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ORIGINAL RESEARCH

Comparison between Dexmedetomidine and Fentanyl Infusion for Short Term Sedation in Mechanically Ventilated Patients in Intensive Care Unit

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ABSTRACT

Background: Dexmedetomidine produces sedation while maintaining a degree of arousability and may reduce the duration of mechanical ventilation and delirium among patients in the intensive care unit (ICU).Data comparing Dexmedetomedine and Fentanyl as an effective sedation in mechanically ventilated patients are lacking.

Methods: In a prospective, bouble blind study, we randomly assigned newly mechanically ventilated patients to receive Dexmedetomidine (0.3 to 0.7mcg/kg/hr) or fentanyl (1 to 3mcg/kg/hr) with doses adjusted to achieve target sedation goals set by clinicians according to the Richmond Agitation–Sedation Scale (RASS, on which scores range from −5 [unresponsive] to +4 [combative]). Midazolam 0.002 mg/ Kg bolus was administered as rescue sedation if the target sedation score could not be achieved within the infusion range. Primary end points were to assess the total dose of the sedative drugs, time required to achieve target sedation as well as total dose of rescue sedation administered.

Results: 62 patients were included in the study, of which 31 received Dexmedetomidine, and 31 received fentanyl infusion. It was observed that there was a significant difference among the two groups with reference to the time required to achieve target Richmond Agitation Sedation score (RASS) of -1.The mean time to achieve target RASS of -1 in Dexmedetomidine group was 2.97 ± 1.278 hours whereas in Fentanyl group 6.29 ± 3.388 hours (p<.001 vhs) . The mean rate of infusion required to achieve target RASS of -1 in Dexmedetomidine group was 0.5 ± 0.1 mcg/kg/min and in Fentanyl group 2.7 ± 0.8266 mcg/kg/hr. The mean dose of Midazolam as rescue sedation was higher in Fentanyl group (2.29 ± 1.657) as compared to Dexmedetomidine (0.39 ± 1.202) mg (P < 0.01).

Conclusion: Dexmedetomidine group achieved adequate sedation in lesser time and in doses within the prescribed clinical range as compared to fentanyl group, in mechanically ventilated patients. Further, the 24 hour midazolam requirement was higher in fentanyl group.

Keywords: Dexmedetomidine, Fentanyl Infusion, Midazolam, Richmond Agitation Sedation score (RASS).

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INTRODUCTION

In mechanically ventilated patients in ICU will require sedation due to numerous reasons, such as, to prevent respiratory fighting and facilitate specific procedures such as tracheal aspiration, physiotherapy and catheter placements.[1] Nearly all such patients also experience

pain whether it is as a result of procedures performed on them, or because of the disease process itself. Therefore the consequences of inadequate sedation and analgesia can be substantial, including self-removal of important intraluminal tubes, vascular catheters, aggressive behavior by patient against care providers and poor patient – ventilator synchrony. Therefore sedation and analgesia becomes an integral part of treatment of patients in ICU instead of being necessary and minor issue.[2]

An ideal sedative agent must have the following qualities. It should have short half-life without cumulative effects on cardiorespiratory systems. It should be titratable and allow for rapid recovery once discontinued. Due to varied pharmacodynamics profile in ICU patients and given the variety of comorbidities in these patients, following a standard protocol for sedation is challenging.[4] Different drugs used for sedation traditionally are benzodiazepines (midazolam, diazepam), opiates (morphine, fentanyl, remifentanyl), propofol. Midazolam is widely used and has substituted diazepam because of its shorter half-life and the absence of active metabolites; however universal use of midazolam in critical medicine is limited because in some critically ill patients, its elimination can take too long.[3]

Opiates which are used more frequently have rapid onset, ease of titration, lack of accumulation of the parent drug or its metabolites, and low cost but also have, Side-effects which includes respiratory depression, hypotension, Sympatholysis (Volume depleted), vagally-mediated bradycardia, histamine release (morphine) ileus, depression of sensorium.[4]

No single agent currently used incorporates all the properties of an ideal sedative. However Dexmedetomidine a highly selective α2- adrenoceptor agonist that possesses most, if not all properties of an ideal sedative that preserves arousability, also includes analgesia, it has predictable hemodynamic effects and it does not cause respiratory depression. These virtues of Dexmedetomidine can lead to new approach to sedation during procedures, in intensive and critical care and weaning from mechanical ventilation.[5] We have done study to assess the effectiveness of the drug Dexmedetomidine in terms of time and the total dose required to achieve adequate sedation, when compared to the most commonly used drug Fentanyl for the first 24 hours in mechanically ventilated patients in ICU.

PATIENTS AND METHODS

A Prospective, randomized double blind study was conducted in patients admitted to Intensive care unit (ICU) at KMC group of hospitals Mangalore in year duration. (Jan2012 – Aug2013).

Ethics committee approval was obtained before the study. Patients fulfilling the study criteria were enrolled after an informed consent by patient's relatives or Bystanders.

Sample Size Calculation

According the past study the estimated mean and standard deviation of intubated patient receiving midazolam in Dexmedetomidine group is 4.9 and 5.9 and in control group is 23.7 and 27.5.

The sample size is calculated using G* power software for independent sample t-test to detect the difference in Dexmedetomidine and controls at1% level of significance and 85% power with effect size 0.95 then the minimum sample size in each group is 31.

Formula applied in the software.

$$n = \frac{\left(Z^2_{1-\alpha/2} + Z^2_{1-\beta}\right) * \sigma^2}{(\mu_1 - \mu_2)^2}$$

Hence the total number of sample size required in the study is 62.

Inclusion criteria included patients with SAPS-II score – < 59, aged 20-60 yrs and mechanically ventilated, with a RASS (Richmond Agitation Sedation Score) ranging + 4 to 0. Patients with SAPS-II score - > 60, RASS (Richmond Agitation Sedation Score) > - 4, Current or recent (within last 30 days) treatment with as well as contraindication or allergy to

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any of the study drugs, Gross obesity (over 60% above ideal body weight), Patients on inotropes / vasopressors were excluded from the study.

The critical status of the patient was evaluated on admission to the ICU. On the very same day, the SAPS II score of the patient was calculated on the basis of 17 variables and the SAPS II score sheet.[7]

Simple random sampling was used to select the respondent to the study. The respondent was selected based on the inclusion and exclusion criteria. Double blinded or masking was used to allocate the participants to a particular group. The third party envelop method was used to allocate the participants and assign them to the group. Third party used to randomly draw the envelop written with either of the two study group name for each participant. Where participants as well as investigator were not aware of the participants assigned to a particular group. The need for tracheal intubation was assessed and the anesthetic technique for intubation was left to decision of the ICU physician and, baseline measurements were recorded (blood pressure, heart rate, oxygen saturation, and respiratory rate). Regular assessments and increase of infusion rate as and when required were done by the on floor anesthesiologist/Intensivist.

An initial loading dose of Dexmedetomidine or fentanyl was given slowly to achieve a steady state plasma concentration. Dexmedetomidine loading dose of 1mcg/kg over 15 mins followed by Dexmedetomidine infusion with 200mcg in 48ml saline [1ml= 4mcg] started at 0.3mcg/kg/hr. Infusion dose range was titrated between 0.3 and 0.7mcg/kg/hr. Fentanyl loading dose of 2mcg/kg over 15 mins followed by infusion with 200mcg in 46ml saline [1ml=4mcg] started at 1mcg/kg/hr. Infusion dose range was adjusted between 1 and 3mcg/kg/hr. The sedation level was measured by RASS (Richmond Agitation Sedation Score) and maintained at -1 to -3.[22]

The Dexmedetomidine infusion rate was increased by 0.1mcg/kg/hr and fentanyl infusion by 0.5mcg/kg/hr. if Richmond Agitation sedation Score of -1 to -3 was not achieved or reduced by 0.1mcg/kg/hr and 0.5mcg/kg/hr respectively, if Richmond Agitation sedation Score of -4 or more was reached. If adequate sedation was not achieved at maximum Dexmedetomidine infusion rate of 0.7mcg/kg/hr and fentanyl infusion rate of 3mcg/kg/hr, midazolam 0.02mg/kg bolus was given as rescue sedation. RASS score was recorded hourly for the first 6 hrs and thereafter every 6 hrs for the next 24 hrs, and prior every infusion rate change.

Vital signs (Heart rate, blood pressure, respiratory rate, peripheral oxygen saturation) will be monitored every hour for the first 6 hrs and thereafter every 6 hr. for the next 24 hrs and prior every infusion rate change. Total doses of the study drugs and the rescue dose of Midazolam required will be recorded.

Cardiovascular adverse events were defined as a change in arterial pressure of >40% from the baseline, bradycardia <50 beats /min. hypotension was treated with Mephentermine 6mg boluses and bradycardia with injection atropine 0.6 mg intravenously. If either persisted in spite of treatment they were excluded from the study.

Data Analysis

Statistical analysis was performed using Mann-Whitney U-test and Median test for the study variables Age, Weight, SAPS-II, Time to RASS and infusion rate of the individual drug and the total dose of Midazolam required in 24 hours. Independent sample T-test was applied to study variables like MAP and heart rate. The Kolmogorov-Smirnov and Shapiro-Wilks test were applied to check the normality of the data.

RESULTS:

62 patients were enrolled in the study; of them all 62 were available for evaluation. Of the 62 patients with complete data, 31 received Dexmedetomidine (25 male, 6 female), and 31 received fentanyl (21 male, 10 female) in this study there was no statistical difference in the demographic data collected among the two groups except for the age.

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Table-1: Comparision of variables in both groups

	Measures	Age	Saps-Ii	Time To Rass (In Hrs)	Infusion Rate For Rass -I (Mcg/Kg/Hr)	Weight
Dexmedetomidine	N	31	31	31	31	31
	Mean	42.43	26.53	2.84	.490	55.485
	Std. Deviation	12.572	4.911	1.157	.0944	6.0526
	First Quartile	33.75	23.00	2.00	.400	50.000
	Median	48.00	27.00	2.00	.500	55.000
	Third Quartile	50.50	28.50	3.00	.500	60.000
Fentanyl	N	31	31	31	31	31
	Mean	51.81	27.84	6.41	2.845	56.032
	Std. Deviation	8.972	5.040	3.449	.6283	4.4757
	First Quartile	50.00	23.00	5.00	2.750	52.000
	Median	55.00	27.00	5.00	3.000	55.000
	Third Quartile	58.00	32.00	6.00	3.000	60.000

Table 1 shows the normality test of some of the study parameters like Age, Weight, SAPS-II, Time to RASS and infusion rate of RASS. But this table shows the data violating the assumptions of normality. Hence these parameters are not eligible for parametric test for comparison. Therefore we have to go for any other non-parametric test for group mean or median comparision. Table number four represents the summary measures mean, standard deviation, median and inter-quartile range of Age, Weight, SAPS-II, Time to RASS and infusion rate of RASS. But it was found that there was a marked difference between the two groups for the time required to achieve Richmond agitation sedation score (RASS) of -1.

Table-2: Time to Richmond agitation sedation score (RASS) of -1.

Group	N	Mean	Std. Deviation	t
Group I	31	2.97	1.278	5.109
Group II	31	6.29	3.388	p<.001 vhs

The mean time to achieve RASS of -1 in Dexmdetomidine was 2.97 ± 1.278 hours whereas in Fentanyl it was 6.29 ± 3.388 hours.(Table -2)

Table-3: Mean arterial pressure in both groups

Mean Arterial Pressure At Time Periods	Group	Mean	Std. Deviation	Mean Diff./Sign
0 Minutes	Dexmedetomidine	90.36	12.372	-0.059
	Fentanyl	90.42	13.507	P-Value = 0.987 (NS)
1 Hour	Dexmedetomidine	85.35	10.815	-3.968
	Fentanyl	89.32	12.831	P-Value = 0.193 (NS)
2 Hours	Dexmedetomidine	84.26	11.281	-3.710
	Fentanyl	87.97	10.477	P-Value = 0.185 (NS)
3 Hours	Dexmedetomidine	83.94	10.237	-4.387
	Fentanyl	88.32	11.757	P-Value = 0.122 (NS)
4 Hours	Dexmedetomidine	84.13	9.538	-2.226
	Fentanyl	86.35	11.786	P-Value = 0.417 (NS)
5 Hours	Dexmedetomidine	84.61	9.653	-1.677
	Fentanyl	86.29	10.543	P-Value = 0.516 (NS)
6 Hours	Dexmedetomidine	84.77	9.244	-1.290
	Fentanyl	86.06	10.020	P-Value = 0.600 (NS)

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12 Hours	Dexmedetomidine	84.29	8.088	-2.839
	Fentanyl	87.13	9.742	P-Value = 0.217 (NS)
18 Hours	Dexmedetomidine	85.10	8.400	-1.613
	Fentanyl	86.71	9.617	P-Value = 0.485 (NS)
24 Hours	Dexmedetomidine	85.06	7.164	-2.742
	Fentanyl	87.81	9.460	P-Value = 0.203 (NS)

Test conforms that there is no statistical significant difference between the mean score for MAP measured at all intermittent time interval among Dexmedetomidine and Fentanyl. From the table-3 it conforms that both the group are almost same in measure of MAP.

Table-4: Comparision of heart rate in both groups

Heart rate	Group	Mean	Std. Deviation	Mean Diff./Sign.
0 minutes	Dexmedetomidine	93.28	15.855	2.345
	Fentanyl	90.94	7.771	p-value = 0.472 (NS)
1 hour	Dexmedetomidine	95.23	14.350	2.774
	Fentanyl	92.45	7.814	p-value = 0.348 (NS)
2 hours	Dexmedetomidine	91.71	14.098	-1.774
	Fentanyl	93.48	6.999	p-value = 0.533 (NS)
3 hours	Dexmedetomidine	92.55	13.147	0.92
	Fentanyl	92.81	7.825	p-value = 0.321 (NS)
4 hours	Dexmedetomidine	93.74	13.317	2.323
	Fentanyl	91.42	6.937	p-value = 0.393 (NS)
5 hours	Dexmedetomidine	93.23	13.601	0.194
	Fentanyl	93.03	7.246	p-value = 0.944 (NS)
6 hours	Dexmedetomidine	93.71	14.584	-1.677
	Fentanyl	95.39	10.673	p-value = 0.607 (NS)
12 hours	Dexmedetomidine	92.71	15.619	0.516
	Fentanyl	92.19	6.300	p-value = 0.865 (NS)
18 hours	Dexmedetomidine	91.52	14.635	-0.903
	Fentanyl	92.42	6.308	p-value = 0.753 (NS)
24 hours	Dexmedetomidine	92.84	12.453	0.258
	Fentanyl	92.58	6.459	p-value = 0.919 (NS)

The results conforms that there is no significance difference between mean heart rate compared between Dexmedetomidine and Fentanyl.

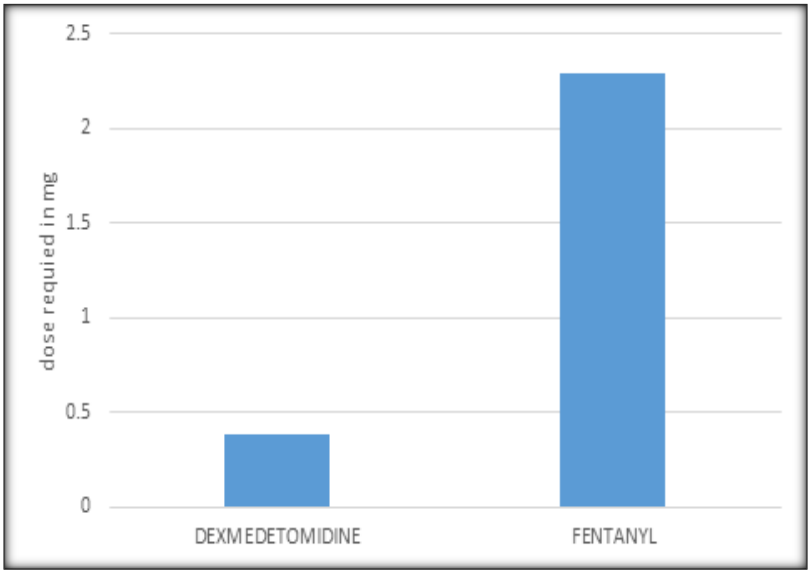

Figure-1: Dose requirement of midazolam in 24 hours in both groups

Results of Mann-Whiteney U-test and Median Test. Both the tests concludes that, there is significant difference between Modazolam requirement. Dexmedetomidine group on an average required almost nil whereas the Fentanyl required average of 2 mg within 24 hours.

Table-5: Hypothesis Test Summary for Age, SAPS-II, Time to RASS, Infusion rate for RASS-I and weight. Applied Mann-Whitney U-test for mean comparison and Median test for median comparison among the study groups

Null Hypothesis	p-value	Decision
The medians of AGE are the same across categories of Group.	.001[c]	Reject the null hypothesis.
The distribution of AGE is the same across categories of Group.	.000	Reject the null hypothesis.
The medians of SAPS-II are the same across categories of Group.	.889[c]	Retain the null hypothesis.
The distribution of SAPS-II is the same across categories of Group.	.353	Retain the null hypothesis.
The medians of TIME TO RASS (In Hrs) are the same across categories of Group.	.000[c]	Reject the null hypothesis.
The distribution of TIME TO RASS (In Hrs) is the same across categories of Group.	.000	Reject the null hypothesis.
The medians of INFUSION RATE FOR RASS - I (mcg/kg/hr) are the same across categories of Group.	.000[c]	Reject the null hypothesis.
The distribution of INFUSION RATE FOR RASS -I (mcg/kg/hr) is the same across categories of Group.	.000	Reject the null hypothesis.
The medians of WEIGHT are the same across categories of Group.	.608[c]	Retain the null hypothesis.
The distribution of WEIGHT is the same across categories of Group.	.643	Retain the null hypothesis.

With respect to the comparison of anthropometric measures there was no difference between the groups. With respect to the requirement of recue sedation the minimum requirement was for dexmedetomidine compared to Fantanyl group. There was a significant difference in the average infusion rate for RASS among Dexmedetomidine compared with Fantanyl with median infusion rate of 0.50 and 3 respectively which was statistically significant.

DISCUSSION

Dexmedetomedine is almost an ideal sedative and analgesic for ICU owing to its no respiratory depressive action and minimal delirium and agitation. The sedative and anxiolytic properties are due to stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus coeruleus in the brainstem. Its primary analgesic effects and potentiation of opioid-induced analgesics result from the activation of the α2 adrenergic receptors in the dorsal horn of the spinal cord and inhibition of substance P release.[8] Previous works by many authors have shown Dexmedetomidine to be an effective and safe agent for sedation in the ICU. Unlike previous studies, this study sought to compare Dexmedetomidine with Fentanyl, one of the established I.V. sedative agents used in ICU. Dexmedetomidine, has been assessed by numerous authors who have compared it with benzodiazepines and Propofol for sedation in ICU. But there is paucity of studies that compare it with Fentanyl. The principal end-points of this study were to see if there were any differences in the 24 hour Midazolam (rescue sedation) requirements in ICU patients receiving either Dexmedetomidine or fentanyl. And to see the time taken to achieve effective sedation which was defined as RASS 0 or -1. In this study Richmond agitation sedation score

(RASS) of -1 was achieved in both Dexmedetomidine and fentanyl group, yet the time taken to achieve RASS of -1 was statistically very highly significant with lesser time required in Dexmedetomidine group as compared to fentanyl group 2.97±1.278 vs. 6.29±3.388 ($p<0.001$). This was similar to Samia elbaradie et al. who compared Propofol Vs Dexmedetomedine for short term sedation in postoperative mechanically ventilated patients, used IV infusions of either Dexmedetomidine 0.2 -0.5 µg/kg/hr or propofopl 0.5-1mg/kg/h and reported that the Ramsay Sedation Score was 4.1±1 and 4± 0.9 for Propofol and Dexmedetomidine, respectively, ($p=0.59$). Total Fentanyl rescue dose in the Propofol group was higher (75±15µg) compared to (15±10.5µg) in the Dexmedetomidine group ($p=0.0045$).[9] This could be attributed to the pharmacological action of Dexmedetomidine on Central nervous system stimulating parasympathetic outflow and inhibiting sympathetic outflow in the brainstem which plays a prominent role in sedation and anxiolysis.[8] In this study the mean infusion rate for Dexmedetomidine to achieve effective sedation as defined by RASS of -1 was 0.5±0.1 µg/kg/h. This was consistent with Tobias et al. Study where Dexmedetomidine at 0.5 µg/kg/h not only provided effective sedation also reduced the rescue doses of morphine required.[10] Venn et al.[1] study concluded that Dexmedetomidine after an initial loading dose of 1 µg/kg/h over 10 min, followed by maintenance dose of 0.7 µg/kg/h provided adequate sedation, but they also reported that 11.88% of patients had adverse cardiovascular effects of either hypotension or bradycardia, which was during bolus infusion. Bloor et al. and Tobias et al.[11,12] confirmed the above findings that the potential adverse cardiac and hemodynamic effects of Dexmedetomidine, like bradycardia, sinus arrhythmia and hypotension, occurred mostly during the initial loading doses.[13,14] In this study no adverse hemodynamic events were observed, probably due to administration of bolus slowly over 15 minutes and careful titration of the further doses. In this study the mean requirement of Midazolam as rescue sedation in Dexmedetomidine group was 0.39±1.202mg which was 87% less compared to the fentanyl group who required a higher dose of midazolam 2.29±1.657mg ($p<0.001$). This was concordant to Venn at al.[15] Study who reported that intubated patients receiving Dexmedetomidine required 80% less midazolam [mean 4.9(5.8) µg/kg/hr vs. 23.7 (27.5) µg/kg/hr, $p < 0.0001$], and 50% less morphine [11.2 (13.4) µg/kg/hr vs. 21.5 (19.4) µg/kg/hr, p¼ 0.0006].

CONCLUSION

This study demonstrated the following potential benefits of Dexmedetomidine over the Fentanyl as a short term sedative for patients on mechanical ventilation in the ICU, this includes faster time to achieve adequate and effective sedation in doses within the prescribed clinical range and lesser 24 hours Midazolam requirement. Whereas it's hemodynamic profile was as comparable to that of Fentanyl. Thus, it is very reasonable to conclude Dexmedetomidine as an effective and safe sedative for routine use in mechanically ventilated patients in ICU. However further studies are required to further confirm the above observations made in this study.

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