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Comparison of the Effect of Midazolam-Fentanyl with Midazolam-Fentanyl-Melatonin in Sedation of ICU Patients

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Abstract

Background: Tolerating the endotracheal tube and mechanical ventilation are among the problems of ICU patients.This is made possible with sedation by which even duration of the use of the above procedures is shortened.There is no definite and single protocol for sedation, and most medications used are selected based on experience or availability.

Objectives: This study compared the effect of midazolam-fentanyl with midazolam-fentanyl-melatonin on sedation of ICU patients.

Methods: In this double-blind randomized clinical trial,a total of 80 patients admitted to the intensive care units of Shahid Rahnemoun Hospital in Yazd were assigned into two groups: midazolam-fentanyl and midazolam-fentanyl-melatonin.The first group of patients (midazolam-fentanyl) were treated with 0.2 mg/k/h midazolam and 1 g/kg/h fentanyl (placebo via NGT) and the second group of patients (midazolam-fentanyl-melatonin)were treated with the mentioned doses of Midazolam and fentanyl and a dose of 6 mg of melatonin administered via NGT (astwo 3-mg dosesat 8 pm and 12 pm) during mechanical ventilation.Sedation rate (from onset to 3 consecutivedays) was assessed and recorded by the researcher every 12 hours at 10 am and 10 pm using the Richmond Agitation-Sedation Scale (RASS). The two groups were further compared in terms of the average need for midazolam and fentanyl and their complications.

Results: The results showed that the two groups were similar in terms of age and sex. There was no significant difference in the RASS score ($P<0.05$) between the two groups at 10 am

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on the first day, but there was a significant difference in the evaluation at 10 pm. A better sedation was achieved on the second and third days in the melatonin group based on the RASS criterion, and the patients were in the target range, i.e.,a score of 0 to -3 ($P<0.05$). Besides, the mean dose of fentanyl and midazolam in the melatonin group was lower than the control group in all 3 days ($P<0.05$).There was no significant difference between the two groups in terms of complications such as jaundice/icterus, hypothermia and decreased hemodynamic variables.

Conclusion: Based on the findings of this study, melatonin can be used to manage sedation and reduce benzodiazepines and fentanyl in patients admitted to the intensive care unit.

Keywords: Midazolam, fentanyl, melatonin, sedation, ICU

Background

Patients admitted to the intensive care unit (ICU) require sedation that refers to creating analgesia and amnesia, and removal of anxiety, or a combination of these. Feelings of fear, anxiety and restlessness in ICU patients are the cause of activation of stressful reactions in these patients (1).Excitement and anxiety are common in ICU patients(2). Anxiety in these patients can be caused by curable causes such as hypoxia, hypoglycemia, pain, sepsis, drug deprivation, invasive procedures, sleep deprivation, patient position, continuous noise, light, and inability to communicate with ward staff (3).Thus, in the International Guidelines for Reducing Anxiety in ICU Patients, two suggestions are put forward: Elimination of any organic or metabolic cause, especially pain and environmental stressors, as well as the use of sedatives to minimize the patient's pain (3).Although providing an adequate level of sedation is one of the primary goals of treatment in ICU patients,this important goal is affected by its complications such as: hemodynamic instability, dysrhythmia, sepsis, ileus and delirium (4). Some evidence suggest that continuous infusion of sedatives and long-acting analgesics prolongs the duration of mechanical ventilation and increases hospital stay and complications such as ventilator-induced pneumonia and septicemia (5). Hence, the need to choose lighter sedation is significant due to its harmful effects as well as the costs associated with deep sedation (6, 7).Among the problems of ICU patients is sustaining the endotracheal

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tube and mechanical ventilation, which is made possible by sedation, and even shortens the duration of use of the above devices. For sedation, there is no single, specific protocol, and most medications used are selected based on experience or availability (8).Therefore, to ward off delays in choosing the type of drug, it seems necessary to define a definitive unique protocol to tranquilize patients. On the other hand, controlling the sedative depth of these patients is also very important and often impossible.Most patients have either excessive sedation or low sedation, which can lead to more serious complications and even death. Common sedatives include benzodiazepines, narcotics, barbiturates, and hypnotics (9).Nowadays, multimodal analgesia is used as a combination of narcotic and non-narcotic drugs with the aim of acting on different pain receptors in the central and peripheral nervous systems as the best method of pain control in ICU patients(10).For instance, the combination of fentanyl and midazolam for sedation in painful procedures as well as the combination of fentanyl and propofol in improving analgesia and rapid awakening of patients in these procedures have been reported. Nevertheless, the risk of respiratory depression with these drugs has increased (11). Meanwhile, melatonin is a neuroprotective drug with sedative, hypnotic and analgesic properties without the complication of respiratory depression that can be used as a sedative in the ICU, thereby diminishing the need for other sedatives (12). Given that there are several methods for sedation in these patients, this study was performed to evaluate the effect of midazolam-fentanyl with midazolam-fentanyl-melatonin on sedation inICU patients.

Methods

This double-blind randomized clinical trial was performed on patients admitted to the intensive care units of Shahid Rahnemoun Hospital in Yazd, central Iran. Patients aged 15-70 years with ASA1-3 (American Society of Anesthesiologists) who were admitted to the ICU were included in the study.Moreover, patients with morphine allergy, hepatic and renal disease, chronic pain syndrome, chronic opioid or antidepressant abuse, and substance abuse were excluded from the study. Sample volume was obtained as 40 patients in each group considering 95% confidence level and 80% test power and considering the difference of 1 unit in the frequency distribution of sedation level based on RASS criteria between the two groups and

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also considering 10% subject attrition rate using the following formula:

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \times 2s^2}{d^2}$$

After the approval of the ethics committee and obtaining informed consent from patients, 80 patients admitted to the intensive care units of Shahid Rahnemoun Hospital in Yazd were included in the study based on inclusion criteria and assigned into two groups: “midazolam-fentanyl” and “midazolam-fentanyl-melatonin” according to the table of random numbers. According to the study protocol, the first group of patients (midazolam-fentanyl) (A) were treated with 0.2 mg/kg/h midazolam and 1 g/kg/h fentanyl (placebo via NGT) and the second group ofpatients (midazolam-fentanyl-melatonin)(B) were treated with the above doses of midazolam and fentanyl and 6 mg of melatonin through NGT (as two 3-mg doses at 8 pm and 12 pm) under mechanical ventilation.Sedation rate (from onset to 3 consecutivedays) was assessed and recorded by the researcher every 12 hours at 10 am and 10 pm using the Richmond Agitation-Sedation Scale (RASS). Data were completed through a questionnaire including age and sex of patients, sedation score, dose of fentanyl and midazolam, complications, and standard RASS instrument, which has been rendered as valid to assess the level of restlessness and relief of ICU patients.To determine the RASS score, first only the patient is observed without any interaction, and if s/he is conscious, the appropriate score of 0 to +4 is considered for him/her. Yet, if the patient is not conscious, their name is called out loud and theyare asked to look at the researcher. If necessary, this can be repeated. If the patient responds to sound, an appropriate score of 1 to 3 is recorded. But if there is no reaction, the patient's shoulder is shaken. If there is no reaction, his/her sternum is squeezed tightly and a suitable score of 4 to 5 is considered (13).The goal was to establish a sedation according to the RASS score of “0 to 3”. In the case of score of <3, the dose of fentanyl and midazolam is reduced by half and in case of score of <0, a dose of 50 μg fentanyl acetate and midazolam 1 mg is injected.For each patient, the amount of fentanyl and midazolam consumed is recorded every 12 hours. All patients were evaluated for complications (hyperbilirubinemia, hypothermia and hemodynamic complications including changes in HR and BP) every 12 hours and the results were recorded.The researcher was blind as to which group the patient

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was in, and the ICU nurse prescribed placebo or melatonin to the patient according to the random numbers table and was blind to the medication. Finally, the data were analyzed with SPSS22 using descriptive statistics (frequencies and relative percentages), Chi-square test, independent t-test, and paired t-test (P=0.05).

Results

The findings of the study revealed that the mean age of patients was 35.05±13.7 years in the midazolam-fentanyl-melatonin group and 33.66±12.9 years in the midazolam-fentanyl group. In the midazolam-fentanyl-melatonin group, 23 (57.5%) were male and 17 (42.5%) were female, and in the midazolam-fentanyl group, 20 (50%) were male and 20 (50%) were female.There was no significant difference between the two groups in terms of age and sex of patients (P<0.05) and these two groups were the same in terms of age and sex. Additionally, the findings of the study suggested that comparison of the frequency distribution of RASS score in patients of the two groups demonstrated that on the first day, the two groups did not have a significant difference in RASS score at 10 am (P=0.1);yet, in the evaluation at 10 pm, the difference was significant. In the midazolam-fentanyl-melatonin group, a better sedation was achieved according to the RASS criterion and the patients were in the target range, i.e., a score of 0 to 3. On the second day,a significant difference was observed in the frequency distribution of RASS scores between the two groups at 10 am and 10 pm.The sedation rate in the midazolam-fentanyl-melatonin group was better than the midazolam-fentanyl group and the patients were also in the target sedation interval, while in the midazolam-fentanyl group, 80.5% were in the target sedation interval at 10 am and 85.4% at 10 pm. A significant difference was observed in the frequency distribution of RASS scores between the two groups on the third day at 10 am and 10 pm. The rate of sedation was better in the midazolam-fentanyl-melatonin group than midazolam-fentanyl. In the melatonin group, patients were in the target sedation interval, while in the other group, 93.7% were in the target sedation interval at 10 am and 90.2% at 10 pm(Table 1).

Other findings of the study showed that the mean of fentanyl and midazolam used in the midazolam-fentanyl-melatonin group was lower in all evaluated times (Table 2).

Finally, the findings revealed that the mean body temperature, blood pressure

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and heart rate at different times in the two groups were not significantly different at any of the studied times.

Discussion

The present study was performed as a double-blind randomized clinical trial with the aim of comparing the effect of midazolam-fentanyl with midazolam-fentanyl-melatonin on sedation of 80 ICU patients in Shahid Rahnemoun Hospital in Yazd. The two groups were the same in terms of age and sex.The results of the present study suggested that there was no significant difference in the RASS score between the two groups at 10 am on the first day, but this difference was significant in the evaluation at 10 pm. Moreover, better sedation was achieved on the second and third days in the melatonin group according to the RASS criterion, and the patients were in the target range, i.e.,a score of 0 to 3. Besides, the average dose of fentanyl and midazolam was lower in the melatonin group than the other group in all 3 days.The study by Mistraletti et al. (2015), aimed at exploring the effect of melatonin in reducing the need for sedation in ICU patients, showed that administration of 6 mg of melatonin reduced the need for neuroactive drugs, pain, restlessness, anxiety and additional sedatives. Furthermore, similar to the present study, the mean dose of midazolam, propofol and morphine in the melatonin-treated group was significantly lower. In addition, a significant difference was observed in the frequency distribution of the RASS score between the two groups;this is consistent with the present study (16).Similar findings have been reported in other studies on the analgesic effects of melatonin (14, 15). In confirmation of these results, the study by Marseglia et al. (2015) showed that melatonin administration can be an alternative to midazolam in cases of sedation for procedures such as MRI in children and adults, and may reduce the dose of other drugs, including propofol (16).These results were also observed in the study by Johnson et al. (2002). Their study revealed that administration of 10 mg of melatonin resulted in adequate sedation in children who did not cooperate for MRI (17).The study by Nishikimi et al. (2018) also demonstrated that administration of 8 mg of Ramleton, a melatonin receptor agonist, reduced the length of ICU stay and also reduced the risk and incidence of delirium in hospitalized patients. Besides, the rate of sedation in intubated patients and the rate of nocturnal waking up in non-intubated

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patients were improved (18). Regarding the study by Frisk et al., which showed that melatonin secretion is lower in ICU patients under mechanical ventilation, it seems that the administration of melatonin in these patients is very effective (19).Studies on the use of melatonin for sedation in ICU patients have been very limited. However, various drugs have been studied in this field. The study by Zaman et al. (2006) showed that although remifentanil causes a more pronouncedreduction in blood pressure and heart rate than morphine, the trend of its changes during 24 hours is constant and stable, and thus it creates more stable conditions for patients. The degree of sedation of patients was evaluated according to Ramsey criteria in their study, showing that remifentanil can significantly bring the patient to the desired level of sedation with a significant time difference earlier than morphine creating a smaller need for other sedative or analgesic drug during use (20).Contrary to their study, no specific adverse side-effects were observed in this study with melatonin administration and the frequency of complications did not differ significantly between the two groups.Mazhari et al.'s study suggested that the sedative score and Minogue criterion in using 0.05 μg of remifentanil is lower compared to 1 μg of fentanyl. In addition, heart rate and mean arterial blood pressure are lower in the remifentanil group. Generally speaking, remifentanil causes more effective sedation and better control of hemodynamic variables in patients under mechanical ventilation. Also, according to the present study, the average daily dose of midazolam was lower in the remifentanil group (21). Regarding the results of the present study and the reviewed articles, it seems that melatonin administration can be effective in improving the sedation status of ICU patients and reduce the use of fentanyl and midazolam. The double-blindness and matching of groups in terms of age and sex were some of the strengths of the present study.The limitations of the study include the lack of evaluation of the CAM-ICU test and longer follow-up of patients.It is also recommended that in future studies, the time of patients' discharge from the ICU, the time for reaching the sedation level and the need for antipsychotic drugs be evaluated.

Conclusion

The results of the present study indicated that administration of 6 mg of melatonin in two 3-mg dosesat 8 pm and 12 pm with fentanyl and midazolam in patients

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admitted to the intensive care unit could improve sedation in patients in the desired range based on the RASS criteria.In addition,it reduced the dose of fentanyl and midazolam.Consequently, melatonin can be used to manage sedation and reduce benzodiazepines and fentanyl in ICU patients.

Ethics approval and consent to participate: The article's proposal was approved by the ethics committee of ShahidSadoughi University of Medical Sciences with id IR.SSU.MEDICINE.REC.1397.205.

Patients admitted to our hospital are asked to sign a general consent upon admission, which covers the collection of patient data and publication of these results. We received administrative permission from (Secretary of University/Regional Research Ethics Committee ShahidSadoughi University of Medical Sciences) to access and use the data.Data used in the study were anonymized. The ethics committee approved this procedure with the above ethical code. The present study was conducted in terms of the principles of the revised Declaration of Helsinki.

Consent for publication:Not applicable.

Availability of data and material:The data-sets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests:All authors declare that they have no conflict of interest regarding this study.

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Authors' contributions:MO and M.H.D have designed the study and supervised the thesis. M.O collected the data and analyzed it. They also prepared the first draft of the manuscript. M.H.J and M.H.D has edited and finalized the manuscript. All authors read the manuscript and approved it.

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Table 1: Frequency distribution of RASS score on the first to third day in two groups: midazolam-fentanyl (A) and midazolam-fentanyl-melatonin (B)

Time		**Group**	**RASS Score**								**P-value**
			-4	-3	-2	-1	0	+1	+2	+3	
First day	10 am	B	0(%0)	3(%7.7)	3(%7.7)	2(%5.1)	11(%28.2)	17(%41)	4(%10.3)	0(%0)	0.10
		A	5(%12.2)	3(%7.7)	0(%0)	1(%2.4)	9(%22)	13(%34.1)	6(%14.6)	3(%7.3)	
	10 pm	B	0(%0)	3(%7.7)	10(%25.6)	7(%17.9)	18(%43.6)	2(%5.1)	0(%0)	0(%0)	0.001
		A	0(%0)	9(%24.4)	6(%14.6)	4(%9.8)	7(%17.1)	7(%17.1)	7(%17.1)	0(%0)	
Second day	10 am	B	0(%0)	5(%12.8)	10(%25.6)	18(%43.6)	7(%17.9)	0(%0)	0(%0)	0(%0)	0.03
		A	2(%4.9)	8(%19.5)	6(%14.6)	10(%24.4)	9(%22)	5(%14.6)	0(%0)	0(%0)	
	10 pm	B	0(%0)	5(%12.8)	12(%30.8)	18(%43.6)	5(%12.8)	0(%0)	0(%0)	0(%0)	0.04
		A	0(%0)	4(%9.8)	9(%22)	11(%26.8)	11(%26.8)	5(%14.6)	0(%0)	0(%0)	
Third day	10 am	B	0(%0)	4(%10.3)	13(%13.3)	20(%48.7)	3(%7.7)	0(%0)	0(%0)	0(%0)	0.02
		A	0(%0)	5(%12.2)	8(%19.5)	13(%31.7)	12(%29.3)	2(%7.3)	0(%0)	0(%0)	
	10 pm	B	0(%0)	3(%7.7)	15(%38.5)	19(%46.2)	3(%7.7)	0(%0)	0(%0)	0(%0)	0.02
		A	0(%0)	5(%12.2)	8(%19.5)	15(%34.1)	10(%24.4)	4(%9.8)	0(%0)	0(%0)	

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Table 2: Comparison of mean consumed dose of fentanyl and midazolam in the two groups: midazolam-fentanyl (A) and midazolam-fentanyl-melatonin (B)

Drug	**Day**	**Time**	**Midazolam-fentanyl-melatonin Group**	**midazolam-fentanyl Group**	**P-value**
			Mean±SD	Mean±SD	
Fentanyl	Day 1	Morning	96.1±28.9	120.7±31.5	0.001
		Night	83.3±23.8	97.5±36.9	0.04
	Day 2	Morning	78.2±25.1	91.4±19.04	0.009
		Night	74.3±25.3	91.4±19.04	0.001
	Day 3	Morning	60.2±20.4	84.15±26.07	0.001
		Night	60.2±20.5	82.9±24.01	0.001
Midazolam	Day 1	Morning	2.46±1.4	3.17±1.3	0.023
		Night	1.97±0.7	2.37±0.9	0.05
	Day 2	Morning	1.64±0.7	2.05±0.6	0.01
		Night	1.54±0.7	1.98±0.7	0.01
	Day 3	Morning	1.21±0.8	1.71±0.6	0.002
		Night	1.21±0.8	1.73±0.6	0.002