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Original Research Article

A better drug for extubation-dexmedetomidine or fentanyl

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ABSTRACT

Background: Patients on Mechanical ventilator support in intensive care unit (ICU) require analgesia and sedation to facilitate synchronized mechanical ventilation. Our aim of study is to compare the efficacy of dexmedetomidine with Fentanyl to facilitate smooth and shorter time of extubation from mechanical ventilation. The study highlights the characteristics of cardiovascular responses, ventilation, extubation and safety profile of both the drugs.
Methods: A prospective randomized double-blind study was done on total of 40 adults mechanically ventilated patients of either sex, aged 18-60 years were selected. Randomized in two groups of 20 patients each received intravenous infusion of dexmedetomidine (0.2-0.7 mcg/kg/h) or fentanyl infusion (1-2 mcg/kg/h) as needed to maintain Ramsay sedation scale ranging 2-4. Extubation following standard extubation protocol was done. Time for extubation and vital parameters were recorded.
Results: The extubation time in the dexmedetomidine group was significantly lesser than in the fentanyl group. Cardiovascular response was stable in dexmedetomidine group than the Fentanyl group.
Conclusions: Dexmedetomidine facilitates shorter time to extubation, more hemodynamic stability, easy arousability, and lack of respiratory depression.

Keywords: Dexmedetomidine, Fentanyl, Weaning Mechanical ventilation, Intensive care unit

INTRODUCTION

Patients on mechanical ventilator support in intensive care unit (ICU) require analgesia and sedation to facilitate synchronized mechanical ventilation. Delayed or unnecessarily prolonged weaning increases length of intensive care unit (ICU) stay, health-care cost, ventilator associated events and adversely affects patient outcome.[1,2] Aggressiveness in weaning off the ventilator, however, must be balanced against the possibility that premature discontinuation may occur.

Patients who are on ventilatory support require intravenous sedative and analgesia to facilitate mechanical ventilation and endotracheal tube tolerance. the invasive procedures, physiotherapy, tracheal suctioning, turning postures, changing of dressings, allays anxiety, blunts excessive hemodynamic, and metabolic responses.[3-5]

In this study, we compared the efficacy of dexmedetomidine with fentanyl to facilitate extubation of patients from mechanical ventilation in terms of the sedative properties, cardiovascular responses, ventilation, and extubation characteristics.

Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist that is structurally related to meperidine. As an analgesic, fentanyl is 75 to 125 times more potent than morphine. Despite the clinical impression that fentanyl has a short duration of action, its elimination half-time is longer than that for morphine. The lungs also serve as a large inactive storage site, with an estimated 75% of the initial fentanyl dose undergoing first-pass pulmonary uptake When multiple IV doses of fentanyl are administered or when there is continuous infusion of the drug, progressive saturation of these inactive tissue sites occurs. As a result, the plasma concentration of fentanyl

does not decrease rapidly, and the duration of analgesia, as well as depression of ventilation, may be prolonged.

Dexmedetomidine, a centrally acting α_2-adrenergic agonist, is a recently FDA-approved agent used for short-term (<24 hours) continuous iv sedation of adults who are tracheally intubated. Like propafol, it has a rapid onset and a relatively rapid elimination half-life and is administered as a loading dose followed by continuous Iv infusion. One of the advantages is that it provides sedation with a lower risk of respiratory depression than many other sedative medications. It provides a hemodynamic stability, sometime causes bradycardia, and hypotension, this can be prevented by avoiding loading dose But there were no clinically important adverse effects on respiration.[6-13] Its sedative properties are unique in that it produces only mild cognitive impairment, allowing easy communication between health-care provider and patient in the ICU.[14,15] It does not affect the respiratory drive and therefore, it should not interfere with weaning from mechanical ventilation.[16]

METHODS

A randomized prospective double-blind study was conducted in a randomized open labeled manner at Renova Neelima hospital, Hyderabad, India from period August-2021 to June-2022.

Selection criteria

A 40 adult patients were selected aged between 18-60 years, being mechanically ventilated for <96 h prior to start of study drug infusion, and were anticipated to be weaned-off mechanical ventilation in next 24 h. Patients with significant liver (Childs Pugh class C) or kidney disease, severe neurological disorders, acute myocardial infarction, heart block, heart rate <50 beats/min, systolic blood pressure <90 mm Hg despite continuous infusions of vasopressors, receiving other sedatives and anticonvulsant drugs, pregnant/lactating females excluded from study.

Procedure

Weaning trial was considered based on following criteria; consciousness, a saturation ≥90%, fraction of inspired oxygen ≤0.4. PaO_2 >60 mm Hg on Abg, Minute ventilation ≤15 L/min, adequate cough on suctioning, respiratory rate (RR) ≤35/min, positive end expiratory pressure ≤10 cm H_2O, no or minimal inotropic or vasopressor infusions, mean arterial pressure >65 mm Hg, To check the readiness for weaning all these patients were subjected to daily sedation interruptions and were assessed hourly for wakefulness, defined as Ramsay sedation scale (RSS) score 1-4. Patients were subjected to a spontaneous breathing trial (SBT). Patients who successfully completed a 2-hour trial of spontaneous breathing were further tried for discontinuation of mechanical ventilation and possible extubation depending upon their ability to maintain and protect airway and their ability to cough and clear secretions. On the other hand, SBT was discontinued if there was tachypnea (RR >35/min for 5 min), hypoxia (SpO_2 <90%), sustained changes in heart rate and blood pressure of more than±20% or increased anxiety and diaphoresis.

Group A: Patients in this group received IV infusion of dexmedetomidine at a rate of 0.2-0.7 mcg/kg/h (adjusted as needed for the desired level of sedation i.e., RSS 2-4).

Group B: Patients in this group received IV infusion of Fentanyl at the rate of 1-2 mcg/kg/h (adjusted as needed for the desired level of sedation i.e., RSS 2-4).

Sedation was categorized into three levels according to Ramsay sedation Scale as: Insufficient: If sedation level was grade 1 on the RSS. Adequate (desired): If sedation level was grade 2-4 on the RSS and excessive: If sedation level was grade 5-6 on the RSS.

Hemodynamic parameters were recorded every 4 hourly during study drug infusion and then every 2 hourly after discontinuation of study drug. The patients were assessed for possible extubation during SBT trial. After meeting the criteria for extubation, the extubation was done following standard extubation protocol and the time for extubation (from start of the study drug infusion until extubation) and duration of study drug infusion given was recorded.

Patients who maintained effective spontaneous breathing without any mechanical assistance for 24 h after extubation were considered as successfully weaned and those who did not, were excluded from the study and were considered as extubation failure.

Ethical approval

This study was conducted after the approval of the institutional ethical committee of hospital.

Statistical analysis

Quantitative data were described in mean ± standard deviation and were compared using Students' t test/Mann-Whitney test. Categorical data described by absolute and percentage frequencies and compared using Chi-square test. Differences considered significant when $p \leq 0.05$.

RESULTS

Patients in both groups were comparable demographically in terms of, sex, age, indication for putting on the ventilator, and duration of ventilation body mass index, prior to start of study drug infusion (Table 1).

Majority of patients in both groups were adequately sedated, this was assessed by Ramsay sedation scale at various intervals. Excessive sedation was seen in only fentanyl group (two patients at 12 h, two patients at 16 h and one patient at 20 h). and there was no Excessive sedation in dexmedetomidine group.

Table 1: Demographic profile.

Groups	Group A-dexmedetomidine	Group B-Fentanyl	P value
Age (Years)	42.25±11.586	39.01±14.117	0.293
Sex (Male/ Female)	12/8	13/7	0.733
BMI (Kg/m^2)	25.776±3.626	25.922±3.082	0.666
Ventilator indication			
Sepsis	8 (40)	7 (35)	
Major abdominal surgery	6 (30)	8 (40)	
Trauma	6 (30)	5 (25)	
Period of ventilation prior to starting drug infusion	92 hours 33 mins	94 hours 14 mins	

Table 2: Adequacy of sedation.

Time (Hours)	Group A-Dexmedetomidine			Group B-Fentanyl			P value
	Inadequate sedation	Adequate sedation	Excessive sedation	Inadequate sedation	Adequate sedation	Excessive sedation	
0	20	0	0	20	0	0	1.000
4	2	18	0	5	15	0	0.387
8	1	19	0	4	16	0	0.296
12	0	20	0	1	18	1	1.000
16	1	19	0	0	18	2	0.153
20	1	19	0	1	18	1	0.799
24	0	20	0	0	20	0	1.010

The time to extubation was found to be significantly lesser in the dexmedetomidine group (24.210±1.6651 h) than in the Fentanyl group (31.350±3.3447 h) (Table 3).

Table 3: Time to extubation.

Groups	Mean ± SD	P value
Dexmedetomidine	24.410±1.7731	0.0230
Fentanyl	31.33±3.2337	

Patients in both groups remained hemodynamically stable throughout the study period. The difference in heart rates in the two groups was comparable and was statistically insignificant at 0-12 h. Whereas, the heart rates in the dexmedetomidine group were significantly lower than in the fentanyl group at 16, 20, and 24 h after the drug infusion. In the intragroup comparison, the mean fall in heart rates from the baseline values was significant in dexmedetomidine group at 16, 20, and 24 h, whereas it was insignificant in fentanyl group. After extubation the heart rate in the dexmedetomidine group was found to be significantly lower than in fentanyl group, when the two groups compared with each other from time of extubation until 12 h post extubation (Table 4 and Figure 1).

Table 4: Heart rate trends before and after extubation.

Time (hours)	Dexmedetomidine group	Fentanyl group	P value
Before extubation			
0	119.34±10.603	118.00±7.340	0.644
4	113.44±9.854	114.70±6.298	0.497
8	111.50±13.567	110.85±5.047	0.785
12	104.83±12.739	111.40±5.458	0.124
16	96.33±16.408	109.50±6.558	0.013
20	91.12±11.660	110.6±5.493	0.023
24	85.60±11.332	108.04±6.352	0.023
After extubation			
0	104.13±13.216	119.24±5.280	0.030
2	85.70±11.503	116.50±6.615	0.027
4	95.70±11.358	110.60±7.532	0.051
6	86.30±11.970	107.00±4.377	0.031
8	86.25±11.652	107.70±6.097	0.021
10	85.40±11.348	108.00±5.026	0.036
12	84.85±9.949	108.95±5.671	0.024

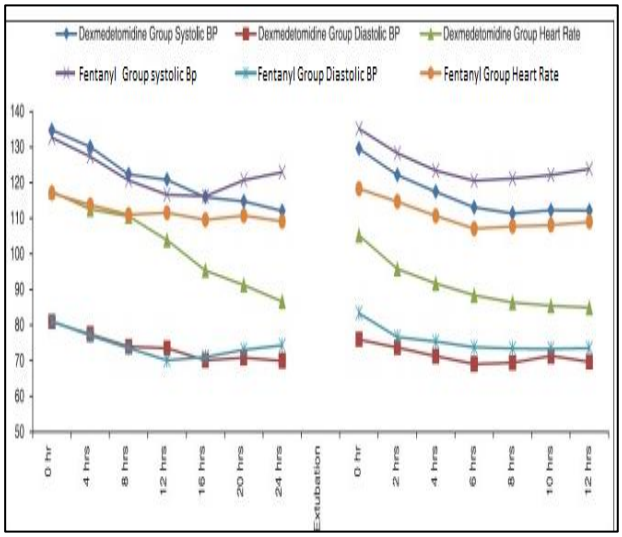

Figure 1: Haemodynamic trends.

The baseline values of systolic blood pressure in the dexmedetomidine group and fentanyl group were statistically insignificant. The change in mean systolic blood pressure from baseline value until 16 h of starting the study drug infusion was statistically insignificant in both groups. However, a significant fall from baseline was observed at 20 h in dexmedetomidine group alone and at 24 h in both dexmedetomidine and fentanyl groups. On intergroup comparison, the fall in systolic blood pressure was comparable in both groups except at 24 h where a statistically significant fall in systolic blood pressure was observed in dexmedetomidine group as compared with fentanyl group. Significantly lower systolic blood pressure values in dexmedetomidine group were observed as compared to fentanyl group at various time intervals after extubation also. The comparative diastolic blood pressure trends at various time intervals before and after extubation were almost similar as that of systolic blood pressure in both dexmedetomidine and fentanyl groups (Figure 1).

DISCUSSION

In this study, we tried to evaluate the better drug for extubation with safety profile in terms of haemodnamic stability and shorter time for extubation. The choice of drug for sedation during mechanical ventilation would be the drug which has a characteristic like providing adequate sedation, rapid onset of action, haemodynamic stability, short elimination time, less accumulation in the body, preferably hepatic and renal independent excretion and time to extubation should be shorter when drug infusion is discontinued. Ideally many of these desirable properties are lacked in most of the drugs which are used in ICU like benzodiazepenes, opioids, propafol. etomidate and ketamine.

The purpose of this study is to search for a drug which contains majority of the above properties. So, we did a comparative study on dexmedetomidine and fentanyl to assess that which can provide adequate sedation, shorter time for extubation when discontinued and with stable haemodynamic responses.

Dexmedetomidine, a new potent alpha-2 agonist acting in the locus ceruleus, inhibits sympathetic stimulation, and provides analgesia and sedation without respiratory depression and hemodynamic instability.[17,18] It produces only mild cognitive impairment allowing easy communication between health-care provider and the patient in ICU. Since its initial approval by the FDA in 1999 for sedation of intubated and mechanically ventilated patients in the ICU, dexmedetomidine has been extensively studied in well-designed, randomized trials in comparison to other sedative drugs. In 2007, the MENDS trial compared dexmedetomidine to lorazepam and found that dexmedetomidine was associated with less delirium and more time spent at the targeted level of sedation.[19] The SEDCOM trial in 2009 compared dexmedetomidine to midazolam and demonstrated a reduced duration of mechanical ventilation and less delirium in patients sedated with dexmedetomidine.[20] The PRODEX and MIDEX trials were conducted jointly and compared dexmedetomidine to propofol and midazolam, respectively. These trials showed a significantly decreased duration of mechanical ventilation with dexmedetomidine compared to midazolam, and a non-significant decrease in the duration of mechanical ventilation with dexmedetomidine compared to propofol.[21] When the sepsis subgroup in the MENDS trial was reanalyzed, a significant mortality benefit was found for patients sedated with dexmedetomidine.[22]

Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist that is structurally related to meperidine. As an analgesic, fentanyl is 75 to 125 times more potent than morphine. Despite the clinical impression that fentanyl has a short duration of action, its elimination half-time is longer than that for morphine. The lungs also serve as a large inactive storage site, with an estimated 75% of the initial fentanyl dose undergoing first-pass pulmonary uptake. When multiple IV doses of fentanyl are administered or when there is continuous infusion of the drug, progressive saturation of these inactive tissue sites occurs. As a result, the plasma concentration of fentanyl does not decrease rapidly, and the duration of analgesia, as well as depression of ventilation, may be prolonged.

There was no statistical as well as clinically significant difference in the haemodynamic parameters, i.e., the pulse, systolic blood pressure and diastolic blood pressure, between the two groups, The frequency of bradycardia in the fentanyl group was significantly less. In the dexmedetomidine group, even though heart rate decreased in the first few hours, it was <10 to 15% of baseline and did not require any intervention. There was no significant hypotension in either group. In a study of Venn et al reported in dexmedetomidine group had significantly lower heart rate with (mean [standard deviation] 75 vs. 90 beats/min) however, no significant differences were found

in arterial pressures between the groups.[4,6,9] In 2004 Shehabi et al also reported a 16% reduction in mean systolic blood pressure and 21% reduction in heart rate over the first 4 h followed by minimal (±10%) changes throughout the infusion.[23,24] In 2008, Arpino et al also found that the heart rate trended down after dexmedetomidine initiation in most patients but did not result in the discontinuation of dexmedetomidine in any patient.[24]

There were 3.6 and 8.5% patients who were inadequately sedated in dexmedetomidine and fentanyl group respectively. There were 4.3% patients over-sedated in fentanyl group and none in dexmedetomidine. Chrysostosmou et al retrospectively reviewed their experience with post-operative dexmedetomidine infusion in pediatric patients undergoing cardiac surgery.[25] Dexmedetomidine was administered in the post-operative unit at a dose of 0.1-0.5 µg/kg/h for 3-26 h, and they reported successful post-operative sedation in 93% of the patients with absent or minimal pain scores. They also reported that 87% of the patients on dexmedetomidine infusion were easily weaned and extubated. Tobias et al 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.[26] 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.

In our study, the time to extubation in the dexmedetomidine group (24.410±1.7731) was found to be significantly lower (7.13 h) than in the fentanyl group (31.330±3.2337 h). Venn et al compared dexmedetomidine with propofol for sedation in the ICU.[9] They showed that the extubation times were similar and rapid with the use of both sedative agents (median (range) 28 (20-50) and 29 (15-50) min (p=0.63) for the propofol and dexmedetomidine groups, respectively). Shehabi et al showed that mean time to extubation was shorter in dexmedetomidine group (24.21 h [22-28 h]) than midazolam group (31.35 h (26-38 h) (p<0.05).[23]

Limitations

Data regarding the cardiac output, pulmonary artery pressure, pulmonary vascular resistance and systemic vascular resistance were not collected. This probably would have given a more definitive information about cardiovascular effects of both the drugs.

CONCLUSION

We conclude that Dexmedetomidine provides comparable sedation, analgesic and stable haemodynamic effects as fentanyl. The advantages being with minimal depression of respiratory drive and early facilitation of extubation makes dexmedetomidine a better alternative to fentanyl.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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