European Journal of Molecular & Clinical Medicine (EJMCM)
ISSN: 2515-8260 Volume 09, Issue 04, 2022

Original research article

A Comparative Study of Propofol and Dexmedetomidine in ICU Sedation

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Abstract

Background: Sedation in Intensive Care patients is to reduce discomfort from interventions, increase tolerance to mechanical ventilation, prevent accidental removal of equipments, and reduce metabolic demands during cardiovascular and respiratory instability.

Methods: Sixty patients requiring post-operative mechanical ventilation admitted in intensive care unit were enrolled, in which 30 patients received Dexmedetomidine and remaining 30 patients received Propofol. All these patients were treated for the period of 24 h. The Ramsay sedation score,visual analogue scale (VAS), haemodynamic variables, were compared using independent sample t test.

Results: The mean total sedation requirement was 495+185 μg in Dexmedetomidine group and 55.7+21.7 mg in Propofol group. The mean hourly dose of sedative was 0.34+0.13 μg/kg/hr. in Dexmedetomidine group and 0.042+ 0.017 mg/kg/hr. in Propofol group. Patients in Propofol group required more number of rescue analgesics compared to Dexmedetomidine group.

Conclusion: Dexmedetomidine and Propofol are safe sedative agents for mechanically ventilated patients. Patient were easily aroused to co-operate without signs of irritations with lessrescue analgesia in the Dexmedetomidine group.

Keywords: Dexmedetomidine, intensive care unit sedation, Propofol

Introduction

Critically ill patients in the intensive care unit (ICU) are prone to many adverse clinical situations because of their coexisting disease or the ICU environment that produce harmful psychological and physiological changes. These changes are due to increased levels of catecholamines and other stress hormones. Confusion and agitation are common either due to altered mental state or pain, which can lead to unfavorable consequences on the outcome of these patients. They frequently need sedative and analgesics to facilitate their care. The critically ill patients in the ICU are subjected to pain and discomfort due to endotracheal

intubation and mechanical ventilation, intermittent physiotherapy, tracheal suction etc. Nursing procedures can also be unpleasant for them.[1]The noise level produced by themonitoring and support equipments are usually high and irritating and the lighting in the ICU surrounding are not pleasant rather it is unsoothing to the eyes, enhancing the adverse reactions.[2] Sedation for the patients in the ICU is used primarily to increase patient comfort through the provision of anxiolysis, analgesia and sedation to minimize resistance to mechanical ventilation. Sedation and analgesia are generally taken as one entity in intensive care unit and disproportionate use of sedative is associated with adverse outcomes including patient's restlessness, excessive sedation, longer ICU and hospital stay, an increased incidence of ventilator-associated pneumonia and greater hospital costs. An ideal sedative should provide a rapid onset of effect and a rapid recovery and should have a low profile to accumulate, leaving no residual effects. It should be easily titratable and should not disturb hemodynamic stability or minimally disturb it.[3]It is still better, if the sedative drug has some analgesic property. Non-pharmacological and pharmacological means can be used to provide comfort and safety to ICU patients. The former include communication, frequent reorientation and maintenance of a day-night cycle, noise reduction and ensuring ventilation synchrony. Pharmacologic agents include hypnotic-anxiolytics, opioids, antipsychotics or a combination of these. Over the years, many drugs have been tried for the purpose of sedation of ICU patients. As the history goes Althesin[4] and Etomidate [5-6] were tried for the purpose of sedation but soon fell out of favour because of anaphylactoid reaction and adrenal suppression caused by them. Inhalational agents like nitrous oxide[7] and isoflurane[8] had limited application in ICU as sedative agents because of ICU environmental pollution and difficulty in the scavenging process of these effects. The opioids were very useful for the purpose of analgesia but their dose of sedation and incidence of side effects were high.[9-11] For decades Gama amino butyric acid (GABA) receptor agonists (including Propofol and Benzodiazepines such as midazolam) have been the mostcommonly administered sedative drugs for ICU patients worldwide.[12] These medications provideadequate sedation but overdosing may be a possibility to achieve adequate sedation. Dexmedetomidine offers the advantage over Propofol due to its minimal effect on respiration , its analgesic efficacy, and its effect on the hemodynamics.[13,14] The ability to sedate and provide analgesia while maintaining patient arousability and respiratory function can lead to an entirely new approach to patient care and weaning from mechanical ventilation. Dexmedetomidine has been effectively used as a single agent or in combination with other drugs in ICU patients. conscious sedation, less likelihood of shivering, no tachyphylaxis or rebound hypertension phenomenon, infusion can be terminated abruptly, no risk of physical dependence, opioids sparing effect hencereduced opioids-related side effects like respiratory depression and nausea.

Objectives

To compare the efficacy of Propofol and Dexmedetomidine in short term ICUsedation in terms of following

Level of sedation using Ramsay Sedation score, Hemodynamic parameters, Number of patients requiring rescue sedative and analgesics using VAS Scale.

Review of Literature

ICU Sedation has been a long debated subject as there is lot of ongoing progress in selection of sedative drugs for ICU use. These patients are generally compromised and we want to use the drug with minimal side effect, so that the hemodynamic & other neurological functions are not disturbed further, at the same time taking advantage of its sedative properties. ICU admission is avery stressful condition where patient suffers from anxiety, pain, restlessness and insomnia. Unfortunately it is observed that pain & anxiety management are taken on a less priority basis. However, a growing awareness about stress management in ICU and the

increasing popularity of some modes of mechanical ventilation have highlighted the need for effective sedation, analgesia and occasionally neuromuscular paralysis.[15] Patients in the ICU are subjected to several adverse factors which may lead to physical and psychological stress. The psychological stress may result from fear, anxiety, depression, pain, discomfort and abnormal sleep patterns. In a study by Bion and Ledingham[16], anxiety and pain were the two most unpleasant experiences in ICU patients. Several non-pharmacological approaches have been applied in the Intensive Care Units to bring relief to patient's anxiety. This includes efforts to reduce the ICU background noise, lighting with day night variations, touching the patient, good communication, restoration of patient's privacy and flexible visiting policy. Other non-pharmacologic methods include relaxation techniques like hypnosis, music therapy, breathing instructions and massages. Sedation for patients on mechanical ventilation has become a necessary point of intensive patient care. Specific reasons to sedate the patients who are mechanically ventilated include increase tolerance to the presence of an endotracheal tube; inhibiting respiratory drive, reducing anxiety, facilitating sleep and improving synchronization with mechanical ventilator. Reducing anxiety helps in reducing oxygen consumption due to stress response and improves gas exchange. Hansen et al.[17] performed a postal survey of the practice of sedation in 265 US hospital medical ICUs in 1991. The average number of medications used for sedation in these ICUs was 4.9, ranging from one to nine different medications. The most frequent used medications were Morphine sulphate, Lorazepam and Diazepam. Intermittent intravenous bolus injections of Diazepam and Morphine have been used for ICU sedation. However Diazepam soon fell out of favour because of its veno-irritant property and a long elimination half-life of 30-90 hours. Desmethyl Diazepam, its principal metabolite had an even longer elimination half-life. Over a period of time, it was realized that continuous infusion of sedatives provided better patient sedation and ICU care by avoiding the peaks and valleys associated with the use of intermittent bolus doses. The use of intravenous infusions enhanced the ability to titrate the effect of newer rapid and short acting sedatives and analgesic drugs to produce the desired effect.Westfall et al. demonstrated the efficacy of continuous intravenous midazolam (1-15 mg/hr) in controlling agitation in patients following major surgery. Patients receiving midazolamin this dose range also demonstrated decreased total opioid requirement to achieve post-operativeanalgesia. This did not result in earlier ICU discharge. Venn RM et al. (2001) in his study said that patients sedated with Dexmedetomidine could be easily aroused to cooperate with procedure without showing irritation. Dexmedetomidine reduces the requirement for opioid analgesia and also may protect against myocardial ischaemia. McKeage K et al.[18] (2003) stated that the efficacy of Propofol in the sedation of adultsin the ICU is well established, and clinical trials have demonstrated a similar quality of sedation to midazolam. Because of a rapid distribution and clearance, the duration of action of Propofol isshort and recovery is rapid.

Material and methods

The study was carried out in patients who were admitted in the intensive care unit (ICU) of Nalanda medical college and Hospital Patna, Bihar. Study duration of Two years. Sixty adult patients aged 18 to 65 years who were on mechanical ventilation for a period of twenty-four hours were included in the study after informed consent was obtained patients preoperatively.

Exclusion Criteria

*Patients with neurological disorders
*Patients with known allergy to Propofol or Dexmedetomidine
*Pregnancy and Lactation
*Gross obesity
*Severe hepatic or renal disease

*Patient treated with α2 agonist or blockers during last 30 days

This study was prospective, randomised, single blinded study and conducted on 60 patients admitted in Intensive Care Unit who were on mechanical ventilation. Patients were randomly allocated into 2 groups by computerized randomisation, thirty in each group.

Group D - Dexmedetomidine group was received a loading dose of 1 mcg/kg over 10 min, followed by a maintenance dose of 0.5mcg/kg/hr. Group P - Propofol group was received a loading dose of 1mg/kg over 5 min, followed by a maintenance dose of 0.5mg/kg/hr. Prior informed written consent was obtained from patients and were counseled and trained about the visual analogue scale.

All the patients shifted to intensive care unit following surgery were electively ventilated for 24 hourswith synchronized intermittent artificial ventilation (SIMV) with pressure support mode. After admission to ICU patients were connected to multiparameter monitors recording ECG, NIBP (SBP,DBP,MAP) , $EtCo_2$ and Spo_2. All the patients were assessed at time interval at 0, 10 min, 30 min , 1 hour,4 hour, 8 hour,12 hour , 16 hour, 20 hour and 24 hour regarding the efficacy and overall quality of sedation and analgesia with ramsay sedation score and VAS . Further hemodynamic parameters were also noted atsame time intervals. The infusion of Dexmedetomidine or Propofol was discontinued after maximum period of 24 hours was reached, to allow weaning from mechanical ventilation.
All complications that could be related to the administration of the drugs were recorded. The total dose ofFentanyl administered over 24 hour as rescue analgesia and any changes in the infusion rate made were also recorded.

Results
Sixty patients were enrolled into the study. Thirty patients were in the Dexmedetomidine groupand thirty in the Propofol group.

Table 1: Demographic characteristics of study population

Parameters	Dexmedetomidine (n=30)	Propofol (n=30)
Age	47.6±12.41	40.1±15.70
Weight	54.60±6.74	55.07±6.11
Male : Female	22:8	20:10

The mean age in Dexmedetomidine group was 47.6±12.41 yrs and in Propofol group was 40.87±15.70. The mean weight was 54.60±6.74 and 55.07±6.11 kg respectively. The male to female ratio was 22:8 in Dexmedetomidine group and 20:10 in Propofol group. There was no difference between the two groups with regards to age, weight and sex.

Sedative and analgesic requirements
The mean total sedative requirement was 495±185 µg in Dexmedetomidine group and 55.7±21.7 mg in Propofol group. The mean hourly dose of sedative was 0.34±0.13µg/kg/hr in Dexmedetomidine group and 0.042±0.017 mg/kg/hr in Propofol group.

Table 2: Sedative requirements in both groups

Parameters	Dexmedetomidine	Propofol (n=30)

	(n=30)	
The mean total sedative requirement	495±185µg	55.7±21.7 mg
Hourly dose of sedative	0.51±0.06 µg/kg/hr	1.21±0.19mg/kg/hr

Table 3: Analgesic requirements in both the group

Parameters	**Dexmedetomidine (n=30)**	**Propofol (n=30)**
Number of patients who needed bolus dose of analgesics		
≤ 3 times	22	15
≥ 4 times	8	15
Total no. of bolus used	87	108

Patients in Propofol group required more number of bolus dose of analgesic compared to Dexmedetomidine group

Table 4:

Age in years	**Dexmedetomidine (n=30)**		**Propofol (n=30)**	
	No.	**%**	**No.**	**%**
18-19	2	6.7	3	10
20-29	1	3.3	8	26.7
30-39	2	6.7	3	10
40-49	10	33.3	3	10
50-59	10	33.3	10	33.3
60-65	5	16.7	3	10

The mean heart rate at the start of infusion was 116.50±14.26 bpm in Dexmedetomidine group and 115.77±12.99 in Propofol group. Following the start of infusion heart rate was lowered in both the groups. The lowest heart rate in both groups was observed at 24 hrs of infusion. At the end of 24 hr, the mean heart rate in Dexmedetomidine group was 94.17 and that in Propofol group was 107.13. The heart rate was lowered to a greater extent in Dexmedetomidine group than in Propofol group at the end of 24 hr of infusion. This was however statistically not significant.

Table 5:

HR (beats per minute)	Dexmedetomidine		Propofol		P- value
	Mean	SD	Mean	SD	
Base line	116.50	14.26	115.77	12.99	>0.05
At 10 min	112.93	14.30	112.77	13.10	>0.05
At 30 min	110.87	14.46	111.23	13.27	>0.05
At 1 hr	110.67	14.90	111.53	13.10	>0.05
At 4 hr	111.00	15.40	111.03	13.27	>0.05
At 8 hr	107.97	14.54	111.50	12.98	<0.001
At 12 hr	103.77	14.37	110.00	12.85	<0.05
At 16 hr	100.80	14.01	108.43	12.96	<0.05
At 20 hr	98.10	13.82	109.30	12.85	<0.001
At 24 hr	94.17	13.31	107.13	12.89	<0.001

The baseline SBP (mm Hg) in the Dexmedetomidine and Propofol groups was 132.70 mm Hg and 133.80 mm Hg respectively. At one hour from start of infusion, the corresponding values were 123.00 and 127.00mm Hg in Dexmedetomidine and Propofol group respectively. The

maximum fall in SBP in Dexmedetomidine group was 118.23 mm Hg at 24 hrs from start of infusion. The maximum fall in SBP in Propofol group was 123.00 at 12 hr of infusion. While comparing the incidence of in adequate and excessive sedation in both the groups, we observed a similar trend in inadequate sedation in both the groups. However the patients in Dexmedetomidine group remained in excessive sedation on considerably fewer occasions compared to patients in Propofol group. This was considered statistically significant. The patients in Propofol group needed more frequent changes in their infusion rate than patients in Dexmedetomidine group.

The mean dose of fentanyl requirement to achieve adequate analgesia was 61.00±19.89 mcg in Group D and that of mean Fentanyl requirement in group P was 131.33 ± 20.63mcg. Statistcal evaluation between the groups showed a statistically significant reduction in the dose of Fentanylrequirement in Group D compared to Group P ($p<0.001$).

Recovery from sedation
The recovery from sedation was significantly rapid in Dexmedetomidine group. Patients in Dexmedetomidine group were easily aroused and gripped observer`s hand earlier after stoppageof sedation. In contrast patients in the propofol group took a longer time to achieve eye openingon command and gripped observer`s hand.

Adverse effects:
We did not observe any other adverse effects attributable to Dexmedetomidine or Propofol during the study period. No patients in either group had hypotension attributable to the sedative to a degree which required fluid or inotrope administration.

Discussion
ICU sedation becomes an integral part in ICU management. Many drugs have been used for this purpose; the earliest drugs which have used were from the Benzodiazepine group like Diazepam or Lorazepam. Propofol was approved by FDA in 1989 for introduction into clinical practice as a hypnoticagent for induction and maintenance of anaesthesia. However, soon after its sedative, anxiolytic and amnesic effect depends its field of use and Propofol was approved by FDA for use for purpose of ICU sedation in 1993. It becomes the standard choice for sedation in ICU due to its rapid onset of action and shorter elimination life. The disadvantages were noticed that it had variable duration of action in critically ill patients, even prolonged recovery time after discontinuation of Propofol infusion have been reported. Dexmedetomidine is the newer drug which now being approved for ICU sedation. It produces analgesic effect by an action on α-2 receptor within the locus cerulus and the spinal cord. Stimulation of α-2 adrenergic receptors at this site reduces central sympathetic output, resultingin increased firing of inhibitory neurons. The presence of Dexmedetomidine at α-2 adrenergic receptors at substantia gelatinosa of the dorsal horn of the spinal cord modulates release of substance P to produce analgesic effects, and their activation inhibits nociception. Venn et al (2001) in their study found that patients sedated with Dexmedetomidine had optimal level of sedation & no respiratory depression than compared with Propofol. Ahmed et al (2013) concluded that ICU patients receiving prolonged mechanical ventilation, Dexmedetomidine was not inferior to Propofol in maintaining light to moderate sedation with minimal respiratory depression. Dexmedetomidine reduced duration of mechanical ventilation compared with Propofol. Shah et al (2014) found that Dexmedetomidine is safe and acceptable ICU sedative agentwhen both the clinician's and patient's perspectives are considered. Depth of sedation is similar to that given by Propofol but with no respiratory depression seen in Dexmedetomidine sedated patients. Guinter et al (2010)[19] in his study said that

Dexmedetomidine was efficacious in achieving sedation goals with only mild respiratory depression as compared with Propofol. Barr et al (2013) said that Dexmedetomidine produces a pattern of sedation that differs considerably from other sedative agents. Patients sedated with Dexmedetomidine are more easily arousable and interactive, with minimal respiratory depression. Siobal et al (2006) in his study revealed that Dexmedetomidine appears to maintain adequate sedation without hemodynamic instability or respiratory-drive depression, and thus may facilitateextubation in agitated difficult-to-wean patients. Curtis et al (2013) in their study concluded that Dexmedetomidine-based sedation resulted in achievement of early extubation more frequently than Propofol-based sedation. Mean postoperative time to extubation and average hospital LOS were shorter with Dexmedetomidine- based sedation and met a statistical level of significance. There was no difference in ICU-LOS orin-hospital mortality between the two groups. Total hospital charges were similar, although slightly higher in the Propofol group. As compared with above mentioned studies, our study also concludes that Dexmedetomidine hadsmooth recovery, early weaning practice from mechanical ventilator, early extubation from sedation as compared to Propofol. This also leads to a potentially a shorter ICU stay and average less hospital charges than seen with Propofol sedated patients. These properties combined with smooth and adequate sedation with minimal respiratory depression, ability of patient to communicate, easily aroused to co-operate with ICU procedures and analgesics sparing[20] effects makes Dexmedetomidine a better choice than traditional sedatives for icu sedation

Conclusion

Dexmedetomidine infusion is found to be a superior sedative and analgesic drug in comparison to Propofol infusion in patients on mechanical ventilation as per Ramsay sedation score and Visual analogue scale. Further it was concluded that requirement of rescue sedation and analgesia was less with Dexmedetomidine group when compared to Propofol group. There are no clinically significant changes in hemodyanamic parameters between the Dexmedetomidine and Propofol group. There were no major adverse effects noted in both the groups.

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