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The effect of preemptive magnesium sulfate on postoperative pain in patients undergoing mastectomy: a clinical trial

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Abstract. – OBJECTIVE: The effects of preemptive magnesium sulfate (MgSO4) infusion on perioperative hemodynamics and postoperative analgesia in female patients who underwent mastectomy were evaluated.

PATIENTS AND METHODS: American Society of Anesthesiologists (ASA) I-II female patients aged 18 years and over who underwent mastectomy were randomized into 2 groups, including 34 individuals each. The study group (Group I) was given 50 mg/kg MgSO4 in 250 ml isotonic 30 minutes before the induction, and the control group (Group II) was given 250 ml of normal isotonic solution. Standardized anesthesia was applied. Perioperative oxygen saturation, mean arterial pressure (MAP), pulse (HR), sedation scores (ss) in the recovery unit, Verbal Numeric Rating Scale (VNRS), need for rescuer fentanyl, and analgesic needs in the surgical period were evaluated.

RESULTS: Demographic variables were similar. There was no statistical difference between the two groups in terms of the MAP, HR, and oxygen saturation values measured at entry, post-intubation, 15th, 30th, 45th, 60th minutes, and after extubation. There was a statistically significant difference between the two groups in terms of VNRS scores in the recovery unit and at the 2nd, 4th, 8th, and 12th hours during the postoperative surgical period (p=0.0001, 0.001, 0.001, 0.004, 0.021, respectively). The need for rescue analgesics in the first 2 hours of recovery was found to be lower in the study group (p=0.005). The need for postoperative analgesics in the surgical period was not statistically significant (p=0.1).

CONCLUSIONS: Preemptive use of $MgSO_4$ reduces postoperative VNRS scores without affecting hemodynamic parameters during induction and maintenance of general anesthesia.

Key Words:
Magnesium sulfate, Postoperative pain, Analgesia, Mastectomy, Breast cancer.

Introduction

Breast cancer is the most diagnosed type of cancer in women in Turkey and the world. According to the World Health Organization[1] data, the newly diagnosed breast cancer rate was 11.6% in 2018. Acute postoperative pain occurs in 40% of patients undergoing surgery for breast cancer[2]. In the early postoperative period, opioids are commonly used analgesics in the treatment of pain, but they have various side effects such as gastrointestinal, urinary, and respiratory symptoms[3].

Non-opioid analgesics can be used to reduce opioid use and thus limit its side effects. Magnesium sulfate ($MgSO_4$) is an N-Methyl D-Aspartate (NMDA) receptor antagonist that has been used for postoperative analgesia and to reduce both the duration and intensity of pain by preventing central sensitization in response to peripheral painful stimulus[4-9]. The primary aim of this study was to investigate the postoperative analgesic efficacy of $MgSO_4$ in patients who were scheduled for mastectomy with the diagnosis of breast cancer. The secondary aim of our study is to evaluate the changes in perioperative vital signs that may occur due to $MgSO_4$.

Patients and Methods

The study was conducted prospectively on a total of 68 patients between January 2021 and January 2022, with the approval number E-60116787-020-152798 of the Non-Invasive Clinical Research Ethics Committee of Pamukkale University Faculty of Medicine (ClinicalTrials.gov ID: NCT05880732).

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Inclusion Criteria

1. Female breast cancer patients scheduled for mastectomy and modified radical mastectomy
2. ≥18 years
3. Patients with ASA score I-II

Exclusion Criteria

1. Patients who refused to participate in the study
2. Drug allergy
3. Unregulated diabetes mellitus and hypertension
4. Cardiac failure with <45% ejection fraction
5. Renal failure (serum creatinine >2 mg/dL)
6. Liver failure (blood transaminase values 2-fold higher than normal)
7. Glaucoma
8. Psychiatric or neurological disorders
9. Communication difficulties with patient
10. Calcium channel blockers or narcotic drugs used before surgery

The patients were informed before the study, and their consent was obtained. The study was planned as a double-blind prospective randomized study. The patients were divided into two equal groups of 34 individuals each. The study group was determined as Group I and the control group as Group II. A list of random numbers for pre-study randomization was handed over to an assistant, and the anesthesia team was informed which technique would be applied to which group before the surgery. The operations were performed by the same surgical team. The study group (Group I) was given 50 mg/kg $MgSO_4$ in 250 ml of isotonic 30 minutes before induction, and the control group (Group II) was given only 250 ml of normal saline isotonic solution. The patients were monitored with standard pulse oximetry, electrocardiogram (ECG), non-invasive blood pressure, and capnography.

Standardized general anesthesia technique was used in all patients. Midazolam (0.03 mg/kg) was given to all patients for premedication. Intravenous (IV) propofol (2 mg/kg) and IV remifentanil (1 μg/kg), and IV rocuronium (0.6 mg/kg) were given for anesthesia. Anesthesia was provided by inhalation of sevoflurane [a minimum alveolar concentration (MAC) of 2-2.5%], and when needed for main muscle relaxation, IV rocuronium (0.1 mg/kg) was used. Tidal volume and respiratory rate were adjusted to maintain end-tidal CO_2 value between 35 and 40 mmHg. If tachycardia and hypotension due to blood loss symptoms were absent, 0.5 μg/kg IV bolus of fentanyl was added to keep heart rate (HR) and mean arterial blood pressure (MAP) at 20% of preoperative values. After closing the incision, neuromuscular blockade was reversed with IV sugammadex (4 mg/kg), and extubation was performed after anesthesia was completely terminated.

Follow-up of Patients

The pain was assessed postoperatively with the Verbal Numeric Rating Scale (VNRS) (0 no pain - 10 severe pain). Sedation was assessed using a four-point sedation scale (1 - patient fully awake, 2 - patient slightly sedated, responding to verbal commands, 3 - patient moderately sedated, responding to physical stimulation, 4 - patient deeply sedated and not awakening). Patients were kept in the recovery unit for the first 2 hours in the postoperative period, and vital signs were evaluated at discharge and 2^{nd}, 4^{th}, 8^{th}, 12^{th}, and 24^{th} hours in the general surgery ward. If the VNRS score was≥3 in the recovery unit, IV fentanyl was initially given at a dose of 0.5 μg/kg. If the pain score was<3, fentanyl 0.25 μg/kg was given. Rescue fentanyl was repeated if necessary, depending on the patient's pain status, within the first 2 hours postoperatively. After the first 2 hours, the pain was treated with diclofenac sodium 75 mg IV according to the patient's request, and the interval between 2 doses of diclofenac was kept at 8 hours. The amount of analgesic used was noted.

Patients and Study Groups

The study group (Group I) was given 50 mg/kg $MgSO_4$ in 250 ml isotonic 30 minutes before the induction, while the control group (Group II) was given only 250 ml isotonic solution.

Statistical Analysis

The data were analyzed with the SPSS package program. Continuous variables were presented as mean±standard deviation, and categorical variables as numbers and percentages. When the parametric test assumptions were met, Student's *t*-test was used to compare independent group differences. When parametric test assumptions were not met, the Mann-Whitney U test was used to compare the differences between independent groups. In addition, the relationships between continuous variables were analyzed with Spearman's or Pearson's correlation analyses, and the differences between categorical variables were analyzed with the Chi-square analysis. A *p*-value <0.05 was considered statistically significant.

Results

A total of 68 patients were included in the study. The patients were divided into 2 groups, each of which had 34 individuals, and whose demographic characteristics were statistically similar. The demographic characteristics of the patients are shown in Table I.

There was no statistical difference between the two groups in terms of the MAP, HR, and oxygen saturation values measured at entry, post-intubation, 15th, 30th, 45th, 60th minutes, and after extubation (Table II-IV).

There was a statistically significant difference between the two groups in terms of the VNRS scores in the recovery unit (p=0.0001). When the VNRS scores of the patients at the postoperative 2nd, 4th, 8th and 12th hours were evaluated, a statistically significant difference was found between the two groups (p-values=0.001, 0.001, 0.004, 0.021, respectively). There was no significant difference between the two groups in the VNRS scores at the postoperative 24th hour (p=0.43). The VNRS scores of the patients are shown in Table V in detail.

When the sedation scores of the patients were examined, no difference was found between the groups (Table VI).

The need for rescue analgesics in the first 2 hours of recovery was found to be lower in the study group (p=0.005) (Table VII). There was no statistically significant difference between the groups in terms of postoperative analgesic needs during the follow-up of the patients in the general surgery ward (p=0.1) (Table VII).

Discussion

In this study, the postoperative analgesic efficacy of preoperative $MgSO_4$ was investigated in patients who were scheduled for mastectomy with the diagnosis of breast cancer. It was determined that the need for rescue analgesics in the early postoperative period was lower in the group to whom $MgSO_4$ was given.

There are many studies[8,9] with different results in the literature on the postoperative analgesic efficacy of $MgSO_4$. In studies[8,10] investigating the efficacy of $MgSO_4$ on postoperative analgesia in gynecologic oncologic surgeries, it was reported that $MgSO_4$ did not decrease the postoperative Verbal Numeric Rating Scale (VNRS) values. In a study[11] evaluating the effect of $MgSO_4$ on

Table I. Demographic characteristics of the two groups.

	Group I (n=34)		Group II (n=34)		
	Mean (SD)	Med (IQR)	Mean (SD)	Med (IQR)	p
Age (years)	52.41 (13.17)	52.5 (41-60.5)	55.91 (12.91)	53.5 (46.5-65)	0.273 (t=-1.107)
BMI	27.88 (4.88)	28 (24-31)	27.26 (5.34)	27 (23-31)	0.62 (t=0.498)
ASA (I-II)	1.94 (0.24)	2 (2-2)	2 (00)	2 (2-2)	0.154 (z=-1.425)

*p<0.05 statistically significant, BMI: Body Mass Index, ASA: American Society of Anesthesiologists; p<0.05 statistically significant; Mean (SD): Mean (Standard Deviation); Med (IQR): Median (25th-75th percentiles); t: Independent samples t-test; z: Mann-Whitney U test.

Table II. Change of mean arterial blood pressure (MAP) (mmHg) values over time and comparison of groups (min: minute).

MAP Time (minutes)	Group I (n=34)		Group II (n=34)		
	Mean (SD)	Med (IQR)	Mean (SD)	Med (IQR)	p
Entry	96.32 (15.2)	95.5 (85.5-106)	97.12 (17.98)	99 (84.5-108.5)	0.845 (t=-0.197)
Post-intubation	95.41 (22.19)	96 (85.75-110)	89.18 (17.1)	88 (75.75-102.75)	0.09 (z=-1.694)
15th min	78.56 (14.64)	78 (69.75-88)	80.21 (12.09)	80.5 (69-90.25)	0.615 (t=-0.506)
30th min	81.44 (14.02)	79.5 (70.75-90.25)	75.85 (11.93)	75.5 (66.25-85.25)	0.081 (t=1.77)
45th min	79.12 (12.53)	76 (67.75-89)	80.47 (13.29)	80.5 (68.5-90.5)	0.731 (z=-0.344)
60th min	78.68 (13.1)	76 (67.5-91.25)	78.94 (9.88)	76 (72.75-86.25)	0.74 (z=-0.331)
After extubation	88.65 (12.48)	89 (83-98.25)	92.18 (12.96)	89.5 (82-101.75)	0.488 (z=-0.693)

*p<0.05 statistically significant; Mean (SD): Mean (Standard Deviation); Med (IQR): Median (25th-75th percentiles); t: Independent samples t-test; z: Mann-Whitney U test.

Table III. Change of mean heart rate (HR) (beats/minute) values over time and comparison of groups.

HR Time (minutes)	Group I (n=34)		Group II (n=34)		p
	Mean (SD)	Med (IQR)	Mean (SD)	Med (IQR)	
Entry	78.94 (14.73)	75.5 (69-90.5)	81.76 (14.22)	80.5 (69.75-93.25)	0.424 (*t*=-0.804)
Post-intubation	84.85 (14.02)	84.5 (74.5-98)	83.32 (17.05)	81.5 (70.75-90.5)	0.688 (*t*=0.404)
15th min	77.21 (13.96)	75 (67.75-88.25)	76.88 (14.03)	73.5 (67-85.5)	0.924 (*t*=0.095)
30th min	72.29 (13.56)	70.5 (63.5-81.25)	73.76 (14.16)	70.5 (62-85.5)	0.75 (z=-0.319)
45th min	71.32 (14.05)	71.5 (60-78.25)	74.47 (12.94)	73 (65-81.25)	0.34 (*t*=-0.961)
60th min	71.88 (12.7)	70.5 (62-79.75)	70.56 (9.07)	69.5 (63.75-75)	0.623 (*t*=0.494)
After extubation	83.68 (15.04)	85 (71.5-95)	82.44 (12.59)	82 (76.5-88.25)	0.715 (*t*=0.367)

*$p<0.05$ statistically significant; Mean (SD): Mean (Standard Deviation); Med (IQR): Median (25th-75th percentiles); *t*: Independent samples *t*-test; z: Mann Whitney U test.

Table IV. Change of oxygen saturation values over time and comparison of groups.

Time (minutes)	Group I (n=34)		Group II (n=34)		p
	Mean (SD)	Med (IQR)	Mean (SD)	Med (IQR)	
Entry	97.38 (1.79)	97 (96-99)	97.76 (1.79)	98 (96.75-99)	0.307 (z=-1.022)
Post-intubation	98.71 (1.06)	99 (98-100)	98.26 (1.42)	98 (97.75-99.25)	0.226 (z=-1.211)
15th min	97.35 (1.52)	98 (97-98)	97.71 (1.29)	98 (97-99)	0.484 (z=-0.7)
30th min	97.29 (1.88)	98 (96-99)	97.56 (1.37)	98 (96-99)	0.782 (z=-0.277)
45th min	97.15 (1.91)	97 (96-99)	94.91 (15.25)	98 (96-98.25)	0.654 (z=-0.448)
60th min	97.32 (1.89)	98 (96-98.25)	97.79 (1.37)	98 (96.75-99)	0.377 (z=-0.883)
After extubation	98.18 (1.53)	99 (97-99)	98.59 (1.05)	99 (98-99)	0.399 (z=-0.844)

*$p<0.05$ statistically significant; Mean (SD): Mean (Standard Deviation); Med (IQR): Median (25th-75th percentiles); *t*: Independent samples *t*-test; z: Mann Whitney U test.

Table V. Assessment of pain in the postoperative period (VNRS) (1-10).

Time (minutes)	Group I (n=34)		Group II (n=34)		p
	Mean (SD)	Med (IQR)	Mean (SD)	Med (IQR)	
Recovery unit	5.06 (1.77)	5 (3.75-6.25)	7.76 (1.46)	8 (7-9)	0.0001* (z=-5.368)
2nd hour	4.12 (1.9)	4.5 (2.75-5)	5.65 (1.7)	5 (5-7)	0.001* (*t*=-3.491)
4th hour	3.26 (1.42)	3 (2-4)	4.59 (1.52)	4 (4-5)	0.001* (z=-3.416)
8th hour	2.59 (1.48)	2.5 (1.75-3)	3.44 (1.26)	3 (3-4)	0.004* (z=-2.898)
12th hour	1.79 (1.17)	2 (1-2)	2.32 (1.04)	2 (2-3)	0.021* (z=-2.315)

*$p<0.05$ statistically significant; Mean (SD): Mean (Standard Deviation); Med (IQR): Median (25th-75th percentiles); *t*: Independent samples *t*-test; z: Mann-Whitney U test.

postoperative analgesia in patients undergoing elective colorectal surgery, it has been reported that $MgSO_4$ does not reduce the morphine consumption and VNRS values of the patients. In the study of Tramer and Glynn[12] in which the analgesic efficacy of preoperative single-dose $MgSO_4$ was evaluated after ambulatory surgery, it was observed that preemptive IV $MgSO_4$ administration had no effect on postoperative pain and analgesic consumption. However, it was stated that diclofenac was administered rectally to the patients in this study just before the surgery.

On the other hand, there are studies[13,14] reporting that bolus $MgSO_4$ is effective in relieving postoperative pain. In these studies[13,14], continuous infusion or repeated bolus $MgSO_4$ was given in addition to the initial bolus magnesium dose. There are other studies[15] showing the efficacy of $MgSO_4$ in reducing postoperative pain after laparoscopic cholecystectomy and coronary

Table VI. Postoperative sedation score.

		Group I (n=34)	Group II (n=34)	p
Recovery	1	16 (47.1%)	18 (52.9%)	0.886 (cs=0.243)
	2	17 (50%)	15 (44.1%)	
	3	1 (2.9%)	1 (2.9%)	
2nd hour	1	33 (97.1%)	29 (85.3%)	0.197δ
	2	1 (2.9%)	5 (14.7%)	
4th hour	1	34 (100%)	34 (100%)	-
8th hour	1	34 (100%)	34 (100%)	-
12th hour	1	34 (100%)	34 (100%)	-
24th hour	1	34 (100%)	34 (100%)	-

*p<0.05 statistically significant; cs: Chi-Square test; δ: Fisher's Exact test.

Table VII. The need for rescue fentanyl in the recovery unit and the need for analgesics in the general surgery ward in the postoperative period.

		Group I (n=34)	Group II (n=34)	p
Need for rescue fentanyl	no	8 (23.5%)	0 (0%)	0.005*δ
	yes	26 (76.5%)	34 (100%)	
Need for diclofenac	no	19 (55.9%)	12 (36.4%)	0.109 (cs=2.566)
	yes	15 (44.1%)	21 (63.6%)	

*p<0.05 statistically significant; cs: Chi-Square test; δ: Fisher's Exact test.

artery bypass grafting. Studies[15-17] also show that magnesium given before mastectomy can provide an excellent prophylactic strategy against post-mastectomy pain symptoms, and protect the quality of life and cognitive function, by limiting comorbidities accompanying breast cancer.

Our study observed that preoperative single-dose $MgSO_4$ decreased VNRS scores in the early recovery unit and in the postoperative follow-ups.

Postoperative sedation scores were not measured in most of the studies[4,10,12,14] on this subject in the literature. In a study[9], it was found that patients receiving $MgSO_4$ were more deeply sedated despite being aroused more easily in the early postoperative period than the control group. This effect has been attributed to magnesium as being a central nervous system depressant. In a study[13] examining the effect of $MgSO_4$ on general anesthetic needs, hemodynamic changes, and postoperative pain in patients undergoing gynecological surgery, modified Aldrete scores were found to be lower in the magnesium group at the recovery unit. No difference was found between the groups in terms of the sedation scores of the patients in our study.

It is known[18] that magnesium inhibits catecholamine release from the adrenal gland and peripheral adrenergic nerve terminals and causes vasodilation in blood vessel smooth muscle. The effects of magnesium on hemodynamic parameters have been studied in various studies[4,12,18,19]. Ryu et al[4] found that magnesium significantly reduced MAP and HR during IV anesthesia. In a study by Tramer et al[20], no hemodynamic difference was found between the groups. In our study, similar to the study of Tramer et al[20], there was no difference in intubation, response to surgery, and intraoperative hemodynamic parameters.

When the postoperative rescue analgesic needs of the patients were evaluated, the need for rescue analgesia in the first 4 hours in the recovery room and at the 8th and 16th hours during the surgical period was found[9] to be lower in the groups that used magnesium. In the study of Tramer et al[20], which is one of the first studies in the literature on the analgesic activity of magnesium, it has been stated that perioperative magnesium reduces the use of postoperative analgesics without any side effects, and provides better sleep quality and patient comfort. In addition, in this study[20], it was shown that there was a 30% reduction in postoperative morphine consumption in the magnesium-treated group.

However, since this molecule is inexpensive, relatively harmless, and the biological basis of its potential anti-nociceptive action is promising. It may be worthwhile to further examine the

role of magnesium in addition to postoperative analgesia[21]. Dabbagh et al[22] reported that $MgSO_4$ could act as an additional analgesic in orthopedic surgeries performed under spinal anesthesia, and therefore less morphine will be consumed in the postoperative period. In our study, the need for rescue analgesics was measured in the recovery room in the first 2 hours and in 2nd, 4th, 8th, 12th, and 24th hours in the later follow-ups. The need for rescue analgesics in the early postoperative period was lower in the magnesium group.

Limitations

The lack of correlation between plasma magnesium and total body magnesium content in healthy subjects is also well known. As we did not measure the preoperative serum magnesium levels of the patients, it can be considered a limitation of our study. Some studies[23,24] have shown that measuring intracellular and extracellular magnesium concentrations does not reflect the magnesium content of the other body tissues.

Conclusions

In conclusion, it was determined in our study that preoperative $MgSO_4$ use decreased postoperative VNRS scores without affecting hemodynamic parameters during induction and maintenance of general anesthesia. It is thought that $MgSO_4$ can be put into routine clinical practice with larger studies evaluating its postoperative analgesic efficacy.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Ethics Approval

All the investigators ensure that the study has been conducted according to the Declaration of Helsinki Guidelines. Ethics Committee approval was obtained by Pamukkale University Non-Invasive Clinical Research Ethics Committee (No. E-60116787-020-152798).

Informed Consent

All patients read and signed the informed consent form.

Availability of Data and Materials

The study data are available at Pamukkale University Hospital archive.

Authors' Contributions

Data collection, Conceptualization (I.H.A, S.Y, S.Y.T), methodology and writing-original draft preparation (I.H.A, S.Y, E.E), writing-review and editing and supervision (I.H.A, S.I). All authors have read and agreed to the last version of the manuscript.

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