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Dexmedetomidine in the emergency department. Assessing safety and effectiveness in difficult to sedate acute behavioural disturbance.

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Abstract

Objectives: To investigate the safety and effectiveness of dexmedetomidine to sedate patients who have failed previous attempts of sedation in the emergency department setting.

Methods: We undertook a study of dexmedetomidine for sedation of patients with acute behavioural disturbance who had failed at least two previous attempts of sedation with other medications. Either a loading dose of dexmedetomidine was administered or a loading dose then an infusion. Administration was titrated to the sedative effect and vital signs. The sedation assessment tool (SAT) was used to assess effectiveness and adverse effects were recorded. Effective sedation was defined as a drop in the SAT by two levels or more for an hour or more.

Results: A total of 13 patients were given dexmedetomidine. Five of the 13 had a loading dose only. Of these five, successful sedation was achieved in two and the other three were only briefly sedated during the loading dose. One patient had hypotension. Eight patients received an infusion after the loading dose. Three were successfully sedated but one developed hypotension. Four patients required a decrease in the infusion rate for hypotension, and in three of these the rate decrease compromised the sedation and one of these required intubation for sedation. The final patient had persistent acute behavioural disturbance which required intubation for management. Five of the eight patients developed hypotension, and of the five, one had bradycardia and one went into atrial fibrillation.

Conclusion: Intravenous dexmedetomidine for difficult to sedate patients with acute behavioural disturbance is not safe in the emergency department setting.

Introduction

A small number of aggressive or agitated patients are difficult to sedate, even after multiple doses of intramuscular or intravenous combinations of benzodiazepines and sedating antipsychotics, or are difficult to re-sedate after emerging with ongoing delirium.[1] The difficulties associated with controlling these patients is disruptive to clinical care, time consuming and dangerous to staff and other patients. Numerous approaches have been attempted to manage and safely sedate these patients, including the use of barbiturates,[2] propofol[2] and ketamine.[3] However, these remain unsatisfactory and there remains considerable risk to patient and staff which often results in the patient requiring intubation, mechanical ventilation and admission to an intensive care unit.

Interest in the use of alpha(α_2)-adrenoceptor agonists for sedation is increasing. The antihypertensive clonidine has been the most popular of these agents and has been used for decades for the purpose of sedation in intensive care including control of opioid and alcohol withdrawal. However, it is long acting and its use is often associated with rebound hypertension following discontinuation.[4] Dexmedetomidine is a newer sedative α_2 -adrenoceptor agonist that is similar to clonidine, but has a shorter half-life allowing sedation to wear off more rapidly and it has less effect on haemodynamics.[5] Dexmedetomidine has been shown to consistently reduce the use of opioids, propofol, and benzodiazepines for sedation in the anaesthetic and intensive care unit (ICU) settings.[6] A major advantage of the α_2 -adrenoceptor agonists is that they cause little or no respiratory compromise.[4-8] The α_2 -adrenoceptor agonists also have a different pharmacological action to benzodiazepines, so may be effective in patients with substantial tolerance to benzodiazepines which is another major problem in this patient group of difficult to sedate patients.

Dexmedetomidine has been studied extensively as a sedative and adjunct anaesthetic agent for patients in ICU and operating theatres. It has been shown to be safe and effective, and it appears to have some advantages over midazolam as a first line agent for sedation.[9,10] The results of two recent studies comparing dexmedetomidine to the commonly used benzodiazepines, lorazepam and midazolam respectively,[9-11] demonstrated it to be a safe alternative in the ICU. Recent studies have also suggested that it is useful for procedural sedation.[7,8]

There is limited evidence available on the effective management of patients with acute behavioural disturbance (ABD) where standard approaches to sedation have not worked. Clinical practice guidelines do not cover the treatment options to manage repeatedly failed sedation. Current practice is to administer anaesthetic agents, which then requires the patient to be intubated and mechanically ventilated.[12] This option is a last resort, which is resource intensive, and fraught with potential complications. No previous studies have explored an alternative management for failed sedation of ABD which does not require anaesthetic agents in the emergency department (ED).

The success of dexmedetomidine in ICU patients[9,11] and anaesthetics,[6,7] make it a good choice for investigation in the sedation of agitated patients in other settings. We hypothesised that dexmedetomidine may be a safe and useful agent for the management of difficult to sedate patients in the ED. The aim of the study is to investigate the effectiveness and safety of dexmedetomidine in a small number of agitated patients in the ED.

Methods

Study Design

We undertook a study of dexmedetomidine for the sedation of difficult to sedate patients with ABD in the ED. The primary outcome was safety of dexmedetomidine as determined by the occurrence of adverse effects. We aimed to recruit approximately 20 patients over a period of 18 months. The study was divided into two parts. In the first part of the study patients received a loading dose and then a repeat loading dose if required. In the second part of the study patients were administered a loading dose followed by a continuous intravenous infusion.

Setting

The study was undertaken from September 2009 to June 2011 in a tertiary teaching hospital with a large number of patients who had ABD and presented to the ED. It is an urban ED with 29,000 annual presentations, with about 6 per 1,000 with ABD.[13] Ethics approval was obtained from the local Human Research Ethics Committee. Consent was waived because of the requirement for immediate treatment and patients' lack of decision-making capacity to consent to medical treatment being given as a duty of care.

Selection of Participants and sample size

All adult patients (>18 years old) presenting to the ED with ABD were sedated according to a standardised protocol which included physical restraint and an initial sedative antipsychotic, droperidol 10mg, followed by a second 10mg if the patient had not been sedated after 15 minutes. Those who had failed at least two previous attempts of parenteral sedation were considered for inclusion if they continued to score +2 or +3 on the sedation assessment tool

[SAT] (Table 1). Exclusion criteria were age < 18 years, pregnancy, baseline blood pressure (BP) < 100mmHg systolic, heart rate (HR) < 60bpm or a history of cardiac disease.

Interventions

Patients with ABD who were not sedated following at least two attempts with other parenteral medications were identified by treating clinicians. The investigators were contacted as to suitability for recruitment to the study. All patients were placed in a resuscitation bay with cardiac monitoring, pulse oximetry and non-invasive BP monitoring. Two intravenous cannulas were inserted if not already in place for drug and fluid administration. All patients received a fluid load prior to dexmedetomidine.

For the first part of the study a loading dose of dexmedetomidine (1mg/kg up to a maximum of 100mcg) was given over 20 to 30 minutes. This could be repeated if the patient was initially sedated and then became agitated again. In the second part of the study the loading dose could be followed by a second loading dose if necessary, and then a continuous infusion. The infusion rate was titrated to the level of sedation, as measured by the SAT, and the patient's vital signs. The infusion was commenced at a rate of 0.7mcg/kg/hr and could be titrated to effect between 0.2mcg/kg/hr to 1.2mcg/kg/hr in 0.1mcg increments.

Data Collection and Processing

Data was recorded prospectively using a standardised chart developed for patients with ABD and then entered into a relational database. The following data were included for the study analysis: patient demographic characteristics (age, sex), cause of ABD, drugs given prior to dexmedetomidine (time of administration, drug related adverse effects), dose and timing of dexmedetomidine, and injuries to patients and staff. Observations were recorded every 5 minutes until the sedation score remained at zero or less for greater than 30 minutes and vital

signs were stable. Observations included heart rate (HR), blood pressure (BP), oxygen saturations and respiratory rate. All patients received an electrocardiogram when they settled.

The level of sedation was recorded using the SAT (Table 1)[14] by emergency staff who were familiar with the SAT as part of a structured protocol for patients with ABD. The SAT was designed for rapid assessment of in patients with ABD in the ED and evaluates both agitation and sedation on the same scale. The scale ranges from most agitated and combative + 3, to unconscious, -3.

If the patient failed to respond to dexmedetomidine, or developed any adverse effects, further intervention was decided by the treating clinician.

Outcome Measures

The primary outcome was the frequency of adverse effects defined as the need for airway support, respiration rate <12 breaths per minute, oxygen saturation <90%, hypotension (BP <90 mmHg), bradycardia (HR < 60 bpm) and an unplanned ICU admission. The secondary outcome was effective sedation defined as a reduction in the SAT score from +2 or +3 by two levels or returning to zero (awake and cooperative), for a period of greater than one hour.

Results

Over a period of 21 months a total of 13 patients were given dexmedetomidine in the ED. All patients were administered with sedative antipsychotics, with or without a benzodiazepine prior to dexmedetomidine. The median age was 41 years (range 24 to 87y). Two patients were over 80 years of age. Eleven patients were male. The cause of ABD was deliberate self-harm (6), alcohol withdrawal (2), recreational drug use (2), post-ictal delirium (1), hyperglycaemia (1) and acute psychosis (1).

There were five patients who only had the loading dose. Two had a repeat loading dose. Three patients were only briefly sedated during the period of loading dose being administered. Only one patient had an adverse effect which was an 87 year old patient who developed hypotension (systolic 85mm/hg) (Figure 1, Table 2)

In the second part of the study, eight patients received an infusion after the loading dose (Figure 1, Table 2). Three were successfully sedated and one of these developed hypotension. One patient had no response to dexmedetomidine and remained at a score of +2 to +3 and required intubation and anaesthesia. Four patients were transiently sedated but then required a substantial decrease in the infusion rate to maintain a normal BP. In three of the four patients the decrease in rate compromised the sedation effect. One of these subsequently required intubation for management of ABD. Five of the eight patients developed hypotension and one of these developed bradycardia. One patient with persistent hypotension developed atrial fibrillation seven hours after the infusion commenced with evidence of first degree heart block on an electrocardiogram prior to this. The study was ceased after the eighth patient with an infusion due to the frequency of patients developing hypotension.

The details of prior sedation and underlying cause of the ABD are outlined in Table 1. Of the total 13 patients, only five patients were successfully sedated. Four of these remained sedated

for 6 to 12 hours (overnight) and none of these four had any adverse effects. Four patients were transferred to the ICU, two for closer monitoring and the two that failed sedation and required intubation. Of the remaining four, two were transferred to the psychiatric emergency care centre and two remained in the emergency department with ongoing ABD. Both patients remained in physical restraints and were administered sedative agents intermittently with minimal effect.

No patient scored -3 (unconscious) on the SAT. The most common score was -1 (asleep but easily rousable) when sedation was achieved.

The most common adverse effect was hypotension which occurred in six of the 13 patients. Five of these were during the administration of the infusion. Hypotension was managed by reducing the rate in three patients and ceasing the infusion in the other two, both elderly patients. Oxygen saturation and respiratory rate were maintained in all patients and no patient had respiratory compromise.

Discussion

Although the majority of patients with difficult to control ABD in the ED were initially sedated by dexmedetomidine, only four of 13 patients were effectively sedated for longer than an hour, without having any adverse effects (Figure 1). The predominant adverse effect was hypotension in six patients. This failure of dexmedetomidine may have been due to the ED being less equipped to manage the cardiovascular effects of dexmedetomidine.

The introduction of the infusion in the second part of the study was to determine if this improved the duration and therefore success of the sedation. The rapid onset and offset of the sedative effects of dexmedetomidine was clearly seen in three of the five patients given only a loading dose. These three patients became agitated again shortly after the loading dose was completed. We found with the introduction of an infusion, sedation was initially achieved in the majority of the patients (7 out of 8). However, the infusion rate in four of these patients was decreased substantially due to hypotension. Subsequently, the decrease in the infusion rate resulted in sedation wearing off in three of these patients.

Hypotension, bradycardia and atrial fibrillation have all been reported in larger ICU studies of dexmedetomidine.[11,15,16] The MENDS study compared dexmedetomidine to lorazepam in 106 ventilated patients and reported atrial fibrillation in three patients given dexmedetomidine, but none given lorazepam.[9] Other studies of dexmedetomidine in anaesthetics and procedural sedation, as well as in healthy volunteers, have reported significant cardiovascular adverse effects,[4,5,7,9,17,18] and the occurrence and effects were thought to be related to the dose and infusion rate[4,19,20]. Studies in healthy volunteers report average decreases in the mean arterial pressure 20 to 29% using recommended doses, [19,20] and a decrease of 18 to 23% in critically ill patients.[18,19] In a study of high dose

versus low dose dexmedetomidine there was no significant difference in the incidence of hypotension and bradycardia between dosing groups.[21] Hypotension was the most common adverse effect, occurring in 38% of patients. These patients had a dose increase more frequently than 30 minutes and had more adjustments to their infusion rate.[21]

Bradycardia is commonly reported in previous studies. In a cohort of critically ill patients in the SEDCOM study, bradycardia occurred in 42%[11] and in 16.5% in the DEXCOM study.[16] In healthy volunteers in a dosing study, HR decreases of 16 to 20% were reported.[5] Correction of the bradycardia is recommended by administering atropine,[19] and/or inotropes[17] to maintain haemodynamics within the pre-determined limits.

In our study the level of sedation and frequency of adverse effects were very sensitive to the infusion rate. The need for titration of the infusion rate plus the limited staffing and the busy nature of the ED may have contributed to the failure of dexmedetomidine. The increased infusion rate required to sedate patients with ABD resulted in hypotension. The study was ceased for safety reasons due to the frequency and severity of adverse effects.

Conclusion

Dexmedetomidine was able to initially sedate all but one patient who had failed previous attempts of sedation in the ED. However, the doses required to achieve the level of sedation required for ABD resulted in almost half of the patients developing hypotension. This frequency of adverse effects is beyond the monitoring capability of most busy ED due to staff-to-patient ratios. Intravenous dexmedetomidine cannot be safely used for sedation of difficult to sedate ABD in the ED.

Competing Interest

The authors declare there are no competing interests.

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Author Contributions

LC helped design the study, coordinated recruitment and data collection and drafted the manuscript. GKI helped design the study, recruited patients, reviewed all drafts of the manuscript, and takes responsibility for the study.

Figure Legends

Figure 1: Flow diagram of the 13 patients recruited to the study.

Table 1

SCORE	RESPONSIVENESS	SPEECH	SCALE
+3	Combative, violent, out of control	Continual loud outbursts	+1 to +3 Agitation
+2	Very anxious and agitated	Loud outbursts	
+1	Anxious / restless	Normal / Talkative	
0	Awake and calm / cooperative	Speaks Normally	Zero
-1	Asleep but rouses if name is called	Slurring or prominent slowing	-1 to -3 Sedation
-2	Responds to physical stimulation	Few recognisable words	
-3	No response to stimulation	Nil	

Table 2

AGE	REASON FOR PRESENTATION	PRIOR MEDICATION FOR SEDATION	DEXMEDETOMIDINE DOSE	ADVERSE EFFECT	SEDATION
41	Alcohol Withdrawal	Diazepam 80mg, Olanzapine 10mg, Droperidol 30mg	100mcg	Nil	Pass
86	Psychosis	Droperidol 20mg	75 + 100mcg	Hypotension	Fail
27	DSP (quetiapine)	Droperidol 10mg, Midazolam 20mg	100 + 100mcg	Nil	Fail
45	Alcohol Withdrawal	Droperidol 20mg	100mcg	Nil	Fail
41	DSP (olanzapine)	Droperidol 20mg	10mcg	Nil	Pass
87	DSP (bleach)	Clonidine 50mcg, Droperidol 10mg	Stat 50mcg + infusion	Hypotension and bradycardia	Fail
46	Ketoacidosis	Droperidol 20mg, Midazolam 15mg	100 mcg = 100mcg + infusion	Intubation	Fail
32	Recreational drug abuse	Lorazepam 2mg, Midazolam 20mg, Droperidol 20mg	100mcg + 100mcg + infusion	Nil	Pass
24	Post-ictal	Droperidol 10mg, Midazolam 30mg	100mcg + infusion	Nil	Fail
41	DSP (diazepam/ethanol)	Midazolam 30mg, Droperidol 20mg, Diazepam 20gm	100mcg + infusion	Hypotension	Pass
34	Amphetamines	Droperidol 30mg	100mcg = infusion	Intubation	Fail
29	Threatened self-harm	Droperidol 20mg	100mcg + infusion	Hypotension	Pass
40	Deliberate self-harm	Droperidol 30mg	100mcb + infusion	Hypotension	Fail

DSP – deliberate self-poisoning

References

1. Knott JC, Isbister GK. Sedation of agitated patients in the emergency department. *Emerg.Med.Australas.* 2008;20:97-100.
2. Skrobik Y. Delirium prevention and treatment. *Crit Care Clin* 2009;25:585-91, x.
3. Roberts JR, Geeting GK. Intramuscular ketamine for the rapid tranquilization of the uncontrollable, violent, and dangerous adult patient. *J Trauma* 2001;51:1008-10.
4. Ebert TJ, Hall JE, Barney JA, et al. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* 2000;93:382-94.
5. Hall JE, Uhrich TD, Barney JA, et al. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg* 2000;90:699-705.
6. Arcangeli A, D'Alo C, Gaspari R. Dexmedetomidine use in general anaesthesia. *Curr Drug Targets* 2009;10:687-95.
7. Candiotti KA, Bergese SD, Bokesch PM, et al. Monitored anesthesia care with dexmedetomidine: a prospective, randomized, double-blind, multicenter trial. *Anesth Analg* 2010;110:47-56.
8. Jewett J, Phillips WJ. Dexmedetomidine for procedural sedation in the emergency department. *Eur J Emerg Med* 2010;17:60.
9. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *Journal of the American Medical Association* 2007;298:2644-53.

10. Devlin JW, Mallow-Corbett S, Riker RR. Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. *Crit Care Med* 2010;38:S231-43.
11. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *Journal of the American Medical Association* 2009;301:489-99.
12. Cheng C, Roemer-Becuwe C, Pereira J. When midazolam fails. *J Pain Symptom Manage* 2002;23:256-65.
13. Downes MA, Healy P, Page CB, et al. Structured team approach to the agitated patient in the emergency department. *Emerg Med Australas*. 2009;21:196-202.
14. Calver LA, Stokes B, Isbister GK. The Sedation Assessment Tool to score acute behavioural disturbance in the emergency department. *Emerg Med Australas* 2011;(in press).
15. Szumita PM, Baroletti SA, Anger KE, et al. Sedation and analgesia in the intensive care unit: evaluating the role of dexmedetomidine. *Am J Health Syst Pharm* 2007;64:37-44.
16. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COMpared to Morphine-DEXCOM Study). *Anesthesiology* 2009;111:1075-84.
17. Talke P, Li J, Jain U, et al. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. *Anesthesiology* 1995;82:620-33.
18. Bloor BC, Ward DS, Belleville JP, et al. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992;77:1134-42.

19. Bekker AY, Kaufman B, Samir H, et al. The use of dexmedetomidine infusion for awake craniotomy. *Anesth Analg* 2001;92:1251-3.
20. Dyck JB, Maze M, Haack C, et al. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology* 1993;78:813-20.
21. Jones GM, Murphy CV, Gerlach AT, et al. High-dose dexmedetomidine for sedation in the intensive care unit: an evaluation of clinical efficacy and safety. *Ann Pharmacother* 2011;45:740-7.