European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 06, 2022

Original Research Article

A randomized clinical assessment of the safety profile of clonidine and dexmedetomidine in patients needing short-term sedation of intensive care unit

Dr. Fathima Ghazala

Senior Resident, Department of Anaesthesiology, Bhaskar Medical College Ranga Reddy, Hyderabad, Telangana, India

Corresponding Author:
Dr. Fathima Ghazala

Abstract

Aim: The purpose of the present study was to compare sedative, analgesic and cardiovascular effects and safety profile of clonidine and dexmedetomidine for patients requiring short-term sedation in ICU.
Methods: The present prospective randomized clinical study was carried out among 50 patients of either sex conducted in the department of anesthesia after approval from the Institutional Review Board and informed written consent. Over a period of 6 months, 50 patients were enrolled in the study to receive sedation with either dexmedetomidine (n = 25) or clonidine (n = 25). These included 38 postsurgical, 7 medical and 5 polytrauma patients evenly distributed in each group.
Results: The mean ± SD maintenance infusion dose was 0.47 ± 0.27 μg/kg/h for dexmedetomidine and 1.67 ± 8.6 μg/kg/h for clonidine. Bradycardia occurred in 2 of the 25 patients in Group I and 3 of the 25 patients in Group II (P = 0.84). Hypotension occurred in 7 of the 25 patients in Group I and 4 of the 25 patients in Group II (P = 0.01). About 50% of the hypotensive episodes occurred within 2-4 h in Group I and at 2 h in Group II. No patient experienced hypotension after 14 h in Group I and after 6 h in Group II.
Conclusion: Both clonidine and dexmedetomidine produced effective sedation; however, the hemodynamic stability provided by dexmedetomidine gives it an edge over clonidine for short-term sedation of ICU patients.

Keywords: Clonidine, dexmedetomidine, intensive care unit sedation

Introduction

Critically ill patients requiring invasive mechanical ventilation (IMV) usually require sedation to minimize discomfort, reduce the risks of self-injury and facilitate care [1, 2]. Randomized controlled trials (RCTs) have demonstrated clear benefits of minimizing sedation in this population, such as a reduction in the duration of mechanical ventilation [3, 4], shorter length of stay in the intensive care unit (ICU) [4-6] and improved overall survival [6].
Typical sedatives used in patients requiring IMV include propofol, benzodiazepines and more recently, dexmedetomidine [7]. Although propofol has a rapid onset of action and provides timely recovery after discontinuation, it can cause clinically significant hypotension [8]. Benzodiazepines may increase the risk of ICU-related delirium and cause oversedation due to

ISSN 2515-8260 Volume 09, Issue 06, 2022

drug accumulation, prolonging the duration of IMV [9].
Compared to benzodiazepines, dexmedetomidine reduces the incidence of delirium and the duration of IMV [10-12], but is not widely available due to cost. Clonidine stimulates pre-synaptic alpha-2 adrenoreceptors within the brainstem, decreasing norepinephrine release while enhancing parasympathetic activity. The sedative, analgesic and anxiolytic effects of clonidine may be due to its effects on the locus coeruleus [13].
Evidence supporting the use of clonidine as a sedative in the critically ill requiring IMV remains scarce. One recent systematic review on the efficacy of alpha-2 agonists for sedation in the pediatric critically ill population included three RCTs using clonidine, but did not pool estimates. They concluded that robust evidence was lacking for the use of clonidine as a sedative in the pediatric critically ill population [14].
Attaining an optimal level of sedation is a challenging act for the ICU clinician. Both inadequate sedation and oversedation compromise patient's recovery and may prolong ICU stay along with associated complications and increased cost [15]. Many of the currently used agents have specific drawbacks that limit their practical utility along the full spectrum of patients and clinical situations that intensivists face every day. The discovery that clonidine has an opioid sparing property and attenuated withdrawal symptoms, sparked further interest in the use of alpha-2 (α2) agonists as intravenous (IV) sedatives [16].
The purpose of the present study was to compare safety profile of clonidine, and dexmedetomidine for patients requiring short-term sedation in ICU.

Materials and Methods

The present prospective randomized clinical study was carried out among 50 patients by the department of anesthesia after approval from the Institutional Review Board and informed written consent.
The main inclusion criteria were age >18 years, mechanical ventilation with endotracheal intubation and clinical need for light or moderate sedation for <24 h.
We excluded pregnant females, patients with a neurological condition, central nervous system trauma, asthma or chronic obstructive pulmonary disease, hemodynamically unstable patients, known cases of conduction defects, cardiac failure, those with a creatinine clearance <30 ml/min and those requiring neuromuscular blockade and prior use of α2 agonists.

Study population

50 patients were enrolled in the study to receive sedation with either dexmedetomidine (n = 25) or clonidine (n = 25). These included 38 postsurgical, 7 medical and 5 polytrauma patients evenly distributed in each group.
The patients were predominantly postsurgical who were operated for major abdominal, Urological, Orthopedic and Spine procedures under general anesthesia on an elective basis. The anesthetic technique was individualized by the anesthetist in-charge; however, fentanyl alone was used for intraoperative analgesia and the dose was recorded. Epidural or spinal technique was not used in any patient. On arrival to the ICU, patients were randomly allocated into two groups, Group I and II, based on computer generated random number tables.

Study drugs

Clonidine was supplied in 1 ml ampoules, containing 150 µg/ml and diluted with normal saline to a concentration of 3 µg/ml. Dexmedetomidine was supplied in 2 ml ampoules that contained 100 µg/ml diluted with normal saline to a concentration of 4 µg/ml.

ISSN 2515-8260 Volume 09, Issue 06, 2022

Monitoring

Physical examination, baseline vitals, electrocardiogram and central venous pressure (CVP) was noted on admission to the ICU. Hematological (complete blood count, coagulation profile) and biochemical profile (electrolytes, glucose, urea, creatinine and liver function test) were obtained prior to the administration of sedatives and 24 h after the study period. Patients were ventilated with oxygen enriched air to obtain acceptable arterial blood gas (ABG) levels. Temperature and ABG was recorded at regular intervals. Apart from the sedative drugs, all management was according to the ICU protocol. Patients were extubated when clinically indicated.

Heart rate, CVP, noninvasive blood pressure (BP), respiratory rate and oxygen saturation (measured by pulse oximetry) were monitored continuously over 24 h. Hemodynamic parameters were recorded at 10 min, 30 min after the commencement of sedative infusions and then 2 hourly for the study period. Hemodynamic monitoring continued for 24 h after cessation of the infusions. Adverse cardiovascular events were defined by hypotension, hypertension, tachycardia and bradycardia.

Protocol for sedation and analgesia

The degree of sedation was assessed by Ramsay Sedation Score (RSS)

1. Patient anxious, agitated or restless.
2. Cooperative, oriented and tranquil.
3. Responds to commands only.
4. Exhibits brisk response to light glabellar tap or loud auditory stimulus.
5. Sluggish response to light glabellar tap or loud auditory sound.
6. No response) obtained on arrival in the ICU, at 10 and 30 min after commencement of the infusion and 2 hourly thereafter for the study period.

RSS of 3-4 was considered as target sedation and the infusion rates were titrated within their respective range until target sedation was achieved. RSS was also assessed prior to and 10 min after any titration in the study drug infusion rate or the use of additional sedation. Infusion was continued as needed until extubation or for maximum allowable time. Group I patients were administered an IV infusion of clonidine 1 μg/kg/h and titration was achieved with dosage increments up to 2 μg/kg/h. Patients in Group II received dexmedetomidine as a loading dose of 0.7 μg/kg over a period of 10 min followed by maintenance of 0.2 μg/kg/h with dosage increments titrated up to 0.7 μg/kg/h. The infusions rates were maintained to achieve sedation within target range.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR) and comparisons made using the unpaired t-test. Medians were quoted for skewed data and were compared using the Mann-Whitney U-test. Nominal or ordinal variables were compared using the Chi-square test. $p<0.05$ was considered as significant. Analysis was carried out using the SPSS 18.0 software (IBM (PASW Statistics 18)).

ISSN 2515-8260 Volume 09, Issue 06, 2022

Results

Table 1: Demographic and intraoperative details: Median (IQR) or number

	Group I (N=25)	Group II (N=25)
Age (years)	45 (44-58)	48 (44-60)
Sex (male: female)	13:12	15:10
Weight (kg)	64 (56-70)	61 (58-69)
Type of patient		
Postsurgical	18	20
Medical	4	3
Polytrauma	3	2
Intraoperative fentanyl usage (μg) (mean ± SD)	270±65	285±45
Duration of sedative infusion in ICU (h)	20 (17-30)	19 (14-28)
Duration of surgery in h (mean ± SD)	3.7±1.5	3.6±1.6

Over a period of 6 months, 50 patients were enrolled in the study to receive sedation with either dexmedetomidine (n = 25) or clonidine (n = 25). These included 38 postsurgical, 7 medical and 5 polytrauma patients evenly distributed in each group. Demographic data and intraoperative details such as operative time, fentanyl requirements, and duration of sedative infusions in the ICU were comparable [Table 1]. The mean ± SD maintenance infusion dose was 0.47 ± 0.27 μg/kg/h for dexmedetomidine and 1.67 ± 8.6 μg/kg/h for clonidine. Bradycardia occurred in 2 of the 25 patients in Group I and 3 of the 25 patients in Group II (P = 0.84).

Hypotension occurred in 7 of the 25 patients in Group I and 4 of the 25 patients in Group II (P = 0.01). About 50% of the hypotensive episodes occurred within 2-4 h in Group I and at 2 h in Group II. No patient experienced hypotension after 14 h in Group I and after 6 h in Group II. Sustained increase in systolic and diastolic pressure and heart recurred after cessation of infusion in Group D, but there were no clinically significant rebound phenomena in any patient.

Discussion

Sedation plays a key role in the management of agitation and anxiety in the intensive care setting [17]. The usual goal of sedation in the intensive care unit (ICU) is a calm, cooperative patient who is easy to rouse and who is able to communicate their needs, particularly for analgesia [18]. Maintaining a light level of sedation in ICU patients is recommended, when possible, given that light sedation is associated with improved outcomes, including a shorter duration of ventilation and a shorter ICU stay [19].

The main results of the present study showed that target sedation was achieved in more number of patients receiving dexmedetomidine with lesser need for additional sedation. The patients in this group were more stable hemodynamically compared with those receiving clonidine. This study and many previous studies have documented dexmedetomidine to be a safe and effective agent for ICU sedation of postsurgical patients [12, 20].

Although mean cumulative sedation scores over the study period were not significantly different in two groups (3.50 + 1.40 vs. 3.30 + 0.85 in Groups I and II, respectively), percentage of patients who attained target sedation was significantly higher in Group II compared with Group I (80 vs. 60% in Groups II and I, respectively, P = 0.03). Dexmedetomidine is 8 times more specific for μ2 receptors than clonidine and the improved specificity for the μ2 adrenoreceptors, especially for the 2A subtype may make it to be a much more effective sedative than clonidine [21]. Our finding of dexmedetomidine treated patients is in concurrence with previous studies [20, 22]. However, our findings are in contrast with those of Riker *et al*. [23] who suggested that dexmedetomidine attained target sedation

less frequently. They recruited only medical patients, while our most patients were postsurgical. This could possibly be the cause of discrepancy.

There is no consensus on appropriate dose regimen of clonidine during ICU sedation [23] and is extremely variable when given by continuous infusion. However, the usual dose is in the order of 100 μg/h [25]. We used an initial dose of 1 μg/kg/h of clonidine for infusion titrated to 2 μg/kg/h as the maximum dose. The dose of dexmedetomidine for ICU sedation varies greatly ranging between 0.2 and 2.5 μg/kg/h [12, 24]. In our study, we used a loading dose of 0.7 μg/kg followed by 0.2-0.7 μg/kg/h. A meta-analysis by Tan and Ho (2010) [26] observed that incidence of bradycardia requiring intervention increased in studies that used both a loading dose and maintenance doses of dexmedetomidine in excess of 0.7 μg/kg/h. Transient hypertensive responses have also been observed with higher doses [27] due to initial stimulation of α2B receptors present in vascular smooth muscles. Hypotension and bradycardia are the most feared side-effects of α2 agonists. Baseline heart rates which were high in both groups settled to an optimal range over the study period. Hypotension was more commonly seen in Group I compared with Group II. 50% of the hypotensive episodes occurred within 2-4 h in Group I and after bolus infusion and within 2 h after maintenance infusion in Group II, as the steady state plasma concentration of the drugs are achieved at this time duration, causing vasodilatation and hypotension.

Conclusion

Both dexmedetomidine and clonidine can be used as sedative agents for short term ICU sedation of postsurgical patients. On the basis of our study data, we derived that dexmedetomidine has a better cardiovascular safety profile. Further trials with both drugs may define their exact role for sedation of ICU patients.

References

1. Mazzeo AJ. Sedation for the mechanically ventilated patient. Crit Care Clin. 1995;11:937.
2. Hansen-Flaschen J. Improving patient tolerance of mechanical ventilation: challenges ahead. Critical care clinics. 1994 Oct;10(4):659-71.
3. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. New England Journal of Medicine. 2000 May;342(20):1471-7.
4. Treggiari MM, Romand JA, Yanez ND, *et al*. Randomized trial of light versus deep sedation on mental health after critical illness*. Crit Care Med. 2009;37:2527-34.
5. Tsuruta R, Oda Y, Shintani A, Nunomiya S, Hashimoto S, Nakagawa T, *et al*. Delirium and coma evaluated in mechanically ventilated patients in the intensive care unit in Japan: A multi-institutional prospective observational study. Journal of Critical Care. 2014 Jun;29(3):472-e1.
6. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, *et al*. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. The Lancet. 2008 Jan;371(9607):126-34.
7. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, *et al*. Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the ANZICS Clinical Trials Group. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. American journal of respiratory and critical care medicine. 2012 Oct;186(8):724-31.
8. Fulton B, Sorkin EM. Propofol. Drugs. 1995 Oct;50(4):636-457.
9. Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care

unit: a systematic review. Jama. 2000 Mar;283(11):1451-9.
10. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, *et al*. Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. Jama. 2012 Mar;307(11):1151-60.
11. Riker RR, Shehabi Y, Bokesch PM, *et al*. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301:489-99.
12. Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, *et al*. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia. 1999 Dec;54(12):1136-42.
13. Jamadarkhana S, Gopal S. Clonidine in adults as a sedative agent in the intensive care unit. Journal of anaesthesiology, clinical pharmacology. 2010 Oct;26(4):439.
14. Hayden JC, Breatnach C, Doherty DR, Healy M, Howlett MM, Gallagher PJ, *et al*. Efficacy of α2-agonists for sedation in pediatric critical care: a systematic review. Pediatric Critical Care Medicine. 2016 Feb;17(2):e66-75.
15. Rowe K, Fletcher S. Sedation in the intensive care unit. Continuing education in anaesthesia, critical care and pain. 2008 Apr;8(2):50-5.
16. Gowing L, Farrell M, Ali R. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Data base syst Rev., 2009.
17. Altshuler J, Spoelhof B. Pain, agitation, delirium and neuromuscular blockade: a review of basic pharmacology, assessment and monitoring. Crit. Care Nurs. Q. 2013;36(4):356-69.
18. Mantz J, Josserand J, Hamada S. Dexmedetomidine: new insights. Eur J Anaesthesiol. 2011;28(1):3-6.
19. Barr J, Fraser GL, Puntillo K, *et al*. Clinical practice guidelines for the management of pain, agitation and delirium in adult patients in the intensive care unit. Crit. Care Med. 2013;41(1):263-306.
20. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. British journal of anaesthesia. 2001 Nov;87(5):684-90.
21. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs. 2000 Feb;59(2):263-8.
22. Riker RR, Ramsay MA, Prielipp RC, Jorden V. Long-term dexmedetomidine infusions for ICU sedation: a pilot study. Anesthesiology. 2001;95:A383.
23. Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidine infusions in humans. British Journal of Anaesthesia. 2001 Jan;86(1):5-11.
24. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, *et al*. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. Jama. 2009 Feb;301(5):489-99.
25. Jamadarkhana S, Gopal S. Clonidine in adults as a sedative agent in the intensive care unit. Journal of anaesthesiology, clinical pharmacology. 2010 Oct;26(4):439.
26. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis. Intensive care medicine. 2010 Jun;36(6):926-39.
27. Sudheesh K, Harsoor SS. Dexmedetomidine in anaesthesia practice: A wonder drug? Indian Journal of Anaesthesia. 2011 Jul;55(4):323.