Original Article

A comparative study of sedo-analgesic effect of dexmedetomidine and dexmedetomidine with ketamine in postoperative mechanically ventilated patients

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Abstract

Background and Aims: To compare the sedoanalgesic effects of dexmedetomidine alone or with combination of ketamine.
Material and Methods: After getting ethical approval and informed patient consent, 60 adult surgical patients, were randomly divided into two groups. Group KD (n = 30); received dexmedotomidine 0.5 μg/kg/h mixed with ketamine 0.5 mg/kg/h and Group DEX (n = 30); received dexmedotomidine at 0.5 μg/kg/h infusion only. In both the groups, study drugs were titrated (dexmedetomidine- 0.2-0.7 μg/kg/h and ketamine 0.2-0.7 mg/kg/h) to achieve target sedation. Hemodynamic variables, pain scores, sedation scores, and patient satisfaction were recorded. Qualitative and Quantitative data were analyzed with Pearson Chi-squared test and analysis of variance test, respectively. All analyses were done by using statistical package for social sciences (SPSS) version 16.0.
Results: Pain scores were higher in group DEX than in group KD at 2 h and 4 h which was statistically significant ($P < 0.05$). At the end of 2 h, sedation scores were higher in group KD than in group DEX and was statistically significant ($P < 0.05$). Length of intensive care unit stay was almost comparable in both groups, and the time to tracheal extubation was lesser in ketamine-dexmedetomidine group as compared to the dexmedetomidine alone group. However the difference was statistically non-significant.
Conclusions: By combining dexmedetomidine with ketamine we observed lower incidence of hypotension and bradycardia. Dexmedetomidine with ketamine combination therapy could be used safely and effectively as sedo-analgesic agent.

Keywords: Dexmedetomidine, ICU sedation, ketamine, sedoanalgesic

Introduction

Elective post-operative ventilation after major surgeries can add to more stress in patients and the goal of sedation in such mechanically ventilated patients has always been to keep them calm and comfortable in order to maximize patient's endotracheal tube tolerance and ventilator synchrony.[1] A protocol-based structured approach to the care of intensive care unit (ICU) patients helps not only to cut down hospital and health care costs but also helps to improve morbidity and patient satisfaction. ICU sedation is a growing topic of interest lately and there exists considerable variations among individual practitioner preferences. Over the last few decades the concepts of ICU sedation has changed with deep sedation no longer the standard of practice as it prolongs length of ICU stay and thus increases morbidity.[2] On the contrary, inadequate sedation can result in unwanted anxiety, agitation,

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ventilator asynchrony, and recall in post ICU phase and thus increase morbidity.[3] Therefore, titration of analgesics and sedatives for every patient is essential in the intensive care unit.

Propofol and midazolam have been used for ICU sedation from a long time; however, as pain is often the culprit in agitation, an analgesic is recommended in the sedation protocol. Side effects of propofol, such as hypotension, respiratory depression, fear of propofol infusion syndrome, and lack of analgesic properties have limited its role in ICU sedation lately. Benzodiazepines are also associated with respiratory depression and have a potential to accumulate after long-term infusions, leading to delay in extubation time. These side effects have led to the use of newer drugs in ICU sedation and to test new drug combinations to achieve adequate ICU sedation.

Dexmedetomidine, a selective α_2-adrenergic agonist, has found use in anesthetic practice because of its combined sedative, analgesic, anxiolytic, and hypnotic effects.[4,5] Dexmedetomidine reduces the dose requirements of analgesics and attenuates the hemodynamic responses of prolonged mechanical ventilation. Ketamine is a dissociative agent that works by disconnecting the central nervous system from external stimuli. It provides excellent analgesia, sedation, amnesia while preserving airway reflexes, respiratory effort, and cardiovascular stability.[6,7] These qualities along with low costs make it an excellent drug for managing trauma patients. Horvath *et al.*[8] showed synergistic interaction with N methyl D aspartate antagonist S-ketamine and the α_2-adrenoceptor agonist dexmedetomidine. The synergistic interaction between these two drugs needs to be explored for therapeutic significance.

The objective of this study was to investigate and evaluate dexmedetomidine in comparison to combination of dexmedetomidine and ketamine in sedoanalgesia for elective post-operative mechanical ventilation after major oncological procedures. We also wanted to compare time to extubation, duration of ICU stay, pain scores, side effect profiles, and patient satisfaction with the two regimens. To our knowledge, this is the first study comparing the sedoanalgesic effects of ketamine-dexmedetomidine combination as ICU sedation.

Material and Methods

After receipt of Institutional Ethical Committee approval and patients'/relatives' written informed consent, 60 American Society of Anesthesiology (ASA) physical status I and II patients, aged between 18 and 65 years, undergoing major abdominal and head and neck oncosurgeries shifted to the ICU for elective ventilation. Patients who were pregnant or nursing; or had abnormal laboratory test results, significant psychiatric, neurological, cardiovascular, renal, or hepatic diseases were excluded. On arrival to the ICU, routine monitors were applied for recording heart rate (HR), electrocardiogram, non-invasive blood pressure monitor, and peripheral oxygen saturation (SpO_2).

Sample size calculation formula - $n = [Z_{1-\alpha/2} \sqrt{2PQ} + Z_{1-\beta}\sqrt{P_1Q_1 + P_2Q_2}]^2/(P_1-P_2)^2$

Where, n = sample size

P_1 is proportion in 1st group

P_2 is proportion in 2nd group

$Q_1 = 1 - P_1$ and $Q_2 = 1 - P_2$

$\alpha = 5\%$ at two tailed tests

$Z_{1-\alpha/2} = 1.96$

$Z_{1-\beta}$ Power of the study

Patients were divided randomly into two groups using computer generated table random number. Group KD ($n = 30$); received with starting dose of dexmedetomidine 0.5 μg/kg/h mixed with ketamine 0.5 mg/kg/h and Group DEX ($n = 30$); received dexmedetomidine at 0.5 μg/kg/h infusion only. In both the groups, study drugs were titrated (dexmedetomidine- 0.2–0.7 μg/kg/h and Ketamine 0.2–0.7 mg/kg/h) to achieve target sedation. For Group KD, 200 μg of dexmedetomidine mixed with 200 mg of ketamine and diluted up to 50 ml by using normal saline. In group DEX, 200 μg of dexmedetomidine diluted up to 50 ml by using normal saline. If patients in either group did not achieved target sedation even after maximum dose of study drug then midazolam infusion was started at 0.01 to 0.05 mg/kg/min until adequate sedation was achieved.

Hemodynamic variables were also recorded at baseline (before the study drug infusion), and at 10, 30, 60, 120 min and then every 6 h interval after the start of infusion till extubation. It was also planned that if hypotension occurred (SBP <80 mm Hg), the patients would be primarily treated with fluid administration (0.9% saline 10 mL kg -1 h-1). Patients were instructed about the visual analogous scale (VAS) self-rating method. All patients used a separate 10-cm VAS device to assess the level of pain (0, no pain; 10, worst possible pain). Sedation was assessed on a five-point scale ('0' = no sedation—patient wide awake and alert; 4' = deep sleep, difficult to rouse). Pain and

sedation were assessed by an assistant at 1, 2, 4, 6 h and post extubation. A pain score <5 was considered adequate. Inadequate analgesia (e.g., increase in mean SBP, 25% above baseline; purposeful movements; swallowing; grimacing), was treated with I.V fentanyl 1 μg/kg as a rescue analgesic. The total dose of fentanyl used for rescue analgesia was also recorded. Sedoanalgesia was defined primarily as VAS <5 and sedation scores >2. During the study period, the number of patients requiring additional fentanyl; and time to extubation and satisfaction of patients was recorded as excellent, very good, good or poor. Incidence of side effects (e.g., nausea, vomiting, hemodynamic events), if any, was recorded.

Statistical analysis

At the end of the study, all the data were compiled systematically and analyzed. Qualitative data were analyzed with Pearson Chi-squared test. Quantitative data, expressed as "mean ± standard deviation (SD)", were analyzed by one-way analysis of variance test. A probability value less than 0.05 was considered statistically significant. All analyses were done by using statistical package for social sciences (SPSS) version 16.0 (SPSS, Chicago, IL).

Results

The two groups of patients were comparable with respect to age, sex, and weight [Table 1]. Systolic blood pressure was lower in group DEX at 30 min, 60 min, 120 min, and 6 h and the difference was statistically significant ($P < 0.05$) [Table 2].HR was lower in group DEX at 30 min and 60 min and the difference was statistically significant ($P < 0.05$) [Table 3]. Pain scores were higher in group DEX than in group KD at 2 h and 4 h which was statistically significant ($P < 0.05$) [Table 4]. Five patients received Inj. fentanyl @ 1 μg/kg at 2 h and 4 patients received Inj. fentanyl @ 1 μg/kg at 4 h in group DEX. Only two patients received Inj. fentanyl in group KD. At the end of 2 h, sedation scores were higher in group KD than in group DEX and was statistically significant ($P < 0.05$) [Table 5]. Midazolam infusion was not started as target sedation was achieved in both groups. After 6 h of surgery, infusion was stopped in both groups. Average infusion dose of dexmedetomidine was 0.7 μg/kg/h in DEX group. In KD group, average infusion dose of dexmdetomidine was 0.4 μg/kg/h and ketamine was 0.4 mg/kg/h. Length of ICU stay was almost comparable in both groups, and the time to extubation was lesser in ketamine dexmedetomidine group as compared to the group which received dexmedetomidine alone; however, it was not statistically significant [Table 6]. There were seven adverse events in all the groups [Table 7]. Two patient who had received dexmedetomidine experienced brief (<1 hour) episode of hypotension (SBP, 60 mm Hg), and it was treated mainly with IV fluid (0.9% saline infusion 10 mL kg^{-1} h^{-1}) administration. Three patients in group DEX experienced nausea and vomiting. Two patients among those who had received dexmedetomidine had bradycardia one of them treated with injection atropine. Hypoxia, hypertension, allergic rash, apnea, and hallucination were not observed in any of the study patients.

Table 1: Demographic characteristics of patients in the study groups

	Group KD (*n*=30)	Group DEX (*n*=30)	*P*
Age	46.7±6.3	44.7±6.1	0.344
Sex	21/9	19/11	0.455
Weight	51.5±7.6	55.5±4.6	0.676

Age, Sex and weight values in the above table are in terms of 'mean±SD'

Table 2: Systolic blood pressure in the study groups

	Group KD (*n*=30)	Group DEX (*n*=30)	*P*
Before infusion	130.9±12.3	134.1±11.4	0.346
After infusion 10 min	140.9±15.4	133.9±19.4	0.211
30 min	142.5±22.6	119.3±18.3*	0.032
60 min	142.9±21.7	114.9±17.4*	0.028
120 min	140.2±20.4	111.9±20.9*	0.026
6 h	140.9±21.6	112.9±20.4*	0.027
12 h	141.1±19.4	132.1±17.4	0.521
18 h	140.9±18.1	134.8±19.1	0.219
24 h	138.4±18.4	132.1±19.4	0.369
Extubation	143.9±22.7	144.9±21.4	0.462

*Values of systolic blood pressure in table are in terms of "mean±SD." *P<0.05*

Table 3: Heart rate in the study groups

	Group KD (*n*=30)	Group DEX (*n*=30)	*P*
Before infusion	96.9±6.3	99.1±7.4	0.467
After infusion 10 min	110.9±9.4	87.9±9.4	0.232
30 min	105.5±2.6	62.3±8.3*	0.046
60 min	107.9±7.7	68.9±7.4*	0.021
120 min	110.2±5.4	94.9±12.9	0.139
6 h	104.9±6.6	91.9±11.4	0.436
12 h	101.1±9.4	93.1±11.4	0.535
18 h	103.9±14.1	95.8±19.1	0.227
24 h	105.4±11.4	97.1±19.4	0.345
Extubation	119.9±12.7	123.9±21.4	0.673

*Values of Heart rate in table are in terms of "mean±SD." *P<0.05'*

Table 4: Pain scores in the study groups

	Group KD (*n*=30)	Group DEX (*n*=30)	*P*
1 h	1.9±2.1	1.6±2.4	0.765
2 h	1.2±1.1	3.1±1.7*	0.021
4 h	0.9±0.7	2.2±0.7*	0.019
6 h	0.3±0.1	0.9±0.4	0.231
Extubation	0.0±0.0	0.1±0.5	0.978

*Values in the above table are in terms of "mean±SD." *P<0.05*

Table 5: Sedation scores in the study groups

	Group KD (n=30)	Group DEX (n=30)	P
1 h	1.6±1.1	2.4±1.4	0.662
2 h	1.4±0.4*	2.3±0.7	0.033
4 h	1.8±0.3	1.9±0.2	0.445
6 h	1.8±0.5	1.8±0.7	0.397
Extubation	0.0±0.0	0.0±0.0	0.788

*Values in the above table are in terms of "mean±SD." *P<0.05*

Table 6: Length of ICU stay and extubation time in study groups

Length of ICU stay (days)	2.5±1.6	3.1±1.8	0.164
Time to extubation (hours)	7.5±1.6	8.5±1.2	0.112

Length of ICU stay and time to extubation values in the above table are in terms of "mean±SD"

Table 7: Side effects in the study groups

	Group KD (n=30)	Group DEX (n=30)
Nausea vomiting	-	3
Hypotension	-	2
Hypertension	-	-
Bradycardia	-	2
Allergic rash	-	-
Hallucination	-	-
Hypoxia	-	-
Apnea	-	-

Discussion

This is an observational, prospective study investigating the effect of dexmedetomidine versus dexmedetomidine and ketamine in patients requiring sedation in oncology post-surgical ICU. Sedatives are used in most patients undergoing elective post-operative ventilation in the surgical ICU especially after major surgeries to reduce anxiety, pain, oxygen consumption, and cardiovascular instability. There are several pharmacologic agents used for sedation in postoperative mechanically ventilated patients. Over recent time's dexmedetomidine has been preferred over benzodiazepines as a first-line sedative agent in the ICU; however, very few studies have directly compared dexmedetomidine and its combination with ketamine for sedative efficacy and patient outcomes.

This study was conducted on patients who underwent major oncological surgeries and were shifted to the ICU for elective post-operative ventilation. We found that sedation with either dexmedetomidine or dexmedetomidine and ketamine resulted in a relatively short time to extubation; however, there was no statistically significant difference in time for extubation in both the groups. It is well known that decreasing the time of mechanical ventilation reduces the risk of ventilator related problems such as pneumonia, stress ulcers, delirium, and health care costs. Although patients had no difference in duration of mechanical ventilation in both the groups or length of ICU stay and mortality, difference was seen between the two groups in other secondary end points, including VAS scores and patient satisfaction.

In the present study, we have demonstrated that two sedoanalgesic techniques provided effective sedation and analgesia during elective post-operative ventilation. To increase the comfort of patients during elective mechanical ventilation, it is necessary to give them a tailored IV sedative along with analgesic and anxiolytic drugs taking into account the self-evaluation of the patient's pain.[9] The effect of ketamine is thought to be the result of N-methyl D-aspartate receptor antagonism, opioid l receptor agonism, and voltage-sensitive sodium channel interactions. In humans, ketamine is an agent for providing intraoperative and postoperative analgesia. The major advantage of ketamine is that it usually preserves airway patency and respiratory function and provides excellent analgesia. In our study, ketamine did not result in any respiratory depression or apnea during the study period.

Dexmedetomidine is a recently developed alpha-2 agonist that shows much greater selectivity for the 2-adrenoceptor than the other widely used agonists (e.g., clonidine).[4] It produces dose-dependent analgesia (involving spinal and supraspinal sites) without respiratory depression.[10] The analgesic profile of dexmedetomidine has not been fully characterized in humans. Kariya *et al.*[11] reported that clonidine counterbalanced the sympathetic stimulation of ketamine by virtue of its action in reducing sympathetic outflow, and the combination of clonidine and ketamine may be useful for patients with hypertension or myocardial ischemia. In the present study, we assume counterbalance of the sympathetic stimulation by ketamine might have been provided by dexmedetomidine. It has also been reported that dexmedetomidine attenuates the hyperadrenergic state associated with ketamine. The most frequently seen adverse effect of ketamine is emergence reactions or hallucinations. Green *et al.*[12] observed in his study that recovery agitation of ketamine has been modestly associated with decreasing age and the presence of an underlying medical condition. In this study, no patient experienced hallucinations or deliriums. Owens *et al.*[13] reported that 2.9% of the patients who received ketamine during sedation experienced side effects such as desaturation, apnea, hypotension. Walker *et al.*[14] in his study stated that no respiratory depression associated with the use of dexmedetomidine had occurred. Similarly, in a recent study, Taghinia *et al.*[15] reported that dexmedetomidine decreased the frequency of oxygen desaturation and reduced the amounts of narcotic and anxiolytic requirement.

In this present study, we did not observe any respiratory depression, hypoxia, or apnea in any group.

Hemodynamic variables were also similar among the groups in each study period, except SBP was significantly lower in dexmedetomidine (DEX) group than in Ketamine – dexmedetomidine (KD) group at 30 min, 60 min, 120 min, 6 h, and 12 h. Also, pain scores were higher in group DEX than in group KD at 2 h and 4 h which were statistically significant. Also sedation scores were higher in group DEX than in group KD at the end of second hour and were statistically significant. The most frequently seen adverse effects of IV dexmedetomidine that have been reported are hypotension and bradycardia.[11] In this study, only two brief episode (<1 h) of hypotension (SBP, 60 mm Hg) and it was treated with IV fluid (0.9% saline 5–10 mL kg-1 h-1) administration. Dexmedetomidine has been reported to be associated with a long arousable sedation, and this could be the reason why sedation scores were significantly higher in the KD group than DEX groups in our study.[16] Green *et al*.[,17] reported that the incidence of emesis after ketamine administration was modestly associated with increasing age. In this study, nausea and vomiting were observed in three patients in group DEX in contrast to Taghinia *et al*.[15] who have reported that dexmedetomidine decreased antiemetic use.

Conclusion

Dexmedetomidine with ketamine combination therapy could be used safely and effectively for sedation and analgesia in postoperative ICU patients requiring elective ventilatory support. A lower incidence of bradycardia and hypotension was observed.

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Conflicts of interest
There are no conflicts of interest.

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