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The Effect Of Ketamine On Ventilator Isolation In Patients With Agitated Delirium In Comparison With Standard Care

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ABSTRACT

Introduction: Agitated delirium causes more problems, especially in patients with mechanical ventilation, due to the increased risk of self extubation. Therefore, recognizing and introducing the delirium time-reducing drug in the treatment process of these patients will be very important.
Materials and Methods: This clinical trial study was performed on 64 patients undergoing ventilator with agitated delirium (RASS≥3) admitted to the intensive care unit of Valiasr Hospital in Arak. These patients were divided into two groups using a random number table. Patients in the ketamine group were given 1-2 mg/h of ketamine daily, and patients in the propofol group received propofol as an infusion. the Tnformation obtained from these patients was recorded in a checklist. Finally, this information was analyzed using SPSS 19.
Results: The mean age (SD) of the ketamine and propofol groups were 39.63 (12.65) and 41.09 (11.81), respectively. There was no significant difference between the two groups in terms of age and gender. There was no significant difference between the two groups in terms of hemodynamic changes during the study period (P> 0.05). The mean (SD) duration of intubation in the ketamine and propofol groups was 82.72±8.73) and 179.81±8.46 hours, respectively (P <0.0001). RASS and pain decreased significantly more rapidly (P <0.0001) in the ketamine group over three days. Conclusion: The use of ketamine was capable of reducing the duration of intubation, pain and agitation of the patient with agitated delirium hospitalized in the intensive care unit while it does not cause hemodynamic changes for the patient.

Keywords: Ketamine, ventilator isolation, agitated delirium, standard care.

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Introduction

Delirium is considered as a sudden change in mental status of fluctuating course (1). The overall prevalence of delirium in hospitalized patients is between 10 and 31%, but this prevalence varies greatly depending on the type of population (2). The highest prevalence of delirium is recorded among weak patients and those with very sensitive and bad conditions, such as patients admitted to the intensive care unit, followed by patients in the surgical ward. More than a third of hospitalized individuals over the age of 80 will experience this condition (3). Despite the high prevalence of delirium, it is often not detected, leading to very high morbidity and mortality. Patients with delirium are at high risk of falls, prolonged hospital stays, prolonged ventilator dependence, difficult separation from the ventilator, accelerated and stable cognitive impairment, and high mortality rates (4).

Agitated delirium is more likely to cause problems, especially in patients with mechanical ventilation, because having mechanical ventilation increases the risk of self-extubation compared to patients with other essential medical devices (5). Therefore, introducing a drug that is capable of reducing the duration of delirium in the treatment of these patients is of great importance. Agitation itself can be dangerous in the ICU and its occurrence may jeopardize care, increase metabolic needs, and ultimately increase morbidity and mortality (6).

Chemically, ketamine is a component of phencyclidines that was developed in 1962. Ketamine is a drug that weakens the central nervous system and anesthetizes (7, 8). Tissue access to the drug after intramuscular dose is 93% followed by 25 to 50% after intranasal dose and about 20% after oral dose. It is activated 30 seconds after intravenous injection and has a half-life of 2 to 3 hours (9). It is commonly used to maintain anesthesia in patients who require a mechanical ventilator. It is also capable of inducing amnesia and analgesia by maintaining respiratory function, cardiovascular stability and airway reflexes (10). In addition to these properties, this drug is cheap and available, which has led to the widespread use of this drug. Although the use of ketamine in patients with mechanical ventilators has not yet been carefully studied, however, in developed countries, given the characteristics mentioned for this drug, it seems that this drug is suitable for these patients (11). Patients with long-term sedation have a higher ICU stage, which involves more expensive treatment procedures and more mortality.Therefore, there is a need for new drugs and methods to prevent these problems. Although the use of ketamine in patients admitted to the ICU is still unclear, ketamine seems to be appropriate for this group of patients in developed countries. Thus, the present study aimed to evaluate the benefits of this drug in these patients.

MATERIALS AND METHODS

Study population

This clinical trial study was performed on 64 patients with agitated delirium who were hospitalized under ventilator in the intensive care unit of Valiasr Hospital in Arak, Iran. Delirium in patients was classified according to the RASS criterion. Patients in whom the number of this criterion was greater than or equal to 3 were classified in the agitated delirium category. Finally,

patients who met the inclusion criteria were included in the study. These patients were divided into two groups of ketamine and propofol using a random number table.

Treatment protocol

In this study, patients who entered the ketamine group received ketamine (1-2 mg/hour daily), and patients in the propofol group received propofol as an infusion. In the case group, if the patient became agitated and the RAAS score was greater than or equal to 4, haloperidol was injected intramuscularly at a dose of 2.5 mg. Also, if the pain score was higher, it would be given fentanyl at a dose of 2 µg/Kg as a stat. In the propofol group, if the patient became agitated and the RAAS criteria was greater than or equal to +4, haloperidol (2.5 mg) was injected intramuscularly. Furthermore, if the pain score was high, fentanyl at a dose of 2 µg/Kg was given as a stat. All patients were evaluated for vital signs, RAAS criteria, pain criteria and extubation time. If the disease was extube, care was taken up to 24 hours after extube. Finally, the results of these evaluations were compared and analyzed in the two groups using SPSS software version 22.

Inclusion and exclusion criteria

Inclusion criteria were: 1) Age 18 to 60 years, 2) No underlying disease: heart, brain, kidney, liver (encephalopathy), 3) RAAS criteria greater than or equal to 3+, 4) No history of addiction to psychotropic substances and drugs, 5) Absence of intracranial space lesion (abscess, EDH, SDH, SAH, IOH), 6) No history of seizures, 7) No seizures at the time of admission, 8) No history of psychosis and personality disorder.

Exclusion criteria included: 1) 24 hours of extubation tolerance, 2) patient death, 3) seizures, 4) tachycardia (HR greater than or equal to 120 beats per minute), 5) blood pressure (MAP greater than or equal to 110 mm Hg), 6) side effects of ketamine (i.e., Arrhythmia (AF, Flutter), agitation, allergic reactions, hypertension, increased heart rate, breathing difficulties, seizures).

Data analysis

Data analysis was performed using SPSS software version 22 and chi-score and t-test were used to determine the differences between the groups.

RESULTS

Table 1 shows the demographic information of patients in the two groups. In this study, none of the vital signs were significantly different in the two groups, the information of which is given in Table 2.

Information on RASS variables, pain score, intubation duration is given in Table 3. The mean (standard deviation) durations of intubation in the ketamine and propofol groups were 82.72 (8.73) and 179.81 (8.46), respectively, where the two groups showed a significant difference in this regard (p <0.0001) (Table 4).

Table 1: The demographic information of patients

P value	Propofol N=32		ketamine N=32		Variable
	Mean(SD)				
0.633	(11.81) 41.09		(12.65) 39.63		Age
	Number(%)				
	Male	Female	Male	Female	
0.802	(53.1)17	(46.9)15	(56.3)18	(43.7)14	Sex

Table 2: Vital signs of patients in two groups

p value	Day 4	Day 3	Day 2	Day 1	Groups
			HR		
0.894	(5.87)89.12	(5.82)91.36	(7.06)92.80	(7.52)94.68	ketamine
	(6.58)88.69	(6.53)91.06	(7.05)92.63	(7.44)93.81	Propofol
			MAP		
0.248	(1.76)95.44	(2.29)96.48	(2.38)96.52	(2.75)96.32	ketamine
	(1.95)95.28	(2.21)95.47	(2.35)95.69	(2.70)96.28	Propofol
			RR		
0.691	(0.83)19.12	(0.37)18.84	(0.61)18.96	(0.71)18.48	ketamine
	(0.62)18.94	(0.40)18.81	(0.59)18.97	(0.66)18.38	Propofol
			T		
0.571	(0.16)37.07	(0.38)37.18	(0.40)37.42	(0.89)37.52	ketamine
	(0.33)37.33	(0.42)37.37	(0.44)37.52	(0.79)37.55	Propofol

Table 3: Pain score and RASS in patients of the two groups

p value	Day 4	Day 3	Day 2	Day 1	Groups

		)Wong-Baker Faces Pain Rating Scale(Pain score			
0.0001	(0.54)0.28	(0.55)1.16	(0.59)2.52	(0.51)3.48	ketamine
	(0.37)2.16	(0.50)2.56	(0.47)3.09	(0.50)3.56	Propofol
			RASS		
0.0001	0	(0)1	(0.35)2.04	(0.49)3.36	ketamine
	(0.30)2.09	(0.49)2.38	(0.25)3.06	(0.48)3.34	Propofol

Table 4: Mean and standard deviation of intubation time in two groups

P value	Mean(SD)	Group
0.0001	(8.73)82.72	ketamine
	(8.46)179	Propofol

DISCUSSION

The highest prevalence of delirium is among weak patients and those with very sensitive and bad conditions, such as patients admitted to the intensive care unit and patients in the surgical ward. More than a third of hospitalized people over the age of 80 will experience this condition (3). Agitated delirium is more likely to cause problems, especially in patients with mechanical ventilation, because mechanical ventilation increases the risk of self-extubation compared to patients with other essential medical devices (5). Therefore, recognizing and introducing a substance that reduces the duration of delirium will be very important in the treatment process of these patients. Achieving a combination that can reduce this time of intubation and delirium has always been one of the goals of anesthesiologists and intensive care unit personnel and has been of great importance in reducing the mortality of these patients, increasing their health and life expectancy, as well as prognosis of disease (12).

In the present study, the mean and standard deviation of age in the two groups of ketamine and propofol were 12.65±39.63 and 11.81 ± 41.09, respectively, which did not show significant deviation (P = 0.633). In addition, the patients consisted of 14 (43.8) females and 18 (56.3) males in the ketamine group and 15 (46.9) females and 17 (53.1) males in the propofol group who did not differ significantly (P= 0.802) These findings indicate that the results of the study are not affected by a specific age group or gender. In this study, the mean (standard deviation) duration of intubation in the ketamine group was 82.72 (8.73) hours and in the propofol group 179.81 (8.46) hours, which were significantly (P <0.0001) less in the ketamine group than in the propofol group. In other words, ketamine has halved the duration of intubation compared to the propofol group and can be a suitable drug to reduce the duration of intubation in patients with agitation.In our study, the duration of intubation in the ketamine group was 3-4 days with an average of 3.45 days. A retrospective by Buchheit et al. (13) on mechanically ventilated patients admitted to surgical ICU wards, showed that low-dose ketamine infusion (1-5 μg /kg /min) resulted in an average duration Intubation of 1.44 days (0.58 to 2.66).

This indicates a low duration of intubation in two studies on ketamine use. Although in our study the intubation time was clearly shorter than in the propofol group, information similar to our study was not found in scientific literature for comparison.In our study, changes in patients' vital signs in the two groups did not show significant changes during the first 4 days (HR: P = 0.894, MAP: P = 0.808, T: P = 0.571, RR: P = 0.691). However, this comparison was done until the fourth day because the duration of intubation in the ketamine group was not more than 4 days and no more information was available from the fourth day for comparison with the opposite group. Therefore, according to the statistical analysis of the ketamine and propofol groups, neither of them has been able to make fundamental changes in the course of vital signs over time. However, as shown by the trend of all these changes, the vital signs exhibited a decreasing trend from the first day to the day of extubation, leading to better vital signs.Heidari et al. (14), examined the effect of intramuscular ketamine versus haloperidol on control of severe agitation in the emergency department, where vital signs were not found to be significantly different between the two groups (P> 0.05). In other words, in this study, ketamine did not have significant changes on vital signs, which is mor or less in line with our study.In our study, changes in RASS score in the first 4 days, when the necessary information was available from both groups, decreased more rapidly in the ketamine group, and this decreasing trend was significantly higher in the ketamine group during 4 days (P <0.0001). In these 4 days, the average RASS score in the ketamine group increased from 3.36 to 0 on the fourth day, while the rate increased from 3.34 to 2.09 in the propofol group.In other words, this score has decreased by 1 unit per day in the ketamine group during 2-3 days, but this amount in the propofol group has been only 1 unit during this whole period. Therefore, ketamine has been able to reduce the rate of agitation with high speed, when reached 0 level in 2-3 days.Our study in terms of RASS score was mor or less in line with the study of Li et al. (15), where they showed that ketamine (IV:1 mg / kg or IM: 2 mg / kg) significantly reduced RASS from 4 to 0 compared to before use (P = 0.001).

Our findings showed that the mean pain score of patients during this period increased from 3.48 on the first day in the ketamine group to 0.28, while this variable increased from 3.56 on the first day to 2.16 units in the propofol group(P <0.0001); in other words, ketamine was capable of reducing patients' pain at a higher rate than the propofol group. Ketamine reduced the pain score by one unit per day during regular treatment and was capable of reducing the mean pain score by more than 3 units over 3

days.In the propofol group, there was a change of about 1.40 in the pain score from the first to the 4th day (from 3.56 on the first day to 2.16 on the 4th day). Therefore, ketamine could be an effective and appropriate drug in reducing pain in patients with agitated delirium hospitalized in the ICU.In this regard, the results of the study of Demir et al. (16) were consistent with our study, so that they examined the prevention of agitation with ketamine in rhinoplasty. In mentioned study, two groups of 70 candidates for elective rhinoplasty (ketamine group and normal saline group) were examined. The ketamine group received 0.5 mg /kg and the saline group received 1 ml of normal saline 20 minutes before surgery. They found that the mean (standard deviation) of the pain score (Numerical Rating Scale [0-10]) in the ketamine group was 2.74 (1.38) and in the normal saline group was 4.51 (1.23). This score is significantly lower in the ketamine group, leading to reduction of postoperative pain in patients. Pain control is a feature of ketamine that has been mentioned in articles. For example, Sleigh et al. (17) in a review study suggested that ketamine may in some cases facilitate endogenous pain. They have suggested that the effects of ketamine on chronic pain, and as an antidepressant, may be due to a secondary increase in synaptic structural connections, which is mediated by the ketamine-induced glutamate on neuronal response.In addition, Cierra et al. (18) in a case series study shared their experiences with the use of continuous ketamine injections for analgesia and sedation in four mechanically ventilated patients with a history of opioid abuse who responded less well to propofol treatment. They found that ketamine was successful in relieving pain and sedation in three patients. At the same time, it reduces the need for other painkillers and sedatives with minimal side effects.

CONCLUSION

The use of ketamine was capable of reducing the duration of intubation, pain and agitation of the patient with agitated delirium hospitalized in the intensive care unit while it does not cause hemodynamic changes for the patient.

REFERENCES

1. Ragnarsson KT, Clarke WR, Daling JR, Garber SL, Gustafson CF, Holland AL, Jordan BD, Parker JC, Riddle MA, Roth EJ, Seltzer MM. Rehabilitation of persons with traumatic brain injury. Journal of the American Medical Association. 1999 Sep 8;282(10):974-83.
2. Marik PE, Varon J, Trask T. Management of head trauma. CHEST Journal. 2002 Aug 1;122(2):699-711.
3. Rao V, Lyketsos C. Neuropsychiatric sequelae of traumatic brain injury. Psychosomatics. 2000 Apr 30;41(2):95-103.
4. Khalili HA, Keramatian K. Effect of methylphenidate in patients with acute traumatic brain injury; a randomized clinical trial. Progress in Neurotherapeutics and Neuropsychopharmacology. 2008 Jan;3(1):189-97.
5. Gill M, Windemuth R, Steele R, Green SM. A comparison of the Glasgow Coma Scale score to simplified alternative scores for the prediction of traumatic brain injury outcomes. Annals of emergency medicine. 2005 Jan 31;45(1):37-42.
6. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, Jr, Inouye SK, Bernard GR, Dittus RS. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291:1753–1762. doi: 10.1001/jama.291.14.1753. [PubMed] [CrossRef] [Google Scholar]
1. 38 .7. Bell, RF; Eccleston, C; Kalso, EA (28 June 2017). "Ketamine as an adjuvant to opioids for cancer pain" (PDF). Cochrane Database of Systematic Reviews. 6: CD003351. doi:10.1002/14651858.CD003351.pub3. PMC 6481583. PMID 28657160.
7. Moyse, DW; Kaye, AD; Diaz, JH; Qadri, MY; Lindsay, D; Pyati, S (March 2017). "Perioperative Ketamine Administration for Thoracotomy Pain". Pain Physician. 20 (3): 173–184. PMID 28339431.
8. Siddall OR. Use of methylphenidate in traumatic brain injury. Annals of Pharmacotherapy. 2005 Jul;39(7-8):1309-13.
9. Fujimoto ST, Longhi L, Saatman KE, McIntosh TK. Motor and cognitive function evaluation following experimental traumatic brain injury. Neuroscience & biobehavioral reviews. 2004 Jul 31;28(4):365-78.
10. Husson I, Mesples B, Medja F, Leroux P, Kosofsky B, Gressens P. Methylphenidate and MK-801, an N-methyl-d-aspartate receptor antagonist: shared biological properties. Neuroscience. 2004 Dec 31;125(1):163-70.
11. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA, Jr, et al. Prevalence and risk factors for development of delirium in surgical and trauma Intensive Care Unit patients. J Trauma. 2008;65:34–41. [PMC free article] [PubMed] [Google Scholar]
12. Buchheit JL, Yeh DD, Eikermann M, Lin H. Impact of Low-Dose Ketamine on the Usage of Continuous Opioid Infusion for the Treatment of Pain in Adult Mechanically Ventilated Patients in Surgical Intensive Care Units. Journal of Intensive Care Medicine. 2019;34(8):646-51.
13. Heydari F, Gholamian A, Zamani M, Majidinejad S. Effect of Intramuscular Ketamine versus Haloperidol on Short-Term Control of Severe Agitated Patients in Emergency Department; A Randomized Clinical Trial. Bull Emerg Trauma. 2018;6(4):292-9.
14. Li M, Martinelli AN, Oliver WD, Wilkerson RG. Evaluation of Ketamine for Excited Delirium Syndrome in the Adult Emergency Department. The Journal of Emergency Medicine. 2019.
15. Demir CY, Yuzkat N. Prevention of Emergence Agitation with Ketamine in Rhinoplasty. Aesthetic Plast Surg. 2018;42(3):847-53.
16. Sleigh J, Harvey M, Voss L, Denny B. Ketamine – More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care. 2014;4(2):76-81.
17. Treu CN, Groth CM, Patel JH. The Use of Continuous Ketamine for Analgesia and Sedation in Critically Ill Patients with Opioid Abuse: A Case Series. J Crit Care Med (Targu Mures). 2017;3(4):148-52.