CABG	IHD, previous CABG, COPD	Propofol 125 mg/h	216	29	1.0	216	Patient ready for ward
30	82	M	17	CABG	HT, angina, CVA, AAA	Propofol 75 mg/h Midazolam 7.5 mg/h	252	31	0.7	252	No longer needed

* Note: there were 30 episodes in 28 patients; episodes 11 and 12 are in one individual, as are episodes 23 and 24. † Bolus medications are not recorded, except for haloperidol. M=male, F=female, APACHE II=Acute Physiologic and Chronic Health Evaluation Score II, Dex=Dexmedetomidine, ICU=intensive care unit, LOS=length of stay, HT=hypertension, COPD=chronic obstructive pulmonary disease, CABG=coronary artery bypass graft, IHD=ischaemic heart disease, GIT=gastrointestinal tract, BIPAP=bi-level positive airway pressure, ARDS=acute respiratory disease syndrome, AF=atrial fibrillation, TIA=transient ischaemic attacks, AMI=acute myocardial infarction, CCF=congestive cardiac failure, CVA=cerebrovascular accident, PVD=peripheral vascular disease, CVVHD=continuous venovenous haemodiafiltration, GORD=gastro-oesophageal reflux disease, AAA=abdominal aortic aneurysm.

a group with complex and difficult clinical conditions complicated by agitation and failure to liberate from mechanical ventilation. Details of the individual patients' characteristics, including admission diagnosis, co-morbidities and pre-enrolment conventional sedation, are outlined in Table 1. It should be noted that some patients had their sedative medications significantly reduced during the 48 hours prior to enrolment due to over-sedation; therefore, the amount of sedation documented may underestimate the true sedation requirements prior to dexmedetomidine infusion.

Immediately prior to dexmedetomidine infusion, 23 (77%) episodes were outside the target MAAS range with seven episodes (23%) within target range, where agitation developed upon sedative withdrawal in preparation for extubation. The number of agitation episodes decreased from 23 (77%) at enrolment to four (13%) by 12 hours (P <0.001). Within six hours after commencement of dexmedetomidine infusion, 28 episodes (93%) were at target sedation level (P <0.001) and this benefit was maintained at 12 hours (26 episodes or 87%, P <0.001; Figure 1). There was no significant difference between the proportion of patients at target sedation level at six and 12 hours post commencement of the dexmedetomidine infusion (P=0.671).

The majority of patients were males with a median age of 70 years. The cohort clinical characteristics including vasopressor requirement and hospital outcome are presented in Table 2. At the commencement of dexmedetomidine infusion, 10 patients (33%) were on noradrenaline or adrenaline and nine (30%) were on dobutamine.

The median maximum dexmedetomidine dose was 0.7 μg/kg/h (range 0.4 to 1.0) with a median infusion time of 62 hours (range 24 to 252). Most patients (72%) required no or low-dose additional sedatives within 48 hours of study infusion. Excluding unrelated clinical deterioration (detailed below), 22 episodes (73.3%) achieved successful weaning from ventilation (extubation). Details of dexmedetomidine infusion and ventilation related outcomes are shown in Table 3.

In 15 episodes (50%) sedation with dexmedetomidine was ceased as planned (Table 3). Of the remaining episodes, sedation with

TABLE 2
Cohort clinical characteristics (n=30)

Variable	Dexmedetomidine (n=30)
Age, median years [IQR]	70.5 [51-76]
Males, %	96.7
APACHE II score, median [IQR]	18 [15-27]
Total ICU LOS, median days [IQR]	14 [7-25]
Hospital LOS, median days [IQR]	24 [16-31]
Episodes survived to ICU discharge, number (%)	24 (80.0)
Episodes survived to hospital discharge, number (%)	24 (80.0)
Dobutamine at baseline, number (%)	9 (30)
Noradrenaline or adrenaline at baseline, number (%)	10 (33)
Requiring reduced vasopressors/inotropes, number (%)	7 (23.3)
Requiring increased vasopressors/inotropes, number (%)	1 (3.3)

IQR=interquartile range, APACHE II=Acute Physiology and Chronic Health Evaluation Score II, ICU=intensive care unit, LOS=length of stay.

TABLE 3
Dexmedetomidine infusion and ventilation-related outcomes

Clinical outcome and infusion characteristics	
Maximum dexmedetomidine dose, μg/kg/h, median [IQR]	0.70 [0.7-1.0]
Dexmedetomidine infusion time, median hours (range)	62 (24-252)
Reason for ceasing dexmedetomidine	*Number (%)*
Ceased as planned	15 (50)
Unrelated clinical deterioration	6 (20)
Lack of efficacy at the dose used (maximum dose not used)	4 (13.3)
Intensivist discretion	3 (10)
Possible adverse events	2 (6.7)
Additional sedative / analgesics up to 72 h post-infusion	*Number (%)*
Nil needed	11 (37)
Low dose propofol infusion 5-30 mg/h	6 (20)
Intermittent propofol boluses	2 (7)
Low-dose fentanyl infusion 10 μg/h	1 (3)
Haloperidol boluses (total 10 mg)	2 (6)
Therapeutic fentanyl/midazolam/morphine/ propofol	5 (17)
Other agents (isoflurane, clonazepam)	2 (7)
Time ventilated prior to enrolment, median hours [IQR]	115 [87-263]
Total ventilation time, median hours [IQR]	179 [123-315]
Post-infusion ventilation time, median hours [IQR]	70 [28-96]
Extubated on dexmedetomidine infusion, number (%)	10 (33)
Post-infusion tracheostomy, number (%)	3 (10.0)

IQR=interquartile range.

dexmedetomidine was discontinued in six patients (20%; patients 3, 10 to 13, 22; Table 1) due to significant unrelated clinical deterioration. Three of these patients experienced severe respiratory failure.

Adverse events recorded included one episode of self-extubation, lack of efficacy (13%) at the dose given, one episode of haemodynamic instability that resulted from sepsis requiring surgery and one episode requiring a moderate increase of noradrenaline and dobutamine dosage at 12 hours. Otherwise, there was no observed increase in vasopressor requirements within 12 hours of the infusion and one episode of elevated liver enzymes.

DISCUSSION

This study demonstrated the feasibility of using dexmedetomidine to facilitate weaning from mechanical ventilation in a group of complex critically ill patients after failure of conventional management. Dexmedetomidine produced rapid resolution of agitation and was effective in facilitating weaning from conventional sedation. Within six hours of dexmedetomidine treatment, MAAS scores were converted to mildly agitated or calm with target MAAS maintained at 12 hours ($P < 0.001$) in most treatment episodes. This allowed successful weaning and extubation in more than half of the patients, and in 75% of episodes excluding those with unrelated clinical deterioration.

The majority of studies of dexmedetomidine in adult ICU patients have involved postoperative surgical cases[17-25]. However, a recent randomised multicentre trial of 375 mostly medical ICU patients who were ventilated for more than 24 hours demonstrated that dexmedetomidine is safe and effective when compared to midazolam and used at doses up to 1.4 μg/kg/hour and for up to 30 days. It also showed a significant reduction in delirium and a shorter ventilation time with dexmedetomidine treatment[26].

However, dexmedetomidine failed to facilitate the weaning process or control agitation at the prescribed dose in 13% of episodes. This highlights the need for a multimodal approach to sedation and analgesia in complex critically ill patients where no single agent can be adequate. It is not clear whether using a higher dose of dexmedetomidine would have resulted in a different outcome. One report found dexmedetomidine was no better than propofol in managing mechanically ventilated patients[17], while another reported enhanced agitation, severe pain and haemodynamic compromise associated with dexmedetomidine therapy[20]. It is important to note that the maximum dose of dexmedetomidine used in the latter study by MacLaren et al was 0.54 μg/kg/hour, which is much lower than the 1.0 μg/kg/hour applied in our study. It is possible that the early weaning of concurrent sedatives (85% of their patients had ceased propofol at six hours and 61% had ceased lorazepam at six hours) combined with a low maximum dose of dexmedetomidine in this study may have contributed to this result. In a small UK phase II study to evaluate the efficacy of dexmedetomidine for sedation in a medical ICU, Venn et al reported that higher dexmedetomidine doses are required to sedate critically ill medical ICU patients than those typically used in post-surgical patients[27]. These reports and our data suggest a dose-related response when using dexmedetomidine for agitated patients. Interestingly, a recent study found even low-dose dexmedetomidine infusion (0.05 to 0.4 μg/kg/hour) to be effective in managing emergence delirium and agitation in Japanese patients, however half received epidural opioids for pain relief and less than half were ventilated[28].

There are few studies exploring the use of dexmedetomidine for agitation or delirium in mechanically ventilated, adult, medical ICU patients[28,29], and even fewer in patients weaning from sedation[20,22]. Dexmedetomidine has been used to successfully facilitate the withdrawal of ventilation in trauma/surgical ICU patients who had failed weaning attempts because of agitation[22]. The authors concluded that dexmedetomidine facilitated extubation by maintaining adequate sedation without haemodynamic instability or respiratory depression. It is likely that higher dexmedetomidine doses than the currently approved Australian maximum[31] of 0.7 μg/kg/hour are needed to effectively manage agitation and sedation requirements in the medical ICU patient population. Data are accumulating regarding the safety profile of dexmedetomidine infusions lasting longer than 24 hours, suggesting that longer durations may be used safely[26]. In order to ensure the safe weaning of a number of the study patients it was necessary to run the dexmedetomidine infusion for up to 11 days, with a median of 2.5 days.

Although the exact mechanism by which dexmedetomidine counteracts agitation remains unclear, animal models show an increase in acetylcholine and reduction in noradrenaline levels in cerebrospinal fluid in response to dexmedetomidine, suggesting a central nervous system-mediated effect[32]. High serum anticholinergic activity

(low acetylcholine levels) is associated with delirium in elderly patients[33], and in our cohort the patients failing conventional treatment were considerably aged (Table 1). In addition, its synergistic effects with benzodiazepines and opioids may result in an overall reduction in sedative and opioid requirements[14].

Our study is limited by its observational nature, the small number of patients and the complex heterogeneous nature of the subjects' illnesses. However, it accurately reflected ICU clinical practice in that conventional therapy was at the discretion of the treating intensivist due to the lack of a 'gold standard' for management of agitated and/or delirious patients. We were unable to accuratey quantify the effect of dexmedetomidine on ventilation time and ICU length of stay due to prolonged ventilation and ICU stay during conventional weaning prior to dexmedetomidine therapy.

Despite these limitations, this study demonstrates that dexmedetomidine can be used successfully to treat emergence agitation in mechanically ventilated medical/surgical ICU patients undergoing weaning. This leads to the question of whether all agitated mechanically ventilated patients could benefit from the earlier use of dexmedetomidine to assist with weaning, rather than waiting until conventional treatment has failed. Such an approach has the potential to avoid extended ventilation times and increased ICU length of stay, but needs to be prospectively studied. Our study adds an important insight to the design of randomised trials to define the possible role of dexmedetomidine in managing agitation and/or delirium.

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CONFLICT OF INTEREST

This study was an investigator-initiated study funded by the Prince of Wales Intensive Care Research Trust Fund. Currently, Dr Shehabi is Chair of the Sedation Advisory Board, supported by an educational grant from Hospira Australia and has received an honorarium for Board meetings. Dr Shehabi has no financial interest in Hospira Inc. shares or products. There is no conflict of interest to report with any of the co-authors.

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