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Comparison of the efficacy of dexmedetomidine and dexmedetomidine-magnesium combination in sedation management in intensive care

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MAIN POINTS

- This study has shown that magnesium can be used safely with other sedative agents for sedation.
- Although magnesium added to dexmedetomidine is not significantly different, it is clear that it provides sufficient sedation.
- It has been concluded that magnesium can be used safely in intensive care patients both in adaptation to mechanical ventilation and in the prevention of delirium.

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ABSTRACT

Aim: The aim of this study was to evaluate the correlation of sedation with subjective clinical sedation scores and compare plasma cortisol levels as an objective marker between two groups: patients sedated with dexmedetomidine alone and patients sedated with a combination of dexmedetomidine and magnesium via mechanical ventilation.

Materials and Methods: A total of 50 patients were enrolled and divided into two groups. Group 1 (dexmedetomidine group) received a loading dose 1μg/kg, followed by a continuous infusion 0.2-1.4 μg/kg/hour for 24 hours. Group 2 (dexmedetomidine+magnesium group) received a loading dose 1 μg/kg of dexmedetomidine, followed by a continuous infusion 0.2-1.4 μg/kg/hour for 24 hours, along with two bolus doses of 2 grams of magnesium and a continuous infusion of 16mg/24 hours. Sedation scale scores, Glasgow coma scores, heart rate, and plasma cortisol levels at baseline and at 24 hours were recorded throughout the 24-hour study period.

Results: On the 24th hour, cortisol levels were significantly lower in Group 2 ($p<0.05$). Heart rate was significantly lower in Group 2, except at baseline ($p<0.05$). No significant differences between the groups regarding sedation scale scores or Glasgow coma scores ($p>0.05$) were found.

Conclusion: Although adding magnesium to dexmedetomidine provided sufficient sedation and may have enhanced compliance with mechanical ventilation, no significant difference was found in achieving the target sedation levels in a clinical setting.

Keywords: Intensive care, Sedation, Dexmedetomidine, Magnesium, Cortisol

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INTRODUCTION

Intensive care units (ICU) are primarily characterized by advanced organ support systems. Mechanical ventilation support, especially in respiratory failure, is life-saving but comes with several challenges. Regardless of the cause, sedation in patients receiving treatment in ICU units constitutes a significant portion of treatment protocols [1]. Sedation in the ICU can benefit both patients and healthcare providers, as it helps reduce anxiety and agitation, improve patient outcomes, and facilitate necessary medical procedures [2].

Patients in ICU often experience severe pain and discomfort due to the nature of their illnesses or injuries, and sedation is used to alleviate these symptoms. In addition, sedation can facilitate invasive procedures such as intubation, mechanical ventilation, catheterization, tracheostomy, and surgical interventions [3].

However, while sedation can be beneficial for critically ill patients, there are potential risks associated with its use. One of the main risks is excessive sedation, which can lead to respiratory depression and other complications. Furthermore, sedation can increase the risk of delirium, a common complication associated with prolonged ICU stays. Despite the potential benefits of sedation and analgesia in ICU treatment protocols, clinicians face multiple challenges in administering

effective and adequate sedation without causing overdose.

Studies comparing sedative drugs have shown that no single sedative stands out significantly above others [4]. The best results are achieved when the depth of sedation, pain, and the presence of delirium can be monitored as standard, and pain is treated quickly and precisely. the minimum effective dose for patient comfort and safety is used, and early mobilization is facilitated whenever possible [5].

Magnesium, as a sedative, analgesic, and antihypertensive agent, can be used alone or as an adjuvant to enhance the effects of other medications. In ICUs, magnesium can prevent nociception related to central sensitization by blocking the NMDA receptor's calcium ionophore, as well as reduce the consumption of other sedatives used for sedation. This can result in faster recovery, earlier extubation, and shorter mechanical ventilation durations [6].

Although the doses of sedative drugs needed to provide comfort and reduce patient anxiety in ICUs are well-determined based on scientific data, the response to sedative agents is often unpredictable, and individual metabolism rates of these agents can vary. Over time, different evaluation scales, classified as objective and subjective methods, have been introduced for clinicians. Among objective methods, the most commonly known is electroencephalography (EEG), which demonstrates the central effects of sedation. Other objective methods include plasma drug concentrations, lower esophageal contractility, bispectral index (BIS) monitoring, and frontolectomyogram. In contrast, subjective methods, which are considered easier and more practical, have gained more traction in clinical practice and include scales such as the Riker Sedation-Agitation Scale (SAS), Motor Activity Scale (MAAS), Ramsay Sedation Scale (RSS), and Richmond Agitation-Sedation Scale.

In this study, it was aimed to evaluate the correlation between dexmedetomidine and dexmedetomidine-added magnesium sedation applications in patients who had to receive primary mechanical ventilation support, using subjective clinical sedation scores. The secondary objective is to compare plasma cortisol levels as an objective finding between the two groups.

MATERIALS AND METHODS

The study was approved by the local ethics committee (Atatürk University Faculty of Medicine Clinical Research Ethics Committee, Decision no: 09) and was conducted at the Atatürk University Faculty of Medicine, Department of Anesthesia and Reanimation, Intensive Care Unit, between May 1, 2022 and May 1, 2023.

Written consent of the patients was obtained. This was a randomized and double-blind study involving a total of 50 patients aged 18-85, who required mechanical ventilation support, with sedation levels sufficient to increase compliance with mechanical ventilation but without requiring deep sedation, and that allowed for rapid awakening upon request.

Patients with cerebral ischemia during ICU admission, those requiring deep sedation, those who had previously undergone cranial surgery, those with a Glasgow Coma Scale (GCS) score of 3 at ICU admission, those with known neurological diseases, or those requiring significant opioid and muscle relaxant infusions at ICU admission, were excluded from the study. Additionally, patients with severe fluid-electrolyte imbalances or those with issues in hemodynamic stabilization and those with serious cardiovascular diseases were also excluded.

Power analysis

Since no similar studies were in the literature, a pilot study was conducted with 20 patients to calculate the sample size. The minimum sample size required for each group was calculated using the G Power 3.1.9.2 program, with a significance level (α) of 0.05, a 95% confidence interval, and a critical t value of 1.6802300. Based on this calculation, the minimum required number of patients per group was determined to be 22. The study was planned with a total of 50 patients, considering potential data losses.

Methods

All patients in the study received standard ICU monitoring, and a standard sedation protocol was applied after randomization. patients were divided into two groups.

- Group 1 (Dexmedetomidine Group): A loading dose 1 μg/kg of dexmedetomidine was given over 10 minutes, followed by a continuous infusion at a dose range 0.2-1.4 μg/kg/hour for 24 hours. As a placebo, an isotonic solution providing a double-blind randomization was infused with a 2 ml bolus over 30 minutes, followed by a 16 ml/24 hours infusion.
- Group 2 (Dexmedetomidine+Magnesium Group): After a 2 g magnesium bolus administered over 30 minutes, a 16 mg/24 hours magnesium infusion was applied in conjunction with a continuous dexmedetomidine infusion at a dose range of 0.2-1.4 μg/kg/hour for 24 hours.

The total amount of dexmedetomidine used by patients in both groups was recorded. Paracetamol was administered if the patients required analgesia, and the doses and times were recorded. Patients were monitored for 24 hours, and if any additional sedative or muscle relaxant agents were administered during this time, the patient was excluded from the study. The individuals administering the medication and the evaluators of the patients' scores were unaware of the group allocation.

The sedation levels of the patients were recorded during ICU admission using the SAS, RSS, MAAS, and concurrent GCS scores. All evaluations and patient inclusion followed a criterion to ensure that patients were normothermic.

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Additionally, during the study period, the patients' SpO_2, heart rate, and non-invasive arterial pressures (systolic, diastolic, and mean pressure) were monitored and recorded. Before the initiation and after the completion of the sedative infusion, laboratory tests were performed to measure biochemical parameters, including urea, creatinine, serum Na^+(Sodium ion), serum K^+(Potassium ion), serum AST (Aspartate Aminotransferase), and serum ALT (Alanine Aminotransferase). Analgesic use was recorded throughout the 24-hour period. Magnesium levels at ICU admission and after sedation cessation were also recorded. Blood samples for plasma cortisol levels were taken immediately before starting sedation and immediately before discontinuation of sedation.

Statistical analysis

Descriptive statistics were used to present continuous data as mean and standard deviation, while categorical data were presented as frequency and percentage. The distribution of numerical data was assessed using the skewness test. For normally distributed numerical data, the Student t-test was used comparison between two independent groups. When the data were not normally distributed, the Mann-Whitney U test was applied. Categorical variables were performed with the chi- square test. P<0.05 was considered significant. IBM SPSS version 23.0 (Armonk, NY: IBM Corp.) was used for statistical analysis.

RESULTS

The average age of the patients was calculated as 53.26 ± 13.48 (Min: 30; Max: 77). There was no significant difference in age between the groups (p>0.05). Additionally, no significant difference was observed between the groups in terms of Body Mass Index (p>0.05) (Table 1).

Of the patients, 62% (n=31) were male, 38% (n=19) were female. No significant difference in gender was found between the groups (p>0.05).

Regarding magnesium (Mg) and cortisol values at hour 0,

Table 1. Demographic characteristics and analgesia amounts of the groups

	Group I (n=25)	Group II (n=25)	P value
Age (year)	56.16±13.31	50.36±13.27	0.130
Height (cm)	167.72±9.08	169.28±9.68	0.560
Weight (kg)	76.32±6.44	74.84±6.47	0.422
BMI (kg/m^2)	27.38±3.97	26.39±4.04	0.387
Analgesia	1350.00±595.81	2062.50±590.72	0.339

All data are given as mean ± standard deviation. BMI: Body Mass Index.

Table 2. Basal and 24th hour Mg and Cortisol levels of the groups

	Group I (n=25)	Group II (n=25)	P value
Basal Mg Levels	2.31±0.46	2.00±0.76$^{\alpha}$	**0.002**
Basal Cortisol levels	35.33±19.59	21.43±9.89$^{\alpha}$	**0.007**
24th hour Mg levels	2.00±0.44	2.77±0.98$^{\beta}$	**<0.001**
24th hour Cortisol levels	32.72±17.80	14.77±5.45$^{\alpha}$	**<0.001**

All data are given as mean ± standard deviation. $^{\alpha}$ p < 0.05 significant decrease in favor of group 2, $^{\beta}$ p < 0,05 significant decrease in favor of group 1.

Table 3. Comparison of changes in heart rate between groups

	Group I (n=25)	Group II (n=25)	P value
Baseline Value	95.64±14.52	96.48±17.99	0.857
2nd hour	94.12±21.66	80.72±18.23$^{\alpha}$	**0.022**
4th hour	98.76±20.57	82.08±19.66$^{\alpha}$	**0.005**
6th hour	95.92±18.51	77.88±18.88$^{\alpha}$	**0.001**
8th hour	96.04±18.49	77.28±22.14$^{\alpha}$	**0.002**
10th hour	93.76±17.63	75.40±17.83$^{\alpha}$	**0.001**
12th hour	95.32±19.89	75.12±15.54$^{\alpha}$	**0.000**
14th hour	95.00±23.29	73.76±17.25$^{\alpha}$	**0.001**
16th hour	93.80±23.20	74.24±18.54$^{\alpha}$	**0.002**
18th hour	92.44±24.22	73.32±19.54$^{\alpha}$	**0.004**
20th hour	90.76±22.42	72.96±19.96$^{\alpha}$	**0.005**
22nd hour	89.08±20.79	75.96±18.01$^{\alpha}$	**0.021**
24th hour	89.60±20.02	75.52±17.81$^{\alpha}$	**0.012**

All data are given as mean ± standard deviation. $^{\alpha}$ p < 0.05 significant decrease in favor of group 2.

Table 4. Changes in Glasgow Coma Scale (GCS) according to groups.

	Group I (n=25)	Group II (n=25)	P value
Baseline Value	6.72±2.92	6.32±2.35	0.597
2nd hour	5.00±2.46	5.00±1.84	0.708
4th hour	4.88±2.35	4.72±1.74	0.902
6th hour	4.96±2.35	4.68±1.79	0.919
8th hour	4.96±2.76	4.92±1.93	0.424
10th hour	4.92±2.70	4.68±1.93	0.644
12th hour	4.96±2.42	4.56±1.75	0.855
14th hour	4.72±2.49	4.52±2.22	0.910
16th hour	4.64±2.27	4.28±1.99	0.875
18th hour	4.68±2.37	4.16±2.03	0.502
20th hour	5.12±2.72	4.16±2.01	0.324
22nd hour	5.16±2.56	4.16±2.01	0.128
24th hour	4.96±2.35	4.16±2.03	0.129

All data are given as mean ± standard deviation.

Table 5. Changes in Sedation Agitation Scale (SAS) according to groups

	Group I (n=25)	Group II (n=25)	P value
Baseline Value	2.96±1.767	2.2±1.555	0.101
2nd hour	1.68±1.03	1.56±0.768	0.877
4th hour	1.56±0.712	1.48±0.653	0.715
6th hour	1.60±0.764	1.48±0.653	0.636
8th hour	1.64±0.952	1.8±1.041	0.559
10th hour	1.64±0.952	1.60±0.816	0.921
12th hour	1.68±0.900	1.52±0.823	0.448
14th hour	1.96±1.428	1.76±1.20	0.679
16th hour	1.76±1.052	1.60±1.155	0.433
18th hour	2.00±1.472	1.56±1.158	0.243
20th hour	2.00±1.291	1.60±1.155	0.229
22nd hour	1.92±1.115	1.56±1.044	0.241
24th hour	1.76±1.20	1.60±1.08	0.729

All data are given as mean ± standard deviation.

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Table 6. Changes in Ramsey Sedation Scale (RSS) according to groups

	Group I (n=25)	Group II (n=25)	P value
Baseline Value	4.36±1.524	4.68±1.406	0.444
2nd hour	5.04±1.06	5.20±0.816	0.553
4th hour	4.96±1.020	5.20±0.913	0.385
6th hour	4.88±1.054	5.12±0.927	0.397
8th hour	4.92±1.222	5.04±0.978	0.703
10th hour	4.88±1.054	5.04±0.978	0.614
12th hour	4.80±1.190	5.12±1.054	0.319
14th hour	4.68±1.406	4.84±1.106	0.657
16th hour	4.96±1.136	4.92±1.187	0.904
18th hour	4.72±1.646	4.92±1.187	0.624
20th hour	4.80±1.155	4.84±1.143	0.903
22nd hour	4.80±1.190	5.00±1.155	0.549
24th hour	5.20±0.866	4.96±1.136	0.405

All data are given as mean ± standard deviation.

group 1 had significantly higher levels ($p<0.05$). At hour 24, the magnesium level was significantly lower in group 1, while the cortisol level at hour 24 was significantly higher in group 1 ($p<0.05$) (Table 2).

Heart rate was significantly lower in group 2 at all time points except for hour 0 ($p<0.05$) (Table 2).

Looking at the Glasgow Coma Scale (GCS) scores, no significant differences were observed between the groups at any time point ($p>0.05$) (Table 3).

When analyzing the Motor Activity Assessment Scale (MAAS) scores, group 1 had significantly higher scores at hour 0 ($p<0.05$), but no significant differences were seen at other time points ($p> 0.05$) (Table 4).

Regarding the Riker Sedation-Agitation Scale (SAS) scores, there were no statistically significant differences between groups at any time point ($p>0.05$) (Table 5).

Similarly, when evaluating the Ramsay Sedation Scale (RSS) scores, there were no statistically significant differences between groups at any time point ($p>0.05$) (Table 6).

DISCUSSION

Patients treated in intensive care units (ICUs) undergo numerous invasive procedures, such as endotracheal intubation and mechanical ventilation. Pain and discomfort are among the most frequent concerns reported by these patients during their ICU stay [7]. Agitation may lead to dangerous situations, such as the accidental removal of endotracheal tubes or intravenous catheters, which can have life-threatening consequences [3]. As a result, sedatives and analgesics are commonly used in the ICU.

In our study, at hour 24, cortisol levels in Group II (dexmedetomidine + magnesium) were significantly lower compared to Group I (dexmedetomidine only), suggesting that the addition of magnesium to dexmedetomidine sedation better suppressed sympathetic stimulation, preventing cortisol release from the adrenal cortex, and ultimately controlling the stress response more effectively. In another study comparing two groups of mechanically ventilated patients sedated with either midazolam or dexmedetomidine, no significant differences in biomarker levels (cortisol, ACTH, adrenaline, and noradrenaline) were observed after 5 days of follow-up. However, our study observed a significant difference in cortisol levels, which we believe is due to the addition of magnesium, an adjunct with direct sedative effects [8].

In a recent randomized controlled study published by Kurni et al., propofol and midazolam sedation were administered separately to 60 patients with traumatic brain injury, and serum cortisol levels were compared at the end of 48 hours. The change in cortisol levels in both groups was found to be similar and no statistical difference was observed. In our study, we think that the addition of adjuvant magnesium in addition to the sedative medication in the second group made a significant difference in the comparison of cortisol levels at the end of 24 hours [9].

When examining heart rate differences, we found decrease in heart rate of dexmedetomidine + magnesium group compared to the dexmedetomidine-only group at all time points. This bradycardia is attributed to dexmedetomidine's effect on alpha-2 adrenergic receptors. The addition of magnesium potentiated the effects of dexmedetomidine, resulting in a more pronounced decrease in heart rate. Sivriköz et al., unlike our study, did not find a statistical difference in the patient groups whom they sedated with a combination of magnesium and dexmedetomidine in terms of heart rate in the groups to which magnesium was added [10] (The preceding in order sentence should be rewritten to clarify the meaning). Again, Havrylov and colleagues found an increase in heart rates in their patients whom they sedated by adding magnesium to dexmedetomidine, unlike our study, although it was not statistically significant [11].

Regarding sedation depth, as assessed by the GCS, SAS, MAAS, and RSS scales, no significant differences were seen between the two groups. This indicates that adequate and comparable sedation depths were achieved in both groups. Altun et al., in their study, showed that, contrary to our results, the depth of sedation in the group in which magnesium was added to midazolam was less than the group in which only midazolam was used [12]. Memiş et al., in their study by adding magnesium to sufentanil, did not find any difference in sedation levels between the groups in which only sufentanil and magnesium were added to sufentanil, which is consistent with our study [13].

Limitations

The limitations of our study include the small sample size, not having an age limit even though all patients were adults, and evaluating cortisol values only as a stress factor and not studying other parameters.

CONCLUSION

In conclusion, although the combination of dexmedetomidine and magnesium achieved sufficient sedation and in-

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creased patient comfort, it did not result in statistically significant differences in sedation depth or other clinical outcomes. While magnesium has proven beneficial as an adjunct in hypertension treatment, analgesia, and muscle recovery, its role as an adjunct in sedation did not significantly impact our study.

Ethics Committee Approval: Ethical approval was obtained for this study from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 31.03.2023, Decision no: 09).

Informed Consent: Written consent of the patients was obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: There is no conflict of interest between the authors.

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