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Efficacy and safety of midazolam/ fentanyl versus propofol/fentanyl in sedating mechanically ventilated patients

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ABSTRACT

INTRODUCTION: Sedation is the process of establishing a state of calm. It plays a pivotal role in the care of the critically ill patient. To achieve the goals of good sedation different combinations of drugs have been used. However, no single one gains full acceptance. In Iraq we are lacking a unified recommendations or guidelines about this issue.

OBJECTIVE: To compare the efficacy and safety of midazolam/ fentanyl combination versus propofol/ fentanyl in inducing sedation in mechanically ventilated patients.

METHODS: A comparative study was done on forty mechanically ventilated patients who were admitted to the intensive care unit at Ghazi Al-Hariri Teaching Hospital for Surgical Specialities/ Medical City Complex in Baghdad/ Iraq from July to October 2013. Patients were randomised conveniently into two groups; *Propofol group* in which patients had received infused propofol in a dose of 1.5 mg/kg/hr plus infused fentanyl in a dose of 5 µg/kg/hr, and *Midazolam group* in which patients had received infused midazolam in a dose of 0.04 mg/kg/hr plus infused fentanyl in a dose of 5 µg/kg/hr. During the study patients were monitored hourly to assess the level of sedation by using Ramsay scale and level of pain comfort by pain score. Vital parameters like tidal volume, minute volume, pulse rate, mean blood pressure, and respiratory rate were compared between the two groups

RESULTS: Forty patients were included in this study. Their age was 30±5 years. The results showed that midazolam/fentanyl combination is as effective as propofol/ fentanyl in inducing sedation. Midazolam had better haemodynamic stability than propofol. Less agitation and more amnesia were recorded in patients using midazolam than those used propofol during recovery stage.

CONCLUSION: Midazolam plus fentanyl in sedating critically ill patients in ICU is as effective as using propofol plus fentanyl for the same purpose, with better haemodynamic stability.

Key words: sedation, midazolam, propofol, fentanyl, Ramsay score, Comfort pain score.

INTRODUCTION

Sedation in the ICU: Sedation is the process of establishing a state of calm. Talking to patients and making adjustments in the ICU environment should be the first step to calm an anxious patient. It derives from a Latin sedare (to soothe).[1] Nearly all critically ill patients will need some kind of soothing. Consideration of the complexity of the critical care scenario allows appreciation of the diverse nature of a patient's need for sedation.[2] Sedation is a broad term; it is often assumed to mean just hypnosis, but it is much more than this and may include:[2,3]

1. Pain relief and reduction of discomfort.
2. Relief from fear and anxiety.
3. The desire for a good night's sleep.
4. Reduction of stimulation and the consequent changes in arterial pressure, ventilation/PaCO2, shivering, cough, posturing – all of which are potentially associated with increase in cerebral metabolic consumption and intracranial pressure, particularly in the neurological intensive care patie nt.

Prior to making specific decisions regarding sedation requirements, consider the followings:

- The need for analgesia, anxiolysis, antipsychosis, or any combination of these.
- Administer the drug that has the best phar-

macokinetic profile.
- Estimate the period of time for which sedation will be required.[4,5]

Monitoring sedation: Under-sedation can cause hyper-catabolism, immunosuppression, hypercoagulability, and increased sympathetic activity, while over-sedation can lead to prolong ICU stay, deep venous thromboses, and muscle wasting.[4] Current guidelines recommend routine monitoring of sedation, and the use of protocols to guide sedation can decrease the time spent on mechanical ventilation by as much as 50%. The following scales are used to monitor sedation in the ICUs:[6,7]

a) Ramsay sedation scale.
b) Riker sedation – agitation scale.
c) Motor activity assessment scale.

Ramsay sedation scale is the most popular among these evaluation protocols and guidelines because of its simplicity and ease of application.[8,9,10] (see table 1)

For pain monitoring; the comfort pain score were adopted to measure the pain that patients suffered from. The comfort scale is a behavioural, unobtrusive method of measuring distress in unconscious and ventilated patients. This scale has eight indicators: Alertness, calmness/agitation, respiratory response, physical movement, blood pressure, heart rate, muscle tone, and facial tension. Each indicator is scored between 1 and 5 based upon a behavioural exhibited by the patient. Total scores can range from 8-40, a score of 17-26 generally indicates adequate pain control.

Table 1: Ramsay Scale for Scoring Sedation

Score	Description
1	Anxious and agitated or restless, or both
2	Cooperative, orientated, and tranquil
3	Drowsy, but responds to commands
4	Asleep, brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6	Asleep and unarousable

Table 2: Comparison between propofol and midazolam.

Parameters	Midazolam	Propofol
Loading dose	0.02–0.1mg/kg	0.25–1 mg/kg
Onset of action	1–5 min	<1 min
Maintenance infusion	0.04–0.2mg/kg/hr	25–75 µg/kg/min
Active metabolites	Yes	No
Respiratory Depression	Low	High

Methods of aiding sedation: It includes non-pharmacological and pharmacological methods. Of pharmacological drugs used for sedation are:

a) Benzodiazepine[11,12] Midazolam, is the main agent used in the ICU from this group.
b) Propofol: widely used in modern ICUs.[12]
c) Narcotics: Fentanyl is the main analgesic used in the ICUs.[13,14]

To achieve the wanted goal in aiding proper sedation you can use any combination of narcotics (fentanyl, hydromorphones, morphine, ramifentanil) plus either benzodiazepen (midazolam, lorazepam) or intravenous anaesthetic induction agent such as propofol.[14] (see table 2)

In Iraq, till now we don't have a clear guidelines or protocols to guide or control the process of aiding sedation to critical care patients; physicians used different combinations to sedate their patients. So we need studies to measure the safety and effectiveness of these combinations of drugs. The aim of this study is to compare the clinical efficacy and safety of Propofol plus fentanyl versus Midazolam plus fentanyl in the sedation of critically ill patients

METHODS

Type of the study and settings: An experimental comparative study was done on forty mechanically ventilated patients who were admitted to the intensive care unit at Ghazi Al-Hariri Teaching Hospital for Surgical Specialities at Medical city complex in Baghdad/ Iraq from July to October 2013. This study was approved by college of pharmacy/Baghdad University and was in agreement with the recommendations of the ethical committee at Ghazi Al-Hariri Teaching Hospital for Surgical Specialities.

Inclusion and exclusion Criteria: All patients who were admitted to ICU and in need for sedation were included in this study if their age was between 25 and 35 years. Patient who had a history of renal or hepatic impairment or allergy to propofol, midazolam or fentanyl were excluded from this study.

Randomisation: BY using convenience sampling, we divided patients into two groups:

Table 3: Comparison in mean Ramsay score between studied groups at different time of evaluation

Days of Follow up with Ramsay score	Propofol group* Mean ± SE	Midazolam group* Mean ± SE	Absolute Mean difference	P-value
Day 1	2.35 ± 0.58	2.45 ± 0.6	0.1	0.30
Day 2	3.25 ± 1.16	3.38 ± 1.2	0.13	0.48
Day 3	2.35 ± 0.58	2.27 ± 0.58	0.8	0.52
Day 4	2.45 ± 0.57	2.35 ± 0.57	0.1	0.70
Day 5	2.2 ± 0.62	2.2 ± 0.6	0	1.0

SE: standard error

* Total number in the group is 20 patients.

Table 4: Comparison in mean Comfort pain score between studied groups at different time of evaluation

Days of Follow up with Comfort pain	Propofol group* Mean ± SE	Midazolam group* Mean ± SE	Absolute Mean difference	P-value
Day 1	21.8 ± 2.8	21.9 ± 2.4	0.1	0.92
Day 2	23.0 ± 2.5	23.5 ± 1.5	0.5	0.49
Day 3	21.8 ± 2.7	23.0 ± 2.5	1.2	0.11
Day 4	21.8 ± 2.7	22.0 ± 2.7	0.2	0.90
Day 5	22.3 ± 2.7	22.6 ± 2.1	0.3	0.64

SE: standard error

* Total number in the group is 20 patients.

- Propofol group: included twenty patients who had received Propofol (diprivan®/Astra zeneca) infusion by syringe pump in a dose of 1.5 mg/kg/hr for 1-5 days.
- Midazolam group: included twenty patients who had received midazolam® (Sandoz) infusion by syringe pump in a dose of 0.04 mg/kg/hr for 1-5 days.

Patients in both groups had received Fentanyl infusion by syringe pump in a dose of 5 µg/kg/hr for analgesia. Propofol and midazolam were given over the night (12:00 midnight-06:00 am) Then we stopped the infusion on a daily basis at 06:00 am in order to allow the patient to be alert and the physician to make a full assessment for the patient's condition regarding agitation and amnesia.

During the study vital signs (pulse rate, tidal volume, minute volume, respiratory rate), monitoring of sedation by Ramsay score, and assessment of pain by comfort pain score were recorded on hourly bases.

Statistics: The data of all patients were studied and analyzed by using Statistical package for social sciences (SPSS) software for windows, version 20, IBM, US. Descriptive statistics were presented as mean ± standard deviation (SD). Standard error of mean (SE) was used for continuous variables; Ramsay score, comfort score, tidal volume and the minute volume.

For categorical variables the descriptive statis-

Table 5: Comparison in mean Tidal volume between study groups at different time of evaluation.

Follow up by mean Tidal volume	Propofol group* Mean ± SE	Midazolam group* Mean ± SE	Absolute Mean difference	P-value
Day 1	414.95 ± 131.5	426.40 ± 116.7	11.45	0.77
Day 2	426.60 ± 127.35	434.70 ± 119.25	8.1	0.84
Day 3	404.80 ± 124.6	451.15 ± 110.9	46.35	0.13
Day 4	389.85 ± 125.98	446.90 ± 105.42	57.05	0.22
Day 5	378.90 ± 115.4	460.65 ± 112.23	81.75	0.029
Mean difference Day 5 vs. Day 1	36.05 ± 14.6	-34.25± 13.2	70.3 ± 19.7	0.001

SE: standard error

* Total number in the group is 20 patients.

Table 6: Comparison in mean Minute volume between study groups at different time of evaluation.

Follow up by mean Minute volume	Propofol group* Mean ± SE	Midazolam group* Mean ± SE	Absolute Mean difference	P- value
Day 1	10.91 ± 4.48	5.60 ± 1.7	5.3	< 0.001
Day 2	8.75 ± 4.0	5.37 ± 1.17	3.37	0.001
Day 3	7.13 ± 2.32	5.32 ± 0.92	1.8	0.008
Day 4	5.76 ± 2.32	5.18 ± 1.47	0.57	0.35
Day 5	5.35± 1.17	5.28 ± 1.22	0.17	0.82
Mean difference Day 5 vs. Day 1	5.65 ± 0.82	0.32±0.13	5.33 ± 0.13	< 0.001

SE: standard error
* Total number in the group is 20 patients.

Table 7: Comparison of mean pulse rate between study groups at different time of evaluation.

Follow up of mean pulse rate	Propofol group* Mean ± SE	Midazolam group* Mean ± SE	Absolute Mean difference	P- value
Day 1	97.00 ± 2.85	91.60 ± 2.14	5.4	0.115
Day 2	92.55± 2.61	89.05 ± 1.87	3.5	0.28
Day 3	89.75 ± 2.91	91.90 ± 1.58	2.15	0.520
Day 4	86.20 ± 3.27	89.90 ± 1.63	3.7	0.32
Day 5	83.90 ± 3.8	90.20 ± 1.5	6.3	0.13
Mean change day 1 vs. day 5	13.1± 2.5	1.4 ± 1.1	11.7± 1.8	<0.001

SE; standard error
* Total number in the group is 20 patients.

Table 8: Comparison of means blood pressure between study groups at different time of evaluation.

Follow up of mean blood pressure	Propofol group* Mean ± SE	Midazolam group* Mean ± SE	Absolute Mean difference	P. value
Day 1	105.20 ± 4.33	3.58 ± 102.25	2.95	0.115
Day 2	101.55 ± 2.72	101.15 ± 4.16	0.4	0.28
Day 3	98.85 ± 2.37	99.0 ± 3.1	0.15	0.283
Day 4	97.10 ± 1.64	99.35 ± 2.11	2.25	0.41
Day 5	95.60 ± 2.15	99.90 ± 1.79	4.3	0.133
Mean change day 1 vs. day 5	9.6 ± 1.2	2.35 ± 0.91	7.25 ± 1.1	< 0.001

SE; standard error
* Number in the group is 20

tics were presented as frequencies and proportions (numbers and percentages), these included having agitation or amnesia with recovery.

Appropriate statistical tests were used to compare between studied groups regarding the different variables under study. Independent student's t test was used to compare between two means at each day of evaluation, also to compare the mean differences between both groups. Paired t test was used to compare means between 1st and 5th days in each group.

Level of significance was set at 0.05 as a cutoff point for significant difference, P value ≤ 0.05 considered as significant, P value ≤ 0.001 considered as highly significant.

RESULTS

The total sample was 40 patients,twenty of them were in propofol group while the other twenty were in midazolam group.

- Table 3 and 4 showed that both drugs having good sedative properties (grade 2-3 on the

Table 9: Comparison of means respiratory rate between study groups at different time of evaluation.

Follow up of mean respiratory rate	Propofol group* Mean ± SE	Midazolam group* Mean ± SE	Absolute Mean difference	P.value
Day 1	27.72 ± 2.48	13.25 ± 0.65	14.475	< 0.001
Day 2	21.50 ± 2.07	12.25 ± 0.45	9.25	< 0.001
Day 3	18.08 ± 1.18	11.85 ± 0.27	6.225	< 0.001
Day 4	14.40 ± 0.99	11.50 ± 0.31	2.9	0.008
Day 5	12.05 ± 0.46	11.25 ± 0.23	0.8	0.128
Mean change day 1 vs. day 5	15.7 ± 1.3	2.0 ± 0.8	13.7 ± 1.2	< 0.001
% of reduction	56.5%	15.1%	41.4%	<0.01

SE; standard error
* Total number in the group is 20 patients.

Ramsay scale) and nonsignificant changes in comfort score.

- Table 5,6,7,8,9 showed good haemodynamic stability and there was less therapeutic failure with Midazolam.
- Table 10 showed that the frequency distribution of recovery with agitation in propofol group were significantly more than with midazolam group (60% rather than 40% in midazolam group).

Table 10: Development of agitation and amnesia during recovery in the studied groups

Follow up time Day 1-5	Amnesia		Agitation	
	Yes	No	Yes	No
Propofol group	10%	90%	60%	40%
Midazolam group	55%	45%	15%	85%
p- value	0.001	0.005	0.001	0.004

DISCUSSION

The search for an ideal sedative agent has been one of the most relevant problems in the ICU. Many drugs including intravenous and inhalational anaesthetic agents, opiates, barbiturates, and benzodiazepines have been used to sedate critically ill patients. No one can claim any drug to be the ideal ICU sedative; however, benzodiazepines remain the most commonly used in this setting.[11] Among the available sedatives, Midazolam and Propofol meet some of the criteria required for prolonged sedation in the ICU.

Level of sedation: Our study found no significant differences in the level of sedation, as was being assessed by using Ramsay score, between midasolam and propofol group (p value > 0.05) and patients in both groups reached a perfect sedation score of 2-3 as shown in table 3. The level of sedation was fluctuated during the first 3 days then reached approximately a constant level at 4th and 5th days which indicated that a proper sedation has been achieved; in addition, patients in midazolam group remained sedated for longer period of time as compared to those in propofol group, which is consistent with pharmacokinetic property of midazolam as having longer duration of action than propofol. Similar findings were reported by Muellejans B, Carrasco G, and Alted-Lopez E.[15]

In addition we found that there is no significant difference between the two groups with regards to comfort pain score as both reached the goal of (17-26) as shown in table 4.

Effect of midazolam and propofol on some vital parameters:

Tidal volume: is the lung volume representing the normal volume of air displaced between normal inspiration and expiration when extra effort is not applied. In a healthy young adult, tidal volume is approximately 500 ml per inspiration or 7 ml/kg of body weight[16]. Our study had found that the mean tidal volume is increased in midazolam group from 426.4 ml in the first day to 460.65 ml in the fifth one. While it is reduced from 414.95 ml in the first day to 378.9 ml in the fifth one in propofol group. This means that midazolam has a positive effect on tidal volume than propofol. (see table 6)

Minute volume: It is the volume of gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from a person's lung per

minute.[16] Our study had showed that the minute volume was remarkably reduced in propofol group from 10.91 ml at the first day to 5.35 ml at the fifth day. While in patients of midazolam group there was no significant change in the minute volume (table 6). The mean difference in minute volume was much higher in propofol group than midazolam group 5.65±0.82 versus 0.32± 0.13 respectively (P- value < 0.05), which again reveals that the midazolam is superior than propofol in this effect.

Pulse rate: In our study we found an obvious decrease, as shown in table 7, in the mean pulse rate at each day of evaluation in the propofol group with a mean difference of 13.1 ± 2.5, while in the midazolam group the mean reduction in mean pulse rate was lower, with a mean difference 1.4 ± 1.1(P< 0.001). This means that midazolam is superior than propofol in this regard too. Also a similar finding was reported by Peter G M et al, in which heart rate was lower in patients who received propofol than those who received midazolam.[17]

Mean blood pressure: In our study we did not find any obvious or statistically significant decrease, as shown in table 8, in the mean blood pressure at each day of evaluation in propofol group with a mean difference of 9.6 ± 1.2 mm Hg, while in midazolam group the mean reduction in mean blood pressure was lower, the mean difference is 2.35 ± 0.91 mmHg (P> 0.001). A similar finding was reported in other studies[17,18] where decreases in blood pressure and heart rate have been reported after the administration of propofol. These side effects are potentially deleterious in severe trauma patients, particularly in patients with head trauma.[16]

Respiratory rate: Our study found that there is an obvious decrease, as shown in table 9, the mean respiratory rate at each day of evaluation in the propofol group from 27.72 ± 2.48 (in the 1st day) to reach 12.05 ± 0.46 at the 5th day with a mean difference of 15.7 ± 1.3, in midazolam group the mean reduction in mean pulse rate was lower, it was 13.25 ± 0.65 (in the 1st day) to reach 11.25 ± 0.23 with a mean difference 2.0 ± 0.8 , respiratory rate in propofol group reduced by 56.5% as compared to only 15.1% in the midazolam group p < 0.01.

Recovery: Midazolam has much better profile during recovery than propofol. Midazolam induces less agitation and more amnesia during recovery than propofol as shown in table 10. Similar findings were reported by Jiayao Chen et al, where intravenous administration of a subhypnotic dose of midazolam or propofol in addition to a low dose of fentanyl just before discontinuing the sevoflurane anaesthesia was both effective on decreasing the incidence and severity of emergence agitation in children undergoing cataract extraction without significant delaying recovery time and discharge.[19]

Finally we would like to admit that these findings need to be studied in a wider age spectrum to be verified in different age groups knowing that the age spectrum has been narrowed to take the most optimum physiological conditions for both groups.

CONCLUSIONS

Addition of midazolam to fentanyl in sedating critically ill patients in ICU is as effective as adding propofol to fentanyl for the same purpose; however, midazolam has better haemodynamic stability. Use of medazolam is associated with less agitation and more amnesia during recovery.

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