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ORIGINAL ARTICLE

Can we use magnesium for sedation in the intensive care unit for critically ill patients: Is it as effective as other sedatives?

Yoğun bakım ünitesinde magnezyum'u kritik hastalar için sedasyon amaçlı kullanabilir miyiz? Diğer sedatifler kadar etkili mi?

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Summary

Objectives: The aim of this prospective, randomized study was to investigate the effect of magnesium added to midazolam on the hemodynamics, transition time to a T-piece, mechanical ventilation duration, additional sedative-analgesic requirement using bispectral index (BIS) monitorization and sedation scales.

Methods: Fifty critically ill patients receiving mechanical ventilation support in the intensive care unit were randomly assigned to 2 groups. Group I received a 0.03-0.3 mg/kg bolus loading dose+0.03-02 mg/kg/hour midazolam infusion; Group II received a 2 g bolus at 30 minutes, 16 mg/24-hour magnesium infusion+0.03-02 mg/kg/hour midazolam infusion. BIS levels and sedation levels were continuously monitored.

Results: The duration of mechanical ventilation in Group I was longer than that of Group II (31±12 hours, 19±11 hours, respectively; p<0.01). The length of time to start spontaneous breathing trials with a T-piece was greater in Group I than in Group II (27±11 hours, 16±11 hours, respectively; p<0.01). The 48-hour insulin requirement of Group I was greater than that of Group II (p<0.05).

Conclusion: Adding intravenous magnesium to the traditional sedation protocols in the intensive care unit decreased midazolam use as well as the additional analgesic requirement and mechanical ventilatory support duration without any side effects.

Keywords: Bispectral Index; Intensive Care Unit; magnesium; midazolam; sedation-analgesia.

Özet

Amaç: Bu prospektif randomize çalışmada, midazolama eklenen magnezyumun hemodinami, T-parçasına geçiş süresi, mekanik ventilasyon süresi ile BIS monitorizasyonu ve sedasyon ölçekleri kullanılarak ek sedatif analjezik gereksinimi üzerine etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Yoğun bakım ünitesinde mekanik ventilasyon desteği alan 50 hasta rasgele olarak iki gruba ayrıldı. Grup I, 0.03-0.3 mg/kg bolus yükleme dozu +0.03-02 mg/kg/saat midazolam infüzyonu aldı; Grup II, 30 dakikada. 2 gr bolus, 16 mg/24 saat magnezyum infüzyonu +0.03-02 mg/kg/saat midazolam infüzyonu aldı. BIS seviyeleri ve sedasyon seviyeleri sürekli olarak monitörize edildi.

Bulgular: Grup I'de mekanik ventilasyonun süresi grup II'den daha uzundu (sırasıyla 31±12 saat; 19±11 saat; p<0.01). T-parçası ile spontan solunum denemelerine başlama zamanı, grup I'de grup II'den (27±11 saat; 16±11 saat) daha uzundu (p<0.01). Grup I'in 48 saatlik insülin gereksinimi grup II'den yüksekti (p<0.05).

Sonuç: Yoğun bakım ünitesinde, geleneksel sedasyon protokollerine intravenöz magnezyumun eklenmesi, midazolam ve ek analjezi gereksinimini, mekanik ventilasyon destek süresini herhangi bir yan etkisi olmaksızın azaltmıştır.

Anahtar sözcükler: Bispectral index; intensive care unit; magnesium; midazolam; sedation-analgesia.

Introduction

The need for sedation and analgesia for critically ill patients undergoing uncomfortable procedures in the intensive care unit (ICU) has often been overlooked. Proper sedation may reduce stress and avoid complications during procedures such as mechanical ventilation, suctioning, invasive procedures.[1, 2] Although midazolam is a short-acting benzodiazepine that was used widely in the ICU, long-term infusions (> or = 3 days) may cause tolerance tachyphylaxis

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which leads to prolonged mechanical ventilation (MV) duration and ICU stay. Withdrawal syndrome is another risk for these patients which is associated with high dose use of midazolam with long terms.[3-5] Thus, the evaluation of the patient will facilitate, and the application of "weaning" to patients with MV can accelerate.[2, 3]

Various pharmacologic agents are used to provide sedation, anxiolysis, analgesia and amnesia. The most commonly used drugs are opioids, γ-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) because of their effectiveness and relatively short elimination half-lives.[2-4]

Midazolam differs from other benzodiazepines because of its rapid onset and short duration of action, low incidence of thrombophlebitis and pain on injection, and minimal cardiovascular effects.[4] However, since its elimination prolonged in critically ill patients resulting in prolongation of its actions causes extubation failure and extend the duration of mechanical ventilatory support.[1-3]

Magnesium, the fourth most abundant cation in the body and the second most abundant intracellular cation, has been used alone or in combination with other drugs to potentiate the actions of these drugs. It potentiates drugs and minimizes side effects by reducing their requirements.[6]

Magnesium is involved in several processes, transmembrane ion flux, including hormone receptor binding, and regulation of adenylate cyclase, muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability, and neurotransmitter release.[6-7]

The analgesic efficacy of magnesium has been remarkable in recent years, and research has focused on this subject. Perioperative magnesium application reduces stress response to intubation and surgery while reducing the dose of anesthetic and analgesic drugs used. Magnesium, which is the NMDA receptor antagonist, prevents induction of peripheral nociceptive stimulation induced by central sensitization and eliminates pre-formed hypersensitivity. The fact that magnesium is also a physiological calcium channel antagonist contributes to analgesic efficiency. Since it does not affect the respiratory drive, it should not interfere with weaning from mechanical ventilation.[7-9]

In this prospective randomized study, our primary aim was to evaluate the results and the effectiveness of adding magnesium sulfate as an adjuvant drug to midazolam; to assess the consumption of midazolam in an overall sedation protocol and to determine patient satisfaction with that treatment.

Materials and Methods

The study protocol approved by the institutional Ethics Committee, and a written informed consent obtained from each patient. The prospective, double-blind, randomized clinical study was conducted by the principles of the Declaration of Helsinki between May 2009-August 2009 in Bakırköy Dr. Sadi Konuk Training and Research Hospital.

The study included a total of 50 adult patients between 18 and 82 years of age; who had to take mechanical ventilation support resulting from respiratory insufficiency due to the internal or surgical diseases. All patients received a standard sedation protocol.

For a patient that is capable of requiring an adaptation to mechanical ventilation instead of deep sedation; surgical patients with respiratory insufficiency due to internal diseases such as chronic obstructive pulmonary disease, congestive heart failure, pulmonary embolism and poisoning cases were selected. Cerebral ischemia, previously known neurological disorder, patients who have to take the muscle relaxant or opioid analgesics already, those who need deep sedation, cranial surgery cases excluded.

After standard monitorisation (noninvasive or invasive blood pressure, pulse oximetry, and electrocardiography) patients randomized into 1 of 2 treatment groups of midazolam group and midazolam + magnesium group. Group I (n=25) took 0.03-0.3 mg/kg bolus loading dose of midazolam and 0.03 - 0.2 mg/kg/hr midazolam infusion; Group 2 (n=25) took 2 gr bolus at 30 min, 16 mg/24 hr magnesium infusion +0.03-02 mg/kg/hr midazolam infusion. The total amount of midazolam used by patients in both groups recorded.

Sedation levels were measured with the Ramsay Sedation Scale (RSS), the pain was assessed with the Pain Intensity Score (PIS). RSS was categorized as 1-Patient is anxious and agitated or restless, 2-Patient is co-operative, oriented, and tranquil, 3-Patient responds to commands only, 4-Patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5-Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6-Patient exhibits no response. PIS was categorized as 0-3 (mild), 4-6 (moderate), 7-10 (severe).[8, 9]

Patient sedation was performed within the ranges of RSS: 2-4; and PIS <4.

If sedation/analgesia were considered inadequate by the bedside nurse and by the physician on duty, rescue analgesic of tramadol of 1-2 mg/kg (max 6 mg/kg/24 hr) and midazolam 2-5 mg bolus was applied (although the drug infusion rate increased to the upper limit; for sedation RSS ≥4, for pain PIS ≥3). Additionally, the Bispectral Index (BIS) (Aspect A-1050, Aspect Medical Systems, Natick, Massachusetts) was used to monitor the depth of anesthesia using electroencephalography data via a set of electrodes (BIS Sensor, Aspect Medical Systems) attached to the patient's forehead per the manufacturer's instructions.[8] The degree of sedation was measured continuously using BIS monitoring. Patients maintained at BIS levels in the range 60–80, which associated with an adequated sedated state.

Patients monitored for 48 hours, 30 minutes intervals and statistical calculations have taken every 2 hours. SPO^2, $etCO^2$, heart rate (HR), invasive arterial pressures (systolic arterial pressure, diastolic arterial pressure, mean arterial pressure) also recorded. APACHE-II and SOFA scores calculated. Biochemical parameters of the patients admitted to the ICU and after 48 hours, such as urea, creatinine, Na, K, AST, ALT, blood glucose, amount of insulin needed for 48 hours, and the amount of rescue analgesic used for 48 hours were recorded. Magnesium levels of the patients who take magnesium admitted to the ICU and at the end of the 48th hour also recorded. Side effects such as arrhythmia, hypotension, hypertension, tachycardia, nausea, vomiting, pruritus, bradycardia, apnea, atelectasis, and tolerance were also recorded.

Statistical Analysis

Statistical analysis was performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software program (Kaysville, Utah, USA). Results expressed as mean±SD. When study data were evaluated, to compare the descriptive statistical methods, as well as quantitative data for the groups with standard distribution Student t-test, used. Scores were analyzed using the Mann Whitney U-test for independent samples. For intergroup comparison of the parameters that had normal distribution the paired samples t-test used. Chi-square test used to compare qualitative data. Spearman's Rho test was used to analyze the relationships between parameters. The results evaluated in a confidence interval of 95% and a p-value 0.05 was considered statistically significant in these analyses.

As a result of the power analysis, when we receive the difference 13 and the standard deviation 14 on the assessment based on the average of the BIS measurements, The number of samples in the groups detected for Power: 0.90 and alfa: 0.05 was n=25.

Results

The study protocol conducted on 50 cases between the ages of 18 and 88; 21 (42%) of whom were female, and 29 (58%) of whom were male. The mean age of the patients was 50.98±21.43 (Table 1). The demographic characteristics of the patients were similar in both groups (p>0.05). Baseline APACHEE II scores and SOFA scores were also similar between the groups (p>0.05) (Table 2).

Table 1. Characteristics of the study patients

	Group I (midazolam) Mean±SD	Group II (Mg+midazolam) Mean±SD
Age (year)	48.76±21.42	53.20±21.65
Weight (kg)	78.80±9.73	79.76±21.59
Height (cm)	170.12±7.65	167.60±21.03
	n (%)	**n (%)**
Sex		
Female	10 (40)	11 (44)
Male	15 (60)	14 (56)

+ Student t test; ++ Chi-square test.

Table 2. APACHE-II and SOFA scores of the patients

	Group I (midazolam) Mean±SD	Group II (Mg+midazolam) Mean±SD	+p
APACHE-II	13.32±3.83	4.52±0.96	0.604
SOFA	12.76±3.75	4.28±1.27	0.456

+ Student t test; ++ Chi-square test.

No statistically significant difference in the mean blood pressure during follow-up found between the groups. The median respiratory rate, median arterial saturation and median peripheric saturation as determined by pulse oximetry and peripheral arterial blood gas analysis were similar in both groups ($p>0.05$).

Heart rate was significantly higher in Group I than Group II except for first hour ($p<0.05$, $p>0.05$).

The duration of mechanical ventilation in Group I was longer than Group II (31±12 hours; 19±11 hours, respectively; $p<0.01$). Time to start spontaneous breathing trials with T-piece was significantly higher in Group I than Group II (27±11 hours in Group I, 16±11 hours in Group II) ($p<0.01$) (Table 3).

The 48-hour insulin requirement of Group I is significantly higher than Group II (45±2 U in Group I; 21±72 U in Group II) ($p<0.05$) (Table 3).

The amount of total midazolam (mg) used was higher in Group I compared with Group II (147±49 in Group I, 103±19 in Group II) ($p<0.01$). The amount of total tramadol (mg) used as rescue analgesia was also higher in Group I compared with Group II (80±4 mg in Group I; 48±3 mg in Group II) ($p<0.01$) (Table 3).

No side effects noted during or after administration of midazolam infusion and midazolam plus magnesium infusion.

The BIS values were higher at all times except the first hours in Group I about Group II ($p<0.05$) (Fig. 1). No, statistically difference was observed in the RSS scores and PIS scores between the groups.

The level of patients' satisfaction noted between the two groups, and no patient described the efficacy of their pain relief as "bad." However, it was available with the twice doses of midazolam and with the adjuvant effect of magnesium in Group II concerning Group I ($p<0.05$).

Discussion

According to our study, a continuous infusion of magnesium moderately reduced overall midazolam consumption in critically ill patients in ICU without severe side effects while providing faster recovery, earlier extubation, shorter mechanical ventilation.

Providing adequate sedation and analgesia for critically ill patients is the primary step in ICUs requiring ventilatory support to facilitate mechanical ventilation and endotracheal tube tolerance. While sedation prevents patients from having painful ex-

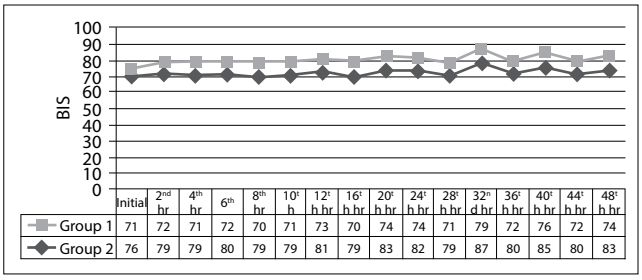

Figure 1. Bispectral index (BIS) values during the sedation protocol.

Table 3. Study outcomes using intention-to-treat anylysis

Data	Group I (midazolam)	Group II (Mg+midazolam)	p
Mechanical ventilation time (hours)	30.80±12.14	18.95±10.86	0.004**
Time to start spontaneous breathing trials with T-piece (hours)	26.80±10.98	15.61±10.58	0.004**
Total midazolam consumption (mg)	146.88±49.32	103.44±18.97	0.001**
Rescue analgesia amount (mg)	79.23±42.51	65.00±31.16	0.424
Total insulin required in 48 hours (unit)	45.00±27.25	21.72±12.32	0.016*

+ Student t test; *p<0.05; ** p<0.01.

periences in ICU, deep sedation and its side effects can compromise the treatment protocols; and inadequate sedative techniques may adversely affect the patient. Because of this, physicians should be aware of the limitations when choosing a sedative medication which does not interfere with the early extubation of the patients.[9-12]

Midazolam is the most used benzodiazepine in ICU because of its rapid onset and short duration of action, minimal cardiovascular and respiratory effects which make midazolam a valuable sedative that can be given via continuous intravenous infusion in the ICU.[7, 8] But prolonged use of midazolam may cause respiratory depression which prolongs the duration of MV and ICU stay.[7]

In the study of Gupta et al.,[13] where they used dexmedetomidine and midazolam for mechanically ventilated patients in ICU, they found significantly longer duration of MV time in midazolam group with compared to dexmedetomidine group.

Similar to this study, we have found longer mechanical ventilation duration in midazolam group (Group I) compared to magnesium and midazolam (Group II) group. Administration of magnesium moderately reduced overall midazolam consumption without severe adverse effects. With related to the reduction in midazolam consumption, recovery time, defined as the time of starting spontaneous ventilation through an endotracheal tube (T piece) and extubation time was significantly longer in Group I compared with Group II ($p<0.01$).

Magnesium has been used alone or in combination as an adjuvant with other drugs to potentiate the actions of these drugs and found to be useful in treating painful conditions. Magnesium could also modulate postoperative pain by preventing nociception associated with central sensitization via blockade of NMDA receptor calcium ionophore and cause a reduction in analgesic consumption during the intraoperative and postoperative periods.[14-18]

Previous studies demonstrated reduced midazolam or other sedative-analgesic drug consumption with various agents in the ICU period. Therefore, adverse effects caused by increased drug doses could minimize.[19-22]

Tramer et al.[14] reported a significant reduction of analgesic requirements in their study. According to their research in the magnesium group, morphine requirement was significantly lower on the postoperative period. In our research, midazolam consumption was lower in the magnesium group. These results are quite similar to what Tramer et al. found in their research.

In the present study, no differences seen between the groups regarding to sedation levels. But, this could be possible with the higher doses of midazolam in Group I. In Group II magnesium reduced the total midazolam consumption. With the decrement in total midazolam consumption in group I, MV duration was also decreased.

Koining et al.[21] and Arcioni at el.[22] have also found a reduction in the analgesic requirement in their studies. In our study, although there was no statistical difference for the cumulative analgesic consumptions between the groups ($p>0.05$); total dose of rescue analgesic requirement (tramadol) was lower in Group II with regard to Group I (rescue analgesia in Group I: 79.2±42 mg and in Group II: 65±31 mg tramadol). In this study the patients undergoing major surgery were excluded. So, the analgesic requirement was similar between the groups. As the amounts of rescue analgesia and midazolam were in moderate levels because of the need of the patients included to the study protocol, the RSS scores and PIS scores were similar between the groups.

Akarsu et al.[15] evaluated the effect of magnesium in preventing remifentanil-induced hyperalgesia in their study and found that with administration of magnesium preemptively reduced remifentanil-induced hyperalgesia, and additional analgesic requirement was lower in magnesium group in all measurement times.

Özkan et al.[19] investigated the effect of a preoperative single dose magnesium on the postoperative morphine consumption, and they found a reduction on postoperative morphine requirement without side effects and with better postoperative patient comfort.

We administered magnesium in the dosage of 2 gr bolus at 30 min, 16 mg/24 hr infusion. This dosage

has been reported to be safe without any adverse effects as published by several workers. It is suggested that NMDA blocking drugs should be given before beginning of nociceptive stimulus to inhibit the process of central sensitization.[17, 18] We started to sedation protocol to the patients as arrival to the ICU.

Unpredictable awakening times and prolonged extubation times have reported with the long-term infusion of midazolam.[18] Tolerance, withdrawal syndrome and tachyphylaxis may also occur with the longer-term and high dose of midazolam infusions which will prolonged the MV duration thus ICU stay. (≥3 days).[1, 8]

Since our study protocol was within 48 hours, we did not see any symptom (shivering, sweating, tachycardia, bradycardia, abnormal movements) related to withdrawal of midazolam.

Magnesium, while has both a calcium antagonist with vasodilator by decreasing peripheral resistance and antidysrhythmic effects and an adrenergic antagonist with principally alpha antagonistic actions, can affect heart rate and blood pressure.[11]

In our study, hemodynamic responses to noxious stimuli efficiently blunted in the magnesium-treated group. Heart rates were significantly lower in Group II compared with Group I which did not need any medical intervention and within the normal ranges; this probably indicates that the sedative and analgesic properties of magnesium reduced sympathetic stimulation.[13-17]

We have also used BIS monitoring and choose a BIS target range of 60-80 which is correlated well with a depth of sedation and increased by not only awareness but also sympathetic activation.

BIS monitoring can be a useful objective measurement for detecting inadequate sedation, analgesia, or both during general anesthesia. BIS values below 60 indicate a low probability of recall and intraoperative awareness.[21-23] In our study, BIS values were significantly higher in Group I due to Group II during the 20th, 24th, 28th, 32nd, 36th, 40th, 44th and 48th hours ($p<0.05$; $p<0.01$). There was no difference during the first hours of ICU staying ($p>0.05$). Concerning these findings, we can say that addition of magnesium as an adjuvant reduced sedation requirements, and provided better sedation during mechanical ventilation.

The role of magnesium in BIS response is debatable in a few studies. According to the Memiş et all.[24] while magnesium (2 g/h infusion) infusion was reducing sufentanil consumption, BIS values did not significantly change. Average BIS values were kept in the range of 61-88 in this study by titrating the dose of sufentanil infusion in groups. In another study, i.v. magnesium (30 mg/kg as a bolus dose followed by a continuous infusion of 10 mg/kg/h) both significantly reduced total midazolam consumption and BIS values in patients under monitored anesthesia care for shockwave lithotripsy.[25]

We have measured serum concentrations of Mg before starting to the sedation and at the end of the 48th hour. There was a difference between the initial and last levels, but it was within the normal ranges and no side effects seen due to the magnesium. The üre-creatinin levels were within the normal ranges.

Intracellular magnesium is essential in regulating insulin action, insulin-mediated glucose uptake, and vascular tone.[4-5] Low doses of intracellular Mg concentrations may result in a defective tyrosine-kinase activity, preceptorial impairment in insulin action, and worsening of insulin resistance.[4-5] In our study due to high blood glucose levels, insulin requirement was significantly higher in Group I in comparison to Group II ($p<0.05$).

Adjunct analgesic-sedative agents are utilized to improve analgesic-sedative outcomes and minimize the side effects of analgesic-sedative agents. As a result of our study findings, we can recommend the use of intravenous magnesium as magnesium may decrease total dose of sedatives, rescue analgesia consumption without any adverse effects; however, small sample size and heterogeneity of methodology in included trials restrict the ability to draw definite conclusions. Higher infusion doses of magnesium might have caused a more significant decrease in midazolam requirement. Therefore, given the apparent safety and efficacy of magnesium, its role as an adjunct sedative-analgesic in ICU should be further investigated with the most current techniques.

In conclusion, as our results demonstrated that addition of magnesium to our sedation protocol lowered the midazolam consumption and analgesic requirement, and resulted in the shorter length of mechanical ventilatory support in a mixed population of ICU patients.

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