www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i4.64

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Article

Comparative Study of Propofol and Midazolam Infusion for Sedation in ICU Patients

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Abstract
Background: *In the modern practice of anaesthesia and intensive care, the intensivist are very concerned about the stressful environment in which patients often experience anxiety, pain and inability to sleep. 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.*
Material & Methods: *The study was carried out in patients admitted in the Intensive Care Unit of IGIMS, PATNA. After approval from ethical committee Forty adult patients, between ASA I to III, who were intubated and expected to be mechanically ventilated for a period of approximately twenty four hours were included in the study*
Results: *We compared the quality of sedation using Ramsay sedation score. At the start of the study 8 patients in propofol group and 6 patient in midazolam group were agitated (RSS = 1). By one hour from start of sedation the numbers had decreased to only 1 patient in propofol group whereas 3 patients in midazolam group were still agitated. Eighteen patients in the propofol group had a baseline Ramsay score of less than optimal (RSS = 3), compared to 16 patients in midazolam group. By end of 1 hr from start of infusion, 9 patients in propofol group had achieved the sedation score of 3 in contrast to only 5 patients in midazolam group.*
Conclusion: *The conclusions of our study is Both propofol and midazolam were effective in providing adequate level of sedation. However propofol provided significantly higher occasions of optimal sedation compared to midazolam. Weaning from mechanical ventilation was significantly better in propofol.*

Introduction

In the modern practice of anaesthesia and intensive care, the intensivist are very concerned about the stressful environment in which patients often experience anxiety, pain and inability to sleep. Critically ill patients in the intensive care unit are subjected to multiple adverse stimuli inherit in their illness and their environment that produce harmful psychological and physiological changes. These changes are due to increased levels of catecholamines and other stress hormones, combined with blunting of normal immunological reactivity. Therefore it is duty of physician to mitigate these adverse influences by appropriate management of patient's state of arousal and pain.

The critically ill patients in the ICU is subjected to pain and discomfort due to endotracheal intubation and mechanical ventilation, intermittent physiotherapy, tracheal suction etc. Nursing procedures can also be very distressing to the patients. The noise level produced by the

monitoring and support equipments are usually high and irritating, and the lighting in the ICU surrounding are not pleasant rather unsoothing to the eyes, enhancing the hostile reactions. 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. The desired drugs and agents should be needs that they cause no adverse haemodynamic or other physiological changes this effect should be minimized.

The ideal sedative agents in ICU should have minimal depressant effects on the cardiovascular and respiratory system. It should not influence the biodegradation of other drugs. IT should be eliminated by different mode of excretion without disturbing their normal physiology and should have shorter elimination half life without active metabolites. The ideal level of sedation should alleviate patients discomfort and facilitate assessment of patients neurological and pulmonary status without compromising his condition.

In recent years, Midazolam, a water soluble, short acting benzodiazepine has been extensively used for the purpose of ICU sediation. However prolonged use of Midazolam has been associated with delayed elimination, accumulation and prolonged sedation after withdrawal of the drug especially in elderly patients.

Assumulation of Midazolam after prolonged sedation has been observed in critically ill patients like:

(i) Septic shock
(ii) Low cardiac output
(iii) Low plasma albumin concentration
(iv) Renal and multiple organ failure and
(v) After major abdominal surgery.

This phenomenon is best explained by decreased liver blood flow since this drug has very high hepatic extraction index.

Propofol (2,6 di-iso propylphenol) was introduced into clinical practices an anaesthetic agent in 1989 after FAD approval. Propofol has many qualities that make it an attractive alternative for sedation of mechanically ventilated patients in the ICU. It has a rapid onset and short duration of action and its metabolism does not appear to be affected by mild renal or hepatic dysfunction. Recovery from sedation is rapid even after prolonged infusions. The reductions in systemic vascular resistance and heart rate are associated with propofol, it also counteracts the pain and stress induced sympathetic responses. Additionally propofol has anticonvulsant properties and is associated with good hemodynamic stability.

Propofol has been shown to be effective agent for the sedation of mechanically ventilated patients it the ICU. Including post surgical general medical patients and patients with head trauma. In short term (<3 days) studies in general medical or post surgical patients, propofol provided a quality of sedation at least as good or even better than that provided by Midazolam and tended to produce a faster recovery than Midazolam, as judged by time to spontaneous ventilation and time to extubation following termination of its infusion.

Propofol preparation as 1% emulsion contains 10% soyabean oil, 2.25% glycerol, 1.2% purified egg phosphatide and 0.005% di-sodium editade was added for retard of growth of microorganism, the use of propofol for long term sedation carries the potential for hyperlipidemia attributable to its lipid content and the development of tolerance to its sedative effects. Moreover there is a need to prepare propofol aseptically and immediately prior to administration discard. The unused portions have to be discarded after 6 hours, to reduce the risk of bacterial contamination.

There seems to be a seamless transition from mild to deep sedation and from there to a state indistinguishable from general anaesthesia (GA). Oversedation may expose the patients to the risk of cardio-respiratory depression and loss of airway control. So, sedation warrants proper monitoring of the patient, especially in paediatric, elderly, and obese patients. Common methods of monitoring the depth of sedation are patient based (e.g., visual analogue scale), observer based (e.g., observer's assessment of awareness/sedation (OAA/S) score)

and machine based (e.g., Bispectral index score (BIS). The OAA/S score has the disadvantage of frequent patient stimulation, which may alter the actual level of sedation. However, the BIS score gives a continuous objective assessment with minimal stimulation to patient. BIS monitor produces a single number to indicate the level of sedation. The derivation of the scale used by this electroencephalogram (EEG) based monitor is in fact not linear. Naturally, the score of this monitor cannot be expected to follow the progression of sedation linearly.

Comparison between the time to onset of sedation measured with BIS and OAA/S scores and finding any correlation thereon would help to understand the sedation properties of these drugs and to use these in a better way where sophisticated instrumental monitoring is not available. Furthermore, it may open up a new dimension for future research. Hence, the present study was designed to compare propofol and midazolam in respect with the time to onset of sedation assessed with BIS monitor and OAA/S score. It was hypothesized that both the scores would tally during the onset of sedation. An endeavour was given to find out any correlation between the BIS score and OAA/S score during the onset of sedation with each drug.

In our study we tried to compare the quality of sedation between continuous infusion of Midazolam and propofol when combined with infusion of morphine as analgesia in ventilated patients in ICU.

Aims & Objectives

The main objectives of this study is to

1. Compare the effectiveness of sedation with propofol and midazolam in critically ill mechanically ventilated patients in our ICU.
2. Time required for recovery from sedative effects of both the drugs.

Define the economic implications of the continuous infusion of both the drugs.

Materials and Methods

The study was carried out in patients admitted in the Intensive Care Unit of IGIMS, PATNA. Forty adult patients, between ASA I to III, who were intubated and expected to be mechanically ventilated for a period of approximately twenty four hours were included in the study

Exclusion Criteria

1. Known or suspected allergy to propofol or midazolam
2. Severe hepatic or renal disease
3. Deranged coagulation profile,
4. Requirement of muscle relaxants, with the exception of succinylcholine for intubation in the ICU and
5. Receiving total parenteral nutrition.

The patients were randomly divided into two groups. One group comprised of patients receiving propofol by continuous infusion and the other group comprised of patients receiving midazolam by continuous infusion. Both the groups received morphine infusion for analgesia. After the baseline vital parameters were recorded, the patients in the propofol group received a continuous infusion of propofol starting at a rate of 1 mg/kg/hour. Patients in the midazolam group received continuous infusion starting at a rate of 0.03 mg/kg/hrour. Both the groups received morphine infusion of 0.02 mg/kg/hour. No bolus dose of midazolam or propofol was administered as a part of the study. However whenever the clinical situation demanded, boluses of the drugs were administered. Midazolam was given in boluses of 2 mg each and propofol was given in boluses of 20 mg. Morphine was administered in boluses of 2 mg when clinically considered appropriate.

Throughout the study, the efficacy of sedation was assessed by using the Ramsay sedation score. Three levels of sedation were considered: (1) Adequate, when the sedation level was grade 2, 3, 4 or 5 on Ramsay scale (2) Insufficient when the sedation level was grate 1 and (3) excessive, when the sedation level was grade 6 on Ramsay scale. Whenever the sedation was not considered

adequate, the rate of continuous infusion of the sedative was increased or decreased by 10% at a time and the efficiacy of sedation was reassessed 15 minutes later. The aim of our study was to achieve a target sedation of grade 3 on Ramsay scale for most of the sedation hours. The efficacy of analgesia was monitored using the visual analogue scale and the Hartepool pain score. The aim of our study was to have a comfortable patient with no pain at rest and minimal pain at moment which corresponds to the Hartepool pain score of 2. Pain was considered as the first cause of inadequate sedation and was treated first before increasing the level of sedation.

All the patients were mechanically ventilated with oxygen enriched air. The mode of ventilation was pressure support ventilation (PSV) and continuous positive airway disease (CPAP) with or without synchronized intermittent mandatory ventilation (SIMV) mode. The ventilatory parameters were adjusted so as to maintain normocapnia and a partial pressure of oxygen in arterial blood (PaO_2) between 75 to 100 mmHg. In patients considered fit for weaning from mechanical ventilation, the SIMV rate was gradually decreased to zero, while patients were still sedated. The total duration of SIMV mode and the number of times the patients were successfully weaned from mechanical ventilation was recorded.

The respiratory rate, spontaneous tidal volume and expired minute volume and the expired carbon-dioxide concentration was recorded every hourly throughout the period of study.

At the end of each shift, the nurse attending the patient was interviewed regarding the efficacy and overall quality of sedation. They were requested to score on a linear visual analog scale from 1 (totally unsatisfactory) to 10 (optimal) based on the patients response to endotracheal tube suctioning, dressing changes, positioning and reaction to ICU environment.

The infusion of propofol or midazolam was discontinued when clinical assessment showed that sedation was no longer required, or when a maximum period of 24 hours was reached, to allow assessment of post sedation responsiveness. When sedation was required thereafter, the usual regimen of our ICU was followed. Post sedation responsiveness was assessed by recording the time from stopping of sedation, until the patient could obey a simple but specific command. The time to eye opening and hand grip on command were recorded to assess this parameter. The assessment was made every 3 minutes for the first 30 minutes and then every 10 minutes thereafter.

Weaning was attempted when arterial oxygen tension was 75 mmHg or more with an inspired oxygen concentration of 40% or less. When considered clinically appropriate, the patient was disconnected from ventilator and oxygen enriched air was provided by a T-piece.

Monitoring

The following parameters were maintained during the study.

1) Continuous monitoring 2-lead electrocardiogram, heart rate, systolic, diastolic and mean blood pressure, central venous pressure and percentage saturation of hemoglobin.
2) Resporatory parameters like respiratory rate, spontaneous tidal volume, expired minute volume and tidal carbon dioxide concentration were recorded at hourly interval.
3) Arterial blood gas analysis was done at start of sedation and every 8 hourly thereafter or more often when clinically indicated.
4) The renal function tests and liver function tests were done at admission of the patient into the ICU and twenty four hours after end of sedation protocol. The hemoglobin, urea, blood sugar and serum sodium and potassium were evaluated every twelve hourly as a part of our ICU protocol.
5) The Ramsay sedation score and Hartepool pain score were recorded every hourly and before all ICU procedures like suctioning of the endotracheal tube, chest,

physiotherapy, positioning and wound dressing.

6) Urine output was recorded every hourly. Any change in the colour of urine in patients receiving propofol was also looked for.

All complications that could be related to the administration of the drugs were recorded. The total dose of propofol, midazolam and morphine used was calculated. The number of times the boluses of these drugs administered and changes in the infusion rate made were also recorded.

For cost analysis of sedation, the cost per milligram of propofol and midazolam was calculated. The total cost of sedatives used for sedation was calculated from it, the number of hours of sedation for comparison between the two groups.

Observations

Patient data

Forty patients were entered into this study. Twenty patients were in the midazolam group and twenty patients were in the propofol group.

Table -1

Parameters	Propofol (n=20)	Midazolam (n=20)
1. Age[a]	38.95±13.42 (14-64)	38.5±15.06 (15-62)
2. Weight[a]	59.10±10.07 (40-75)	56.3±12.24 (35-80)
3. ASA grades I/II/III	8/9/3	11/7/2
4. Male : Female	13 : 7	14 : 6
5. Types of surgery		
- General Surgery	11	14
- Ent	3	2
- Gynaecological	3	3
- Orthopaedic Surgery	2	1
- Urology	1	0
- Ophthalmic Surgery	0	0

Table 1 showing demographic characteristics of study population. The patient population in both the groups were found similar with regards to the above parameters [a] = values indicate mean ± SD. Values in parenthesis indicate ranges.

Sedatives and analgesic requirements

Table 2

Parameters	Propofol (n=20)	Midazolam (n=20)
1. Total dose of sedative in 24 hr (in mg)	1722.3±345.23 (1000-2308)	55.75±21.75 (26-128)
2. Hourly dose of sedative (in mg/kg/hr)	1.21±0.19 (0.83-1.56)	0.042±0.017 (0.025-0.047)
3. No. of patients who needed bolus dose of sedative (n 24 hrs)		
≤ 3 times	15	13
≥ 4 times	5	7
4. Total number of boluses used	42	52
5. No. of patients in whom the rate of infusion had to be changed in 24 hrs		
- < 2 times	2	0
- 2 – 5 times	9	11
- ≥ 6 times	9	9
6. Mean number of boluses used in each patients	2.10±1.65 (0.5)	2.20±1.58 (0-5)

Table 2 showing sedative requirements in both the groups. Patients in propofol and midazolam group required similar number of boluses. Values indicate mean ±SD. Values in parenthesis indicate ranges.

Table 3

Parameters	Propofol (n=20)	Midazolam (n=20)
1. Total dose of morphine in 24 hr (in mg)	35.5±6.6 (28-55	36.0±8.51 (19-54)
2. Hourly dose of morphine (in mg/kg/hr)	0.025±0.003 (0.020-0.032)	0.027±0.005 (0.021-0.047)
3. No. of patients who needed bolus dose of analgesics ≤ 3 times ≥ 4 times	 14 6	 10 10
4. Total number of boluses used	58	69
5. No. of boluses of morphine used in each patient	3.0±1.38 (1-6)	3.55±1.64 (1-6)

Systolic Blood Pressure

The baseline systolic blood pressure in propofol and midazolam group were 132.7 ±15.0 and 136.0 ± 16.8 mmHg respectively.

Table 4

Time	Baseline	10min	30min	1hr	4hr	8hr	12hr	16hr	20hr	24hr
Propofol Group	132.75± 15.05	124.6± 13.93	122.25± 15.7	123± 15.01	123.2± 14.38	117.35± 14.28	118± 11.18	121.4± 13.8	121± 12.17	118.2± 10.84
Midazolam Group	136.5± 16.83	128.6± 15.76	124.25± 18.44	126.75± 16.47	129.7± 13.36	124.8± 20.35	123.4± 15.76	125.3± 15.97	121.85± 13.6	122.2± 10.97

Table 4 showing systolic blood pressure in mmHg in both the groups. The change from baseline over 24 hours was found to be statistically significant in both the groups ($p<0.001$). Values indicate (mean±SD). Values in parenthesis indicate ranges.

Mean arterial pressure

The mean arterial pressure at the start of the study was 97.2 ± 11.1 mmHg in propofol group and 98.8 ± 12.2 mmHg in midazolam group. The mean arterial pressure fell after start of infusion in both the groups

Table 5

Time	Baseline	10min	30min	1hr	4hr	8hr	12hr	16hr	20hr	24hr
Propofol Group	97.2± 11.11	92.55± 10.09	90.15± 11.61	92.6± 10.58	92.4± 12.97	90.9± 12.28	89.75± 11.39	89.4± 10.42	88.45± 11.95	89.85± 9.8
Midazolam Group	98.8± 12.2	93.05± 10.23	91.45± 11.27	93± 11.94	94.4± 11.04	93.15± 14.26	91.85± 14.19	92.1± 11.89	91.05± 12.48	93± 10.82

Table 5 showing mean arterial pressure in both the groups. The fall from baseline in both the groups over the period of study was found to be statistically significant. ($p=0.009$ in propofol group and $p=0.001$ in midazolam group). Values indicate mean ±SD. Values in parenthesis indicate ranges.

Central venous pressure

The baseline central venous pressure (CVP) was 10.5 ± 3.0 mmHg in propofol group and 10.7 ± 2.6 mmHg in midazolam group. In both the groups there was a significant fall in CVP with time the fall being greater in propofol group ($p<0.001$ in propofol group and $p=0.001$ in midazolam group).

Table 6

Time	Baseline	30min	1hr	4hr	8hr	12hr	16hr	20hr	24hr
Propofol Group	10.55± 2.98	8.9± 2.53	8.85± 1.98	9.6± 2.46	9.8± 2.26	10.3± 2.20	10.4± 3	9.45± 2.16	10± 2.34
Midazolam Group	10.75± 2.57	9.9± 2.43	9.55± 2.34	10.4± 2.23	10.45± 2.50	11.25± 2.61	92.1± 11.89	10.05± 2.37	10.85± 2.03

Table 6 showing central venous pressure in both the groups. With progression of time the fall from baseline value was statistically significant in both the groups the fall being greater in propofol group ($p<0.001$ in propofol group and $p=0.001$ in midazolam group). Values indicate mean ±SD.

Heart rate

Table 7

Time	Baseline	10min	30min	1hr	4hr	8hr	12hr	16hr	20hr	24hr
Propofol Group	115.15± 23.92	109.8± 23.11	109.15± 23.78	109.7± 24.87	110± 25.39	106.9± 24.38	105.75± 25.14	107.45± 23.31	106.35± 21.56	105.75± 22.74
Midazolam Group	113.75± 23.8	111.7± 22.29	111.05± 20.68	111.5± 20.6	111.1± 21.3	112.7± 24.62	109.25± 23.9	108.15± 24.7	110.85± 21.12	111.95± 20.07

Table 7 showing heart rate per min. in both the groups. The change in heart rate was similar in both the groups and was not found to be statistically significant. Values indicate mean ±SD.

Respiration and weaning

Eighteen patients in both the groups were on SIMV mode of ventilation at the start of infusion. With the progress of time, weaning attempts were made in both the groups whenever the patient was considered clinically fit for weaning and when arterial oxygen tension was 75 mmHg or more with a inspired oxygen concentration of 40% or less. The mean baseline spontaneous respiratory rate at the start of infusion was 22.1± 4.8 breaths per minute in propofol group and 22.0 ± 6.0 breaths per minute iin midazolam group. The lowest respiratory rate in propofol group was observed after 14 hour from start of infusion when it was 18.9 breaths per minute (14.5% below the baseline values). The lowest respiratory rate in midazolam group was 20.3 breaths per minute (8.1% fall from baseline). At the end of the study, the respiratory rate in both the groups were similar; it was 20.6 breaths per minute compared to 20.5 per min in midazolam group (6.8% fall from baseline in both the groups). These values did not reach statistical significance when compared using repeated analysis of variance (RANOVA).

The total duration of SIMV mode of ventilation was 15.65 ± 8.41 hours in propofol group and 18.55 ± 8.34 hrs in midazolam group ($p = 0.17$). All the patients in both the groups maintained a percentage saturation of oxygen above 95% and end tidal carbon dioxide concentration between 40-45 mmHg while on spontaneous breathing throughout the period of study. The total amount of morphine sed during the study period was similar in both the groups. Weaning attempts were made in 18 patients in propofol groups and 16 patients in midazolam group. Eleven patients in propofol groups were successfully weaned off SIMV mode during the 24 hours study period compared to only 4 patients in midazolam group. This was considered statistically significant ($p<0.05$). At the end of the study 7 patients in propofol group were in SIMV mode in contrast to 12 patients in midazolam group.

Table 8 showing spontaneous respiratory rate in both the groups. The change in respiratory rate was similar in both the groups and was not found to be statistically significant. Values indicate mean ±SD.

Table 8

Time	Baseline	10min	30min	1hr	4hr	8hr	12hr	16hr	20hr	24hr
Propofol Group	22.10± 4.79	21.15± 5.53	19.95± 5.03	20.10± 5.47	19.85± 5.62	19.75± 5.75	19.35± 4.21	19.10± 2.85	19.95± 4.37	20.6± 4.15
Midazolam Group	22± 5.98	20.38± 4.56	20.2± 4.43	20.5± 4.58	21.85± 4.98	20.75± 5.13	21.15± 4.76	20.8± 4.29	20.35± 3.37	20.5± 3.52

Table 9 showing weaning parameters in the study population. Patients in midazolam group remained on SIMV mode for a significantly longer time compared to propofol group. More number of patients in propofol group were weaned successfully than patients in midazolam group (<0.05).

Table 9

Parameters	Propofol (n=20)	Midazolam (n=20)
1. Number of patients on SIMV mode at start of study	18	18
2. Number of patients on SIMV mode at end of study	7	12
3. Number of patients in whom weaning was attempted	18	16
4. Number of patients successfully weaned off SIMV mode in 24 hours	11	4
5. Number of patients who were extubated before 24 hrs	4	2
6. Total number of weaning attempts	51	38

Quality of sedation

We compared the quality of sedation using Ramsay sedation score. At the start of the study 8 patients in propofol group and 6 patient in midazolam group were agitated (RSS = 1). By one hour from start of sedation the numbers had decreased to only 1 patient in propofol group whereas 3 patients in midazolam group were still agitated. Eighteen patients in the propofol group had a baseline Ramsay score of less than optimal (RSS = 3), compared to 16 patients in midazolam group. By end of 1 hr from start of infusion, 9 patients in propofol group had achieved the sedation score of 3 in contrast to only 5 patients in midazolam group.

With comparing the incidence of inadequate and excessive sedation in both the groups, we observed a similar trend in inadequate sedation in both the groups. However the patients in propofol group remained in excessive sedation on considerably fewer occasions compared to patients inmidazolam group. This was considered statistically significant. The patients inmidazolam group needed more frequent change in their infusion rate than patients in propofol group.

Table 10

Parameters	Propofol (n=20)	Midazolam (n=20)
1. Number of patients who were agitated (RSS=1) at the start of infusion	8	6
2. Number of patients who were still agitated (RSS=1) by 1 hour of start of infusion	1	3
3. Number of patients who had a RSS<3 at start of infusion	18	16
4. Number of patients who had achieved a RSS of 3 by 1 hour of start of infusion	9	5

Table 10 showing sedation parameters in the sudy population. More number of patients in propofol group achieved adequate sedation score by first hour than patients in midazolam group. RSS = Ramsay Sedation Score.

Table 11

Time Period	Propofol Group (n = 20)			Midazolam Group (n = 20)		
	Agitated (RSS=1)	Adequate (RSS=2-5)	Excessive (RSS=6)	Agitated (RSS=1)	Adequate (RSS=2-5)	Excessive (RSS=6)
Baseline	8	12	0	6	14	0
1 hr	1	19	0	2	17	0
4 hr	0	20	0	2	18	0
8 hr	0	20	0	1	18	1
12 hr	0	19	1	0	18	2
16 hr	0	20	0	1	17	2
20 hr	0	19	1	0	18	2
24 hr	0	20	0	0	20	0

Table 11 showing incidence of agitation, adequate sedation and excessive sedation in the study population. While more number of patients in propofol group were agitated at the start of infusion, adequate sedation was achieved in more number of patients in propofol group compared to midazolam group by 1 hr of start of sedation. RSS = Ramsay Sedation Score.

Table 12

Parameters	Propofol (n=20)	Midazolam (n=20)
No of patients who had inadequate sedation (RSS=1) during 24 hrs on		
• No occasion	8	10
• Less than 3 occasions	8	7
• 3 or more occasions	4	3
No. of patients who had excessive sedation (RSS=6) during 24 hrs on		
• No occasion	11	4
• Less than 3 occasions	7	9
• 3 or more occasions	2	7

Table 12 showing comparison of inadequate and excessive sedation in both the groups. Using chi-square for linear trend analysis, the distribution of inadequate sedation was found to be similar between both the groups. However, patients in midazolam group tended to have excessive sedation more often than patients in propofol group. This was found to be statistically significant (p=0.036)* RSS=Ramsay Sedation Score.

Table 13

Ramsay Sedation Score	Total No. of observations in Propofol Group (n=480)	Total No. of observations in Midazolam Group (n=480)
RSS=1 (Inadequate)	23	31
RSS=2	75	87
RSS=3 (Optimal)	183	137
RSS=4	140	149
RSS=5	48	57
RSS=6 (Excessive)	11	19
RSS=2 to 5 (Adequate)	446	430

Table 13 showing no. of observations made in each Ramsay Score between both the groups. More no. of observation were made at target score of 3 and acceptable score of 2-5 in patients in Propofol Group than Midazolam Group. RSS=Ramsay Sedation Score. The difference at target score was statistically significant (p=0.002). Although the difference in acceptable score was not statistically significant, it showed a tend towards it (p=0.08).

Recovery from sedation

The recovery from sedation was significantly rapid in propofol group. Patients in propofol

group opened eye in 2.7 ± 2.3 minutes on command and gripped observer's hand in 4.9 ± 2.9 minutes on command, after stoppage of sedation. In contrast patients in the midazolam group took a longer time (5.6 ± 4.0 minutes and 9.6 ± 5.0 minutes respectively) to achieve these parameters. These results were statistically significant. (p=0.007 and 0.008 respectively).

Table 14

Parameters	Propofol (n=20)	Midazolam (n=20)	P Value
1. Time from stoppage of sedation to opening of eye on command (in minutes)	2.70±2.27	5.60±4.03	0.007
2. Time from stoppage of sedation to handgrip on command (in minutes)	4.90±2.85	9.60±5.02	0.008
3. Nurse's assessment of quality of sedation on a 10 point scale	7.68±0.76	7.33±0.84	NS

Table 14 showing recovery characteristics in the study population. Patients in propofol group had significantly shorter time to opening of eye and gripping observers hand on command, compared to patients in midazolam group.

Adverse effects

One patient in midazolam group developed severe respiratory depression at 12 hrs. We did not observe any other adverse effects attributable to midazolam or propofol during the study period. No patient in either group had hypotension attributable to the sedative to a degree which required fluid or inotrope administration.

Cost of sedation

Propofol was used from 50 ml vials, that contained 500 mg of propofol and midazolam was used from 10 ml vials which contained 1 mg midazolam/ml.

Table 16

Cost of sedation	Propofol Group (Rs.)	Midazolam Group (Rs.)
Mean ± SD cost	1230 ± 250.00*	245 ± 70.46
Median cost	1256	270

Table 16 comparing cost of sedation in propofol and midazolam group. Propofol was approximately 5 times were costly than midazolam. This was considered statistically highly significant, $p < 0.001$*.

Discussion

ICU sedation becomes a integral part of ICU management**.** Midazolam introduced in the market in the year 1976 and this drug was routinely used as it being water soluble having rapid onset of action & short elimination half life, but the disadvantage were noticed that it had variable duration of action in critically ill patients, even prolong recovery time after discontinuation of midazolam infusion have been reported.

Propofol is the newer drug which was also introduced for ICU sedation in the year 1987, the advantage of this drugs are, it has rapid onset of action, it is rapidly metabolized and virtually then is no accumulation. So to say it does not have any residual effect. This drug is very suitable for ICU sedation.

The primary objective of this study was to evaluate the sedation characteristics of propofol and midazolam in postoperative mechanically ventilated patients our ICU. The study was conducted for a period of 24 hours.

Sedative agents in ICU have to be not only rapidly reversible but also effective to achieve the desired effect. We tried to evaluate quality of sedation at hourly intervals for a period of 24 hours. In our study, more number of patients in propofol group achieved the optimal sedation (Ramsay score 3) earlier and remained for a significantly longer time period than patients in midazolam group. However the acceptable sedation level (Ramsay

score 2 to 5) was similar between both the groups. The patients in midazolam group had significantly more incidences of excessive sedation episodes than patients in propofol groups, while the incidence of inadequate sedation was similar in both the groups.

The dose of propofol used in our study was similar to the doses used in earlier studies. For short term sedation of post operative patients, the dose ranged between 0.9 to 1.77 mg/kg/hr. this was lower than the dose used in several other studies that ranged between 2.5 to 3 mg/kg/hr. Our mean dose of midazolam was also lesser than the dose used in many earlier studies.

We did not assess weaning time and time of extubation in our study, only wake up time and time to perform a simple but specific motor function were assessed. This is because the underlying medical condition of the patients and the nature of the surgery limited their early extubation. Further as a part of our ICU protocol, extubation were avoided in the night time. The length of the ICU stay was thus influenced primarily by the underlying disease and not by wake up time.

The propofol group in our study had a faster recovery from discontinuation of sedative infusion. In our study, patients in propofol group opened eye to command and gripped observer's hand earlier than patients in midazolam group. This difference was found to be statistically significant and could be clinically important when a rapid recovery from sedation in necessary to assess neurologic functions.

We did not use bolus doses of the sedative and observed a more gradual decrease in these parameters from baseline with progressive hours of sedation. In our study both propofol and midazolam had a significant fall from baseline values of systolic and mean arterial pressure, the fall being greater in propofol group. However, at similar time points, the fall was similar when compared between the groups.

We observed a lower heart rate in propofol group patients than midazolam group patients

When using injection propofol, the achievement of OAA/S score 3 was closely followed by a fall in BIS score to 70, even when patients were severely anxious. Thus, a moderate to strong correlation between the instrumental and clinical monitoring seems to exist regarding the onset of sedation using the propofol. This was not the case with midazolam, where a divergence between the time to reach BIS score 70 and time to achieve OAA/S score 3 was evident and was supported by a poor correlation between the two. The time to reach BIS score 70 was lower for sedation with propofol (4.8±3.3 min) than with midazolam (14.9±9.9 min). Similarly, in severely anxious patients in both the groups, the difference to reach BIS score 70 was strikingly high (6.5±4.4 min with propofol vs. 20.6±8.6 min with midazolam). The time to achieve OAA/S score 3 was 3.5±1.9 min with propofol sedation and 5.3±2.9 min with midazolam, the values being comparable. Likewise, the time to achieve OAA/S score 3 was also comparable in severely anxious patients receiving propofol (4.7±2.3 min) or midazolam (6.4±3.5 min).

Propofol was found to suppress the alpha rhythm to theta and delta rhythms. Higher doses of the drug efficiently produced burst-suppression. Midazolam usually converted the alpha rhythm to a beta rhythm within 60s. By 60 min of infusion, this rhythm either developed into a resistant beta rhythm of low amplitude or reverted back to alpha rhythm. This pattern of change in cerebral activity was typical of the benzodiazepines. Anxious patients had heightened cerebral activity. So, the benzodiazepines took a longer time for cerebral suppression. It is worth mentioning that the BIS score is derived from analysing the EEG, i.e., the cerebral activity. A longer time to suppress the cerebral activity especially in severely anxious patients might cause a delayed decrease in BIS scores in patients sedated with midazolam despite the patient being clinically asleep. This resulted in a great divergence between the time to reach BIS score 70 and time to achieve OAA/S score 3 in patients sedated with midazolam, although much

explanation remains to be sought for. From the above findings, it is apparent that OAA/S scores may not correlate with BIS score during onset of sedation using midazolam.

The CVP fell more sharply in propofol group.

In our study, both sedative drugs were easy to titrate and infuse through a central venous line. No patients in either group experienced excitatory effect, wheezing, bronchospasm, apnea, hypotension of >20% fall from baseline, flushing or urticaria. We did not observed any incidence of pain on injection or greenish discolouration of urine in patients receiving propofol. We did not observe any incidence of thrombocytopenia attributable to lipid emulsion of propofol. The hematological and coagulation values were similar to those at start of the study. The screening of biochemical parameters did not demonstrate worsening in renal function or in any of the studied parameters.

Although propofol is considerably more expensive than midazolam, the quality of sedation and shorter weaning time associated with propofol sedation as compared with midazolam sedation makes it a more efficient choice for sedating mechanically ventilated patients. Although the cost of propofol was higher in our study, the ease of titrability, optimal sedation and rapid recovery offered by it makes it a superior choice upon midazolam. Cost may not be a primary concern in situation where sedation needs to be frequently interrupted to assess neurological functions and it is in such circumstances that propofol proves to be a superior agent.

Our use of Ramsay sedation score had some limitations. The scale is a compromise between accuracy, simplicity and ease of use. As a result, most series do not differentiate between sedation anxiety depression and pain, but provide an estimate of overall patient comfort. Our cost comparison study did not take into account the hospital costs and charges. No cost difference could be attributed to drug preparation and administration because both required same time for preparation and were administered by a similar infusion device. Differences between the two drug may not have become apparent in our study because of low concentrations short duration of infusion and small sample size.

Summary and Conclusion

We studied the effect of continuous infusion of propofol and midazolam on fourty postoperative patients who were mechanically ventilated, for a duration of twenty four hours. The conclusions of our study is Both propofol and midazolam were effective in providing adequate level of sedation. However propofol provided significantly higher occasions of optimal sedation compared to midazolam. Weaning from mechanical ventilation was significantly better in propofol than midazolam sedation. Patients in propofol group had a shorter duration on SIMV mode of ventilation, and were weaned more rapidly. Propofol treated patients had a significantly better profile of recovery from sedation. They opened eye and gripped observer's hand, on command, in significantly shorter time period. The cost of propofol sedation was significantly higher than midazolam sedation.

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