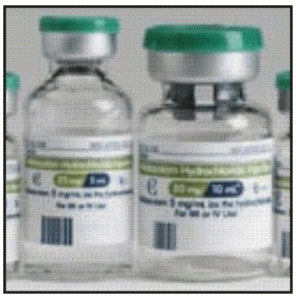
ORIGINAL PROF-889

PROPOFOL VS MIDAZOLAM;
SEDATION IN MECHANICALLY VENTILATED PATIENTS



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ABSTRACT ... Objective: A study was conducted to evaluate the benefits of propofol versus midazolam for providing ICU sedation in mechanically ventilated patients. **Design:** An observational analytical study. **Place and Duration:** The study was conducted at CMH Rawalpindi and PNS Shifa Hospital Karachi, from February 2000 to July 2001 in the Department of Anaesthesia and Intensive Care. **Subjects and Methods:** Propofol and midazolam infusions were administered to two randomly distributed groups of patients (n=25, each group) who received standardized dosage of morphine chloride and muscle relaxant. Patients were thoroughly evaluated for haemodynamic alterations caused by both the drugs, in terms of heart rate and blood pressure variability. A commercially available program was used to assess the statistical analysis of data (SPSS for Windows 8.0, Standard version, and www.SPSS.com). **Results:** No significant differences were found in age (p=.837), gender (p=.763), and weight distribution (p=.827). The time under sedation was longer for the group on midazolam than for the group administered with propofol (p=.001); but it did not affect the overall length of stay in ICU to the same extent (p=.028) or the patients' outcome. Mean daily dosage of the sedative agent (mg/day) and total dose administered to the patients, were also significantly higher for group on propofol (p=.000). Wake-up time after stopping infusions of sedative drugs, was shorter in the group on propofol (p=.000). In both groups, most of the haemodynamic variables did not show significant difference (p=.274 - .916) except maximum systolic (p=.000) and maximum mean (p=.009) blood pressures, which are lower in the group receiving propofol. **Conclusions:** Midazolam and propofol were similar in providing haemodynamic stability to our ICU patients. With midazolam, there were less therapeutic failures; while propofol offered shorter wake-up times. More research is needed to determine the most effective agent to sedate ICU patients.

Key Words: ICU sedation, Midazolam, Propofol, Mechanical ventilatory support, Haemodynamic variables.

INTRODUCTION

Critical illness can cause tremendous stress and mobilize the stress response[1]. In the short-term, the stress response benefits haemodynamic stability. However, in the long-term, it can increase morbidity and mortality[2]. Anxiety, agitation, delirium, and pain are potential consequences of critical illness[3,4]. A survey of critically ill patients conducted after discharge from the ICU revealed that almost 40% recalled pain and about 55% developed anxiety, during their treatment in ICU[5]. Nearly

50% described mechanical ventilatory support as unpleasant and stressful, resulting in feelings of helplessness, fear, agony and panic[6]. Hence pain management and sedation are important considerations in any ICU setting. In Pakistan, ICU sedation may be a relatively newer subject but internationally, many drugs have been used for this purpose. Despite of that, no protocol has been established as the standard to use in intensive care units[7,8]. Midazolam, because of its convenient pharmacodynamic and pharmacokinetic properties[9], has become the most widely used benzodiazepine for this purpose in Spain[10], Although its indications have been limited because of the wide variability in consciousness recovery times observed after stopping the drug infusion[11]. The use of propofol, a 2,6-disopropyl phenol in a soybean emulsion, has got a significant growth in ICUs and anaesthesia units since it appeared in the market in 1990[12]. Its pharmacokinetics allows an easily controllable level of sedation, as well as a prompt consciousness level recovery after the drug infusion is withdrawn[13,14].

The present study was undertaken to evaluate the benefits of propofol versus midazolam for providing ICU sedation for mechanically ventilated patients.

PATIENTS AND METHODS

The study was conducted at Combined Military Hospital, Rawalpindi and PNS Shifa Hospital, Karachi from February2000 to July 2001.

A total of 50 patients who required mechanical ventilatory support in our ICU, for at least more than two days, were selected. They were randomly divided into two groups A and B of 25 patients each. The age range was 15 to 50 years. The variation in weight was not more than 20% of ideal body weight. Patients with neurological disease, neurosurgery or trauma patients having GCS < 12, patients with renal or hepatic failure and those with allergy to propofol or midazolam or morphine were excluded from the study.

Patient randomization and evaluation was begun only after an initial stabilization period, including emergency room admittance, radiographic assessment, and surgery, if indicated. Informed consent was taken from respective next of kin. 'Group A' received propofol infusion while midazolam infusion was administered to 'Group B' patients, in order to provide them sedation to ease their experience of being on ventilator.

To facilitate intubation, boluses of midazolam and morphine were used to achieve a desired sedation level. Patients were put on Bennett Adult-star ventilators. A modified Ramsay scale (level 1-4) was used to assess the level of sedation (Table-I).

Table I: Modified Ramsay Scale for assessment Scale for level of sedation and analgesia

Sedation levels	Clinical Features
Level I	Patient is anxious and agitated
Level II	Patient is oriented, calm and co-operative
Level III	Patient is asleep and responds to verbal stimuli
Level IV	Patient only responds to pain or is unresponsive

Group A (n=25) received a continuous intravenous infusion of 0.1-mg/kg/hr midazolam. The infusion rate was adjusted to a maximum of 0.35 mg/kg/hr to achieve a desired sedation level of 3-4, monitored hourly by trained nursing staff[15,16]. A higher requirement was considered a therapeutic failure, the patient was withdrawn from the study, and the administration of other sedative was allowed.

Group B (n =25) received a continuous infusion of 1.5 mg/kg/hr propofol[17,18]. The dose was adjusted up to a maximum of 6 mg/kg/hr, to achieve a desired sedation level. Higher requirements were considered a therapeutic failure and patient was withdrawn from the trial. Patients from both groups received analgesic coverage with morphine chloride, at a dosage ranging from 0.02 to 0.04 mg/kg/hr. In patients requiring muscle relaxation because of intracranial hypertension or severe respiratory failure, a simple scale based on clinical signs, the Evans scale[19] (Table-II) was used for assessment of

level of sedation. On improvement in the patient's clinical condition, midazolam and propofol infusions were stopped. Wake-up time was recorded as the time elapsed from sedation discontinuation, to the time the patient could obey commands.

Table II: Assessment scale for level of sedation and analgesia in patients under muscle relaxant (Evans scale)			
Parameter	**0**	**1**	**2**
Rise in blood pressure over basal values	<15%	15% to 30%	30%
Rise in heart rate over basal rate(%)	<15%	15% to 30%	30%
Perspiration	No Perspiration	Clammy skin	visible sweating
Tearing	Normal/eyes open	Tearing/eyes open	Tearing/eyes open

Haemodynamic changes were recorded before the bolus infusion and every 5 minutes for a period of 20 minutes thereafter. Any systolic pressure reduction below 100 mm Hg or a reduction > 20 mm Hg in mean blood pressure was considered an after-bolus haemodynamic change. Other variables including history of drug or alcohol abuse, ICU outcome (discharge or death), length of stay, mean level of sedation (mean of all observations recorded), duration of sedation (in days), daily infusion rate of sedative (in mg per day), total dosage of sedative (in mg), any post-stabilization increase in dose requirement and need for muscle relaxants were also recorded. Data were presented as mean±SD or as percentages. Student's t-test was used to compare the means and p-values calculated. A P<0.05 was considered statistically significant.

RESULTS

A total of 88 patients were admitted to our ICU during the study period, 38 patients were excluded for various reasons and 50 patients were included in the study for data analysis. There were 38 male (76%) and 12 female patients, with a mean age of 34.92±10.97 years.

No significant differences were found in age (p=.837), gender (p=.763), and weight distribution (p=.827). All of the patients, during their stay on ventilator, received equal dosages of morphine chloride and were monitored by the same procedure. The time under sedation was longer for the midazolam group (11.10±3.62 days) than for the propofol group (7.42±2.39 days) showing significant difference (p=.001) but it did not affect the length of stay in ICU (p=.028) or the patient's outcome. Most patients required deep sedation because of the presence of respiratory failure; recorded sedation level was3.81±.4 in the midazolam group and 3.84±.37 in the propofol group (p=.793). The need for an increase in sedation dosage was similar in both groups (p=.274) and always within the first 4 days. Muscle relaxant requirements were also similar in both groups (p=.792). The mean sedation level in those patients under muscle relaxation was similar in both groups (0.3±0.01 in the midazolam group and 0.4±0.02 in the propofol group, p=.191, by the Evans scale).

No significant difference was found in the proportion of hours with desired sedation versus total sedation time between the groups (247 of 266 hrs for the midazolam group vs. 142 of 156 hrs in the propofol group). Four patients from propofol group while two from midazolam group declared to have therapeutic failure (p=.395), after maximal dosage of sedative agent. Mean daily dosage of the sedative agent (mg/day)(p=.000) and total dose were also significantly higher (p=.000) for group receiving propofol.

The analysis of haemodynamic variables revealed interesting findings. No significant differences were found in several haemodynamic variables analyzed in both groups (P=>.05) except maximum systolic (p=.000)

and maximum mean (p=.009) blood pressures, which were significantly lower in group on propofol. Changes in other blood pressure values, detected during continuous infusion or after a sedative bolus were slight, as well as similar for the two groups (Table IV).

Wake-up time was significantly shorter in the patients who were on propofol as compared with those on midazolam (84.53±34.58 minutes versus 380.38±30.14 minutes, p=.000) (Table III).

Table III Characteristics of patients in both the sedation groups

Parameters	Midazolam	Propofol	P-Value
Age (years)	38±11.8	36±18.7	.837
Weight (Kg)	77±11	76.6±12.4	.827
Relaxants (%)	14	15.1	.792
Duration of sedation (days)	11.1±7	5.2±3.1	.001
Mean dose of sedative agent (mg/day)	297.8±103.8	3800±2222	.000
Total dose of sedative agent (mg)	3466.6±2595.3	21857±20865	.000
Length of stay in ICU (days)	20.25±13	24±18	.028
Mean level of sedation	3.8±0.2	3.7±0.3	.793
Increase in sedative agents %	74.2	72.7	.274
Day of increase in sedative agent	4.34±1.8	2.5±0.8	.000
Morphine dose	0.026±0.003	0.025±0.002	.197
Wake-up time	372±491	95.5±70.3	.000

Table IV: Haemodynamic variables in the two groups

	Midazolam (Mean±SD)	Propofol (Mean±SD)	P-Value
Maximum Systolic Blood Pressure (mm Hg)	183.8±11	160±16	.000
Minimum Systolic Blood Pressure (mm Hg)	118.8±12	115±14	.271
Maximum Diastolic Blood Pressure (mm Hg)	81.4±10.9	81±8	.461
Minimum Diastolic Blood Pressure (mm Hg)	58.4±6.4	58±8	.916
Maximum Mean Blood Pressure(mm Hg)	109.36±13	103±8	.009
Minimum Mean Blood Pressure (mm Hg)	79±8.2	78±7	.875

DISCUSSION

The search for the ideal sedative agent has been one of the most relevant problems in the ICU. Many drugs including intravenous anaesthetic agents[20], inhalational anaesthetic agents[21], opiates[22], barbiturates[23] and benzodiazepines[24] have been used to sedate critically ill patients. No one can claim any drug to be the ideal ICU sedative, and benzodiazepines remain the most

commonly used in this regard[25]. In the USA during 1991, lorazepam, diazepam and midazolam were used almost equally[26]. Sedation practices in ICUs in Pakistan are not well documented. Although some workers did contributed in this regard[27].

Most of the drugs have proved to be unsuitable for this purpose because their pharmacokinetics and pharmacodynamics do not allow effective long-time sedation, which is easily reversible and without adverse effects on patients' haemodynamic variables.

Among the available sedatives, midazolam and propofol meet some of the criteria required for prolonged sedation in the ICU. These are the two most frequently used drugs for prolonged sedation in the ICU in Europe[28,29].

Midazolam, is a benzodiazepine. It has been proved useful for continuous sedation of critically ill patients[30], because of its less active metabolite and faster elimination process. Its use is, however, limited because of the variability in duration of time for attaining consciousness after stopping the drug infusion in some patients[31]. The use of propofol preparations (2,6-diisopropyphenol presented in a soybean oil emulsion) has grown rapidly since 1990. This drug has a rapid distribution, metabolism and elimination process. Many trials, have been carried out internationally, comparing the drugs (midazolam and propofol) in several variables, such as efficacy, safety, and cost-benefit profiles[32,33]. One of the main differences between the two drugs is in their metabolic effects. Propofol, because of its preparation in a soybean oil emulsion, increases the lipid load in patients who already has impaired lipid metabolism and clearance[34]. In our work, we intended to find a better regimen for ICU patients in our set up.

Regarding analgesia and sedation level evaluation, several scoring systems have been used[35]. Sophisticated techniques, such as continuous bispectral electroencephalogram (BIS) are not available in our ICU settings[36]. Therefore simpler techniques based on clinical experience are more frequently used to monitor the level of sedation in our ICUs. Ramsay scale is the most popular among these evaluation protocols because of its simplicity and ease of application[37,38]. We used a simple, modified version of the Ramsay scale, which could easily be used by our attending nursing staff. It is always difficult to monitor the sedation level in patients who require neuromuscular blockers. For such patients, we used a simple scale (Evans scale), which is based on clinical experience and has shown a good reproducibility when used by trained nursing and medical staff.

In our study, patients on midazolam remained under sedation for a longer duration of time as compared to the patients, on propofol. This could be because of early therapeutic failures found in the group receiving propofol. The withdrawal of these patients from the study could have shortened the mean sedation time in this group. As a matter of fact, when the patients with therapeutic failure were withdrawn from the data analysis, no significant difference was found in the duration of time for which both groups remained under sedation (10±6 days in the midazolam group and 9±4 in the propofol group). Our findings are in agreement with the studies carried out by Hall RI and others[39,40]. However Bernard. Walder claimed shorter sedation times in patients receiving midazolam[41].

Another interesting finding of our study was a higher proportion of therapeutic failures found in the group receiving propofol, compared with on midazolam (4/25 versus 2/25). These patients required an infusion of propofol at a rate of >6 mg/kg/hr especially during the initial sedation days. This resulted in significant difference in the mean daily dosage of the sedative agent (p=.000) and in the total dosage administered on discontinuation of infusion (p=.000), found in the group on propofol.

Although propofol significantly lowered maximum systolic and maximum mean blood pressures, there was no other difference in the haemodynamic variables while midazolam and propofol were being administered in the two groups of patients. Blood pressure monitoring did not reveal any significant fluctuation related to modifications in the infusion rates of the two drugs and remained

stable.

CONCLUSION

Prescribing a sedative regime to our ICU population placed on mechanical ventilatory support was proved to be very beneficial in terms of haemodynamic stability and generalized comfort of the patients.

Midazolam is already being used in our set up satisfactorily. Patients showed good haemodynamic stability and there was less therapeutic failure with midazolam. Wake-up time was relatively shorter in patients receiving propofol. It was also a satisfactory agent for sedation of critically ill patients and compared favourably with midazolam. More research is needed to determine the most effective agent with which to sedate adult patients who require mechanical ventilation in intensive care units.

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