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Comparison of post-operative ICU sedation between dexmedetomidine and fentanyl in adult patients

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Abstract

Background: Patients on mechanical ventilation in intensive care unit (ICU) are often uncomfortable because of anxiety, pain, and endotracheal intubation. Therefore, require sedation, alpha2 agonists are known to produce sedation. Aims: The present study was undertaken to evaluate the efficacy and safety of dexmedetomidine in comparison to fentanyl in the management of sedation for postoperative intensive care unit (ICU) patients, as a sedative agent.

Methods: Total thirty patients of either sex, age between 18-70 years and who were ambulatory and who required the postoperative mechanical ventilation or postoperative sedation were enrolled and divided in two equal groups. Group D received dexmedetomidine and group F received fentanyl. All these patients were treated for the period of 8 to 24 h. Pulse rate, respiratory rate, blood pressure (Systolic/Diastolic), mean arterial pressure and SPO2; Ramsay sedation scale, VAS, recovery time from sedation and analgesic requirement were noted.

Results: Pulse rate, respiratory rate and blood pressure were comparable between two groups. Depth of sedation and extubation time were similar. To maintain analgesia throughout the study period, patients receiving fentanyl infusions required significantly more analgesics than patients receiving dexmedetomidine.

Conclusions: Dexmedetomidine appears to be a safe and acceptable ICU sedative agent when both the clinician's and patient's perspectives are considered.

Keywords: Dexmedetomidine, Fentanyl, Mechanical ventilation, Intensive care unit, Endotracheal intubation

Introduction

Critically ill patients are often uncomfortable because of pain, anxiety, and reluctance to undergo mechanical ventilation. This discomfort is treated with continuous sedation, usually in combination with an opioid at low dose [1]. The concepts of analgesia and sedation in intensive care medicine have changed considerably over the last decade. Attaining an optimal level of sedation is a challenging act for the ICU clinician. Both inadequate sedation and over sedation compromise patient's recovery and may prolong ICU stay along with associated complications and increased cost [2]. 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. Therefore, analgesics and sedatives must be carefully titrated to individual needs [3].

The α_2 agonist dexmedetomidine is a new sedative and analgesic agent which has been licensed recently in the USA as ICU sedation for up to 24 h after surgery. Dexmedetomidine provides haemodynamic stability [4] and appears to have no clinically important adverse effects on respiration [5]. It sedates via interaction with the locus ceruleus, and has less effect on arousability and patient interaction [6,7]. Its sedative properties are unique in that it produces only mild cognitive impairment, [6] allowing easy communication between health-care provider and patient in the ICU [4]. Fentanyl is a synthetic opioid with a rapid onset (5–15 minutes) and a short duration of action (30–60 minutes). It is easily titrateable as a continuous infusion secondary to its short half-life. However, because it causes less histamine release than morphine and does not undergo renal elimination, it is the preferred opioid analgesic in hemodynamically unstable patients or those with renal insufficiency [8].

Hence, the present study was carried out with an objective to evaluate and compare the efficacy and safety of dexmedetomidine in comparison to fentanyl in the management of sedation for postoperative intensive care unit (ICU) patients.

Materials and Methods

After obtaining Institutional Ethics Committee approval and written informed consent from patient or relatives, this prospective, randomized clinical study was conducted in 30 patients, who required the post-operative mechanical ventilation or post-operative sedation after surgery. They were randomized in two groups of 15 patients in each to receive either dexmedetomidine (Group D) or fentanyl (Group F). All patients were treated for the period of 8-24 hours. Patients undergoing surgery on an inpatient basis, with age from 18 to 70 years of both gender and willing to give the consent were included in the study. Patients currently being treated or were treated within the last 30 days with alpha-2 agonist and blockers, with central nervous system (CNS), cardio vascular system (CVS), liver, renal problems, history of obstructive sleep apnea, pregnant or lactating females, in whom, fentanyl would be given for anesthesia were excluded from the study.

When each patient had VAS ≥4 and Ramsay sedation score ≤2. Dexmedetomidine was administrated by a loading dose of injection with 1 mcg/kg over 10 min, followed by a maintenance infusion of 0.2-0.7 mcg/kg/h. The loading doses of 1 mcg/kg of fentanyl were given over 10 minutes until the pain was controlled, followed by infusion rates of 1-2 mcg/kg/h. The rate of the maintenance infusion was adjusted to achieve the desired level of sedation. A minimum period of 5 min between adjustments was allowed for the onset of peak drug effect. Pulse-rate, respiratory rate, blood pressure (Systolic/Diastolic), mean arterial pressure and SPO2; Ramsay sedation scale, VAS, recovery time from sedation and analgesic requirement were noted. Efficacy was assessed to achieve Ramsay score of 2-3 after the surgery as early as possible. RSS is a six-item observer-rated scale to assess the sedation states, in which Score 1- represents anxious or restless or both, 2- co-operative, orientated and tranquil, 3- responding to commands, 4- brisk response to stimulus, 5- sluggish response to stimulus and 6- represents no response to stimulus. VAS is a 0-10 observer-rated scale to assess the pain in which score 0 means no pain and score 10 means severe pain.

The primary efficacy parameter was to evaluate cardio-respiratory end points at equi-sedative doses of dexmedetomidine and fentanyl in the ICU. Patient's global assessment of pain intensity (0-10 VAS), global assessments of the treatment efficacy by the patient and by the investigator were also noted. Data were analyzed using Student's *t*-test and Chi-square test. The value of $P < 0.05$ was considered as statistically significant.

Observations and Results

Thirty patients were selected for the study, divided into Group 'D' and Group 'F'. In Group 'D' there were 46.6% males and 53.3% females whereas in the Group 'F' there were 60 % males and 40% females. The demographic data with respect to age, sex and weight in both the groups were comparable and were not statistically significant (Table 1). The average duration of sedation was around 18 h in both groups. There was no statistically significant difference in the requirement of rescue sedation between the two groups as seen in Table 1.

There was no statistical as well as clinically significant difference ($P > 0.05$) in the cardio respiratory parameters, i.e. the mean pulse-rate, respiratory rate, blood pressure between the two groups (Table 2). Both the groups were comparable with respect to laboratory parameters before and after the drug. Over the whole study period, the mean RSS was between 2-4 and 2-3 for dexmedetomidine and fentanyl groups respectively, which was not statistical significant, (Table 3).

The comparison of severity of pain through VAS shows statistically significant difference among the two groups (Table 4). Over the whole study period, the mean VAS score was maintained between 2-3.5 and 2-3 for dexmedetomidine and fentanyl groups respectively. However, patients receiving fentanyl infusions required additional dose of analgesics than patients receiving dexmedetomidine. No adverse event was observed in this study.

As shown in (Table 5), with respect to patients assessment for efficacy, nine patients (i.e., 60%) out of 15 in dexmedetomidine group had shown excellent rating whereas only one patients in fentanyl group has shown excellent rating, in addition to excellent rating 6 (40%) and 9 (60%) patients had given "Good" rating and 0 and 4 (26.66%) patients had given "Poor" rating on treatment with dexmedetomidine and fentanyl therapy, respectively. However, according to investigators, assessment for efficacy represented in ten patients (66.67%) out of 15 in dexmedetomidine group had shown excellent rating as compared to 2 (13.33%) patients in fentanyl group, whereas 5 (33.33%) and 10 (66.67%) patients had given "Good" rating and 0 and 3 (20.00%) patients had given "Poor" rating on treatment with dexmedetomidine and fentanyl therapy respectively.

According to investigators, assessment for safety, 10 (66.67%) and 3 (20%) patients had given "Excellent" rating, whereas 5 (33.33%) and 9 (60.0%) patients had given "Good" rating and 0 (0%) and 3 (20.0%) patients had given "Poor" rating upon treatment with dexmedetomidine and fentanyl, respectively (Table 6).

Discussion

In postsurgical ICU, most patients require sedation and analgesia to facilitate mechanical ventilation, allay anxiety, relieve pain, encourage sleep and prevent sudden increase in systemic or pulmonary vascular resistance and to prevent inadvertent dislodgement of indwelling catheters or drainage tubes by frequent movement.

Dexmedetomidine when compared with conventional sedatives and opiates has been demonstrated to be associated with both sedative and analgesic effects, reduced delirium and agitation, minimal respiratory depression and predictable and desirable cardiovascular effects [9,10]. Central nervous system stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus coeruleus in the brainstem plays a prominent role in sedation and anxiolysis [11]. Decreased noradrenergic output from the locus coeruleus allows increased firing of inhibitory neuron (GABA). Centrally acting α adrenergic agonists also activate central sympatholytic effects, leading to decreased heart rate and blood pressure [10,12]. Primary analgesic effects and

potentiation of opioid induced analgesics result from the activation of the α-adrenergic receptor in the dorsal horn of the spinal cord and inhibition of substance P release.

In present study, we compared the central α agonist dexmedetomidine with the analgesic fentanyl based sedation. The study demonstrated that both infusions of dexmedetomidine and fentanyl produced sedation, and significant analgesia. Cardiovascular stability and respiratory function were both well maintained. Park et al [13] compared hypnotic based sedation (propofol and/or midazolam) with analgesia based sedation (remifentanil) in a general intensive care unit, and found that analgesia based sedation provided more satisfactory sedation during mechanical ventilation. Muellejans et al [14] compared remifentanil versus fentanyl for analgesia based sedation in the intensive care unit and concluded that analgesia based sedation with fentanyl or remifentanil was comparable. Tobias et al [15] in a prospective randomized study showed that dexmedetomidine at 0.5 µg/kg/h provided more effective sedation and decreased the rescue doses of morphine. In our study, the sedation levels in the dexmedetomidine group were adequate and comparable with the fentanyl group; the rescue doses of fentanyl required were comparable in both the groups.

Venn et al [4] in a prospective randomized study showed that dexmedetomidine at an initial loading dose of 1 µg/kg/h over 10 min followed by maintenance dose of 0.7 µg/kg/h provided optimal sedation, but 18 of 66 patients had adverse haemodynamic effects of either hypotension or bradycardia, in 11 of 18 patients the haemodynamic effects were during bolus infusion. Bloor et al [16] and Tobias et al [10] in their experience with dexmedetomidine concluded that the potential adverse cardiac and haemodynamic effects of dexmedetomidine, like bradycardia, sinus arrhythmia and hypotension, occur with the initial loading doses. In our study, the cardio respiratory parameters were comparable between two groups. Even though the heart rate decrease in the fentanyl group in the first few hours, was <7% to 10% of baseline and did not require any intervention, there was no significant hypotension in either group.

Dexmedetomidine is associated with little respiratory depression. This study confirmed a lack of a clinically significant respiratory effect. Belleville et al [17] reported that dexmedetomidine could be associated with episodes of obstructive apnea, and this was increasingly common at doses of 1 and 2 mg/kg that were given for 2 minutes and presumably associated with a rapid increase in sedation. Obstructive apnea was not evident in our study. An obstruction resulting in apnea is more likely related to the deep sedation and oral/pharyngeal anatomic events that are common to deep sleep. These properties might prove to be useful in a postoperative setting or in the intensive care unit.

Tables

Table 1: Demographic data of the patients

Parameters	Group D	Group F	P value
Age (Years)	49.08±12.48	49.82±11.22	>0.05
Sex (M/F)	7(46.6%)/8(53.3%)	9(60%)/6(40%)	
Weight (Kg)	56.78±10.54	56.42±8.70	
Duration of sedation (h)	18	18	
Rescue sedation (lg)	3.64±0.14	3.75±0.12	

Table 2: Cardio respiratory variables

Cardio respiratory variables	Group D		Group F	
	Pre-operative	Post-operative	Pre-operative	Post-operative
Pulse-Rate (Min)	74.97±12.11	84.40±17.50	89.56±12.42	96.65±15.21
Respiratory Rate (Min)	17.42±3.84	18.10±2.85	18.12±2.56	21.11±3.2
SBP (mmHg)	125.31±17.12	130.34±25.13	123.92±21.3	121.54±8.61
DBP (mmHg)	77.54±8.78	78.06±12.75	76.95±5.45	76.24±8.12
MAP	88.45±10.35	91.54±12.21	91.79±8.26	88.54±7.25

Table 3: Ramsay sedation scale

Time point	Group D	Group F
20 min	3.18±1.48	2.42±1.22
1.5 h	2.88±1.08	2.68±0.68
2.5 h	2.46±0.54	2.52±0.67

4 h	2.46±0.48	2.68±0.68
6 h	2.46±0.48	2.56±0.65
10 h	2.38±0.68	2.47±0.67
15 h	2.26±0.43	2.28±0.66
21 h	2.16±0.37	2.28±0.66
24 h	2.16±0.37	2.08±0.51

Table 4: Visual analogue score

Time point	Group D	Group F
20 min	1.78±1.32	3.72±2.62
1.5 h	1.85±1.28	2.28±1.22
2.5 h	2.00±1.54	2.47±1.42
4 h	2.46±1.56	2.47±1.18
6 h	2.36±1.48	2.46±1.18
10 h	1.92±1.04	2.37±0.97
15 h	2.16±1.04	2.58±0.79
21 h	2.46±0.77	2.53±1.06
24 h	2.49±0.78	2.58±1.21

Table 5: Overall assessment of efficacy by patient and Investigators.

Efficacy by Patients	Group D	Group F
Excellent	9 (60%)	1 (6.66%)
Good	6 (40%)	9 (60%)
Poor	00	4 (26.66%)
Total	15 (100%)	15 (100%)
Efficacy by Investigators	**Group D**	**Group F**
Excellent	10 (66.67%)	2 (13.33%)
Good	5 (33.33%)	10 (66.67%)
Poor	00	3 (20.00%)
Total	15 (100%)	15 (100%)

Table 6: Overall assessment of safety by investigators

Safety by Investigators	Group D	Group F
Excellent	10 (66.67%)	3 (20.00%)
Good	5 (33.33%)	9 (60.00%)
Poor	00	3 (20.00%)
Total	15 (100%)	15 (100%)

Conclusion

In present study, dexmedetomidine appears to be a safe and acceptable ICU sedative agent when both the clinician's and patient's perspectives are considered. Dexmedetomidine provides comparable sedation, analgesic and stable cardiovascular respiratory variables as fentanyl. These properties, combined with the analgesic qualities and lack of respiratory depression seen with dexmedetomidine, have advantages for patients at risk from myocardial ischemia. In conclusion; dexmedetomidine therapy could be used safely and effectively, in postoperative ICU as sedative and analgesic agent.

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