e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(5); 450-457

Original Research Article

Randomized Comparative Assessment of the Safety Profile of Clonidine and Dexmedetomidine in Patients Needing Short-Term Sedation of Intensive Care Unit

Mahesh Kumar[1], Saurabh Singh[2]

[1]Associate Professor, Department of Anesthesiology, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India.
[2]Senior Resident, Department of Anesthesiology, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India.

Received: 11-03-2022 / Revised: 20-04-2022 / Accepted: 10-05-2022
Corresponding author: Dr. Saurabh Singh
Conflict of interest: Nil

Abstract

Aim: To compare sedative, analgesic and cardiovascular effects and safety profile of two 2 agonists, clonidine, and dexmedetomidine for patients requiring short-term sedation in ICU.

Material & Method: On arrival to the ICU, patients were randomly allocated into two groups, Group C and D, based on computer generated random number tables. 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.

Results: Over a period of 18 months, 100 patients were enrolled in the study to receive sedation with either dexmedetomidine (n = 50) or clonidine (n = 50). These included 83 postsurgical, 10 medical and 7 polytrauma patients evenly distributed in each group. The baseline hemodynamic parameters were comparable in both groups. A significant reduction in systolic and diastolic BP from the baseline ($P < 0.05$) occurred after bolus infusion in Group D but in none of the patients fall was >30% from baseline. Patients receiving clonidine (Group C) had significantly lower heart rates from baseline ($P < 0.05$). On comparison, the hemodynamic parameters were comparable between the two groups during the study period ($P > 0.05$).

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

The first α2-adrenoceptor agonist was synthesized in the early 1960s to be used as a nasal decongestant. Early application of the new substance, now known as clonidine, showed unexpected side effects, with sedation for 24 hours and symptoms of severe cardiovascular depression. Subsequent testing led to the introduction of clonidine as an antihypertensive drug in 1966. [1]

The use of α2-adrenoceptor agonists as anesthetics is not new. Veterinarians employed xylazine and detomidine for a long time to induce analgesia and sedation in animals, and much of our knowledge was gained from this application [2].

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. [3] 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 agonists as intravenous (IV) sedatives. [4] A resurgence in the research of α 2 agonists for sedation developed after the approval of dexmedetomidine for ICU sedation.

In 2013, dexmedetomidine was introduced into the Swiss market. +e number of reports describing the benefits of dexmedetomidine is growing continuously since then:dexmedetomidine reduced the lengths of mechanical ventilation and hospital stay, and it lowered the overall costs compared with that of propofol [5-7]. perioperative use of dexmedetomidine was associated with a decreased incidence of postoperative complications, delirium, and mortality up to one year after cardiac surgery [8]. However, dexmedetomidine treatment is expensive and might not be universally available.

Unlike most other sedative drugs, α 2 agonists produce both sedation and analgesia with minimal respiratory depression. [9] This unique combination makes them highly beneficial especially in the ICUs. [9] Therefore, study to compare sedative, analgesic and cardiovascular effects and safety profile of two α 2 agonists, clonidine, and dexmedetomidine for patients requiring short-term sedation in ICU. [9]

Material & Method:

The present study was conducted in Department of Anesthesiology, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India during the period of 18 months, 100 adult patients of either sex were enrolled for this study.

Inclusion and exclusion criteria

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 α 2 agonists.

Methodology

The patients were predominantly postsurgical who were operated for major abdominal, gynecological or urological 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 C and D, based on computer generated random number tables.

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.

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. If systolic BP reduced below 80 mmHg or increased above 180 mmHg, diastolic BP reduced below 50 mmHg or increased above 100 mmHg or heart rate was below

50 or above 120 bpm, they were labeled as adverse cardiovascular events. Any change >30% from the baseline in BP and heart rate were also considered as adverse cardiovascular event.

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 C patients were administered an IV infusion of clonidine µg/kg/h and titration was achieved with dosage increments up to 2 µg/kg/h. Patients in Group D 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. Additional sedation with IV diazepam bolus of 0.1 mg/kg was given if the patient did not achieve target sedation on titrating the sedative to the maximum selected dose (2 µg/kg/h for clonidine and 0.7 µg/kg/h for dexmedetomidine) or if the patient experienced side-effects (hypotension) with the drugs. Assessment of pain was by direct communication of the patient and fentanyl was given prior to anticipate noxious stimulus. Inadequate analgesia was treated with IV bolus of 20 µg of fentanyl or infusion if pain persisted.

Statistical analysis:

A sample size of minimum 32 patients/group was expected to have an 80% power to detect a 30% reduction in additional sedation requirements (primary endpoint) with a significance level of 5%. All data were recorded and noted on observation charts and were analyzed at the end of the study. 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)).

Results:

Over a period of 18 months, 100 patients were enrolled in the study to receive sedation with either dexmedetomidine (n = 50) or clonidine (n = 50). These included 83 postsurgical, 10 medical and 7 polytrauma patients evenly distributed in each group [Table 1]. Demographic data and intraoperative details such as operative time, fentanyl requirements, APACHE II scores, and duration of sedative infusions in the ICU were comparable [Table 1].

The mean ± SD maintenance infusion dose was 0.44 ± 0.25μg/kg/h for dexmedetomidine and 1.60 ± 8.2μg/kg/h for clonidine. Median infusion dose was 0.4 μg/kg/h (Group D) and 1.5μg/kg/h (Group C). A total of 320 observations of RSS were obtained for Group C, of which 225 (70.3%) observations were in the target sedation range (RSS: 3–4). In Group D, a total of 418 observations were obtained, of which 358 (85.6%) were in the target sedation range. The proportion of time spent in the target sedation range was greater in Group D (P = 0.05). A score 1-2 was observed on 94 (29.3%) occasions in Group C and 48 (11.4%) occasions in Group D (P = 0.066). RSS: 5-6 was achieved in 36 (11.2%) observations in Group C and 32 (7.6%) observations in Group D (P = 0.073).

The baseline hemodynamic parameters were comparable in both groups. A significant reduction in systolic and diastolic BP from the baseline ($P < 0.05$) occurred after bolus infusion in Group D but in none of the patients fall was >30% from baseline. Thereafter, mean values remained well within range throughout study period [Figures 1 and 2].

Mean heart rate also decreased from baseline 2 h after commencement of sedative infusion in Group D, but at none of the observation times fall was significant (P = 0.082) [Figure 3]. In Group C significant fall from baseline values in BP were noted 2 and 4 h after sedative infusion was started; but thereafter, it showed minimal change [Figures 1 and 2]. Patients receiving clonidine (Group C) had significantly lower heart rates from baseline ($P < 0.05$) [Figure 3].On comparison, the hemodynamic parameters were comparable between the two groups during the studyperiod ($P > 0.05$).

Bradycardia occurred in 5 of the 50 patients in Group C and 4 of the 50 patients in Group D (P = 0.36). Hypotension occurred in 10 of the 50 patients in Group C (20%) and 6 of the 50 patients in Group D (12%) (P = 0.01).

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

		Group C	**Group D**
Age		44 (44-52)	48 (46-65)
Sex (male: female)		**19:17**	**20:18**
Type of patient			
Postsurgical		**37**	**46**
Medical		**6**	**4**
Polytrauma		**4**	**3**
Intraoperative fentanyl usage (μg) (mean±SD)		**261:75**	**279:58**
APACHE II		**17 (16.2:19)**	**15 (16-18)**

Duration of sedative infusion in ICU (h)		**19 (18-29)**	**18 (15-26)**
Duration of surgery in h (mean±SD)		**4.2±2.1**	**3.8±1.8**

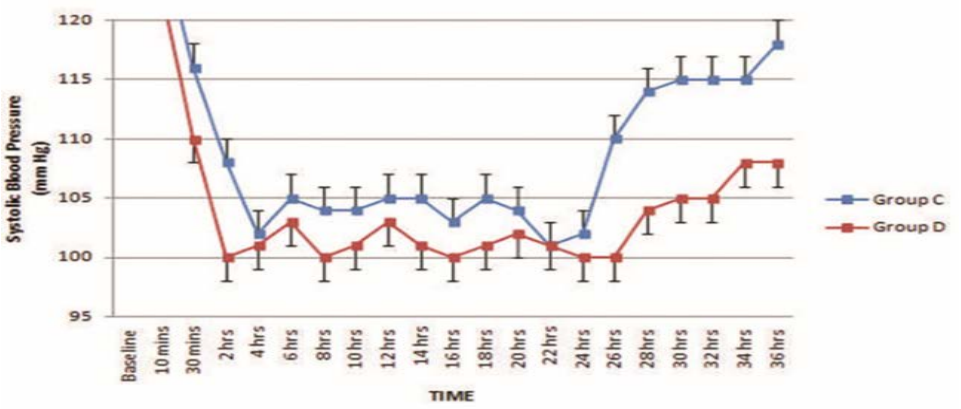

Figure 1: Systolic blood pressure (mean ± standard error of the mean) during dexmedetomidine and clonidine infusion and after discontinuation

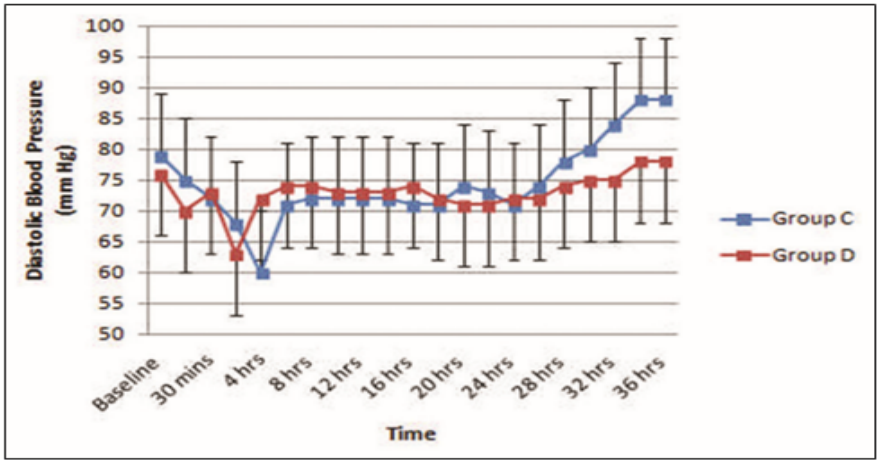

Figure 2: Diastolic blood pressure (mean ± standard error of the mean) during dexmedetomidine and clonidine infusion and after discontinuation

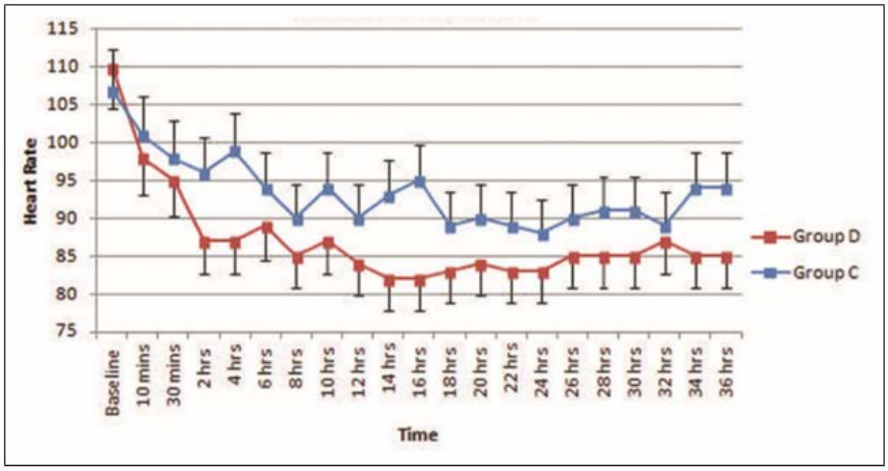

Figure 3: Heart rate (mean ± standard error of the mean) during dexmedetomidine and clonidine infusion and after discontinuation

Discussion:

The chief results of this 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. [10-11]

There is evidence that dexmedetomidine alters the pharmacokinetics of intravenous anesthetic agents by decreasing cardiac output [12] and by inhibiting alfentanil micro some metabolism in the liver [13] but not the pharmacokinetics of inhaled agents such as isoflurane. The first report of reduced isoflurane requirements in humans with dexmedetomidine was published in 1991 [14]. Aho et al showed 25% reductions of maintenance concentrations of isoflurane in patients who received dexmedetomidine. Khan et al found 35% to 50% reductions of isoflurane requirements in patients treated with either low or high doses of dexmedetomidine and isoflurane without premedication [15].

Riker *et al*.[16]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.

In a recent report about respiratory effects, respiratory rates and arterial blood gas values of postsurgical patients were reported. This study showed no differences in the respiratory parameters. Respiratory rates were lower in treated patients and respiration was more economic, with preserved minute ventilations, which yielded better oxygenation [17].

Many agents used in the ICU have been shown to modify immune response. Midazolam, a frequently used sedative agent, has been shown to reduce phagocytic effects and decrease the interleukin-8 release in response to lipopolysaccharide, an effect not seen with opioids. On the other hand, dexmedetomidine at clinically relevant concentrations did not influence chemotaxis, phagocytosis, or O2 – free radical production by neutrophils. Also, α2-adrenoceptor agonists failed to scavenge the O2– generated by the cell-free system [18]. Overall, there seems to be little evidence for any clinically relevant immunomodulation by dexmedetomidine.

Although α2-adrenoceptor agonists appear to be beneficial in terms of ischemic adverse events, there is some controversy about the vasoconstrictive effects of α2 agonism. A2-Adrenoceptoragonists may cause peripheral and coronary vasoconstriction by stimulation of post junctional α2-adrenergic receptors [19].

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 C compared with Group D. 50% of the hypotensive episodes occurred within 2–4 h in Group C and after bolus infusion and within 2 h after maintenance infusion in Group D, as the steady state plasma concentration of the drugs are achieved at this time duration, causing vasodilatation and hypotension. In general, hemodynamic stability was preserved in most patients receiving dexmedetomidine, a finding in agreement with many previous studies. [20-22]

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.

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