

# Effect of *Intraoperative infusion* Magnesium Sulfate Infusion on Postoperative Quality of Recovery in Patients Undergoing Total Knee Arthroplasty: A Prospective, Double-Blind, Randomized Controlled Trial

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**Background:** Magnesium sulfate, an intravenous adjuvant, has recently attracted immense attention in multimodal analgesia. Previous studies confirmed the crucial role of magnesium sulfate in postoperative pain and nociceptive hypersensitivity. However, the effect of magnesium sulfate in multimodal analgesia on the quality of recovery (QoR) for elderly patients has not been thoroughly studied. Therefore, the present experiment aimed to investigate the effect of continuous intravenous magnesium sulfate on the quality of postoperative recovery in elderly patients undergoing total knee arthroplasty (TKA).

**Patients and Methods:** In this study, a total of 148 patients scheduled to undergo unilateral total knee arthroplasty were randomized into a magnesium sulfate group (Group M, n=68) and a control group (Group C, n=66) using a double-blind, randomized controlled trial. Before induction of anesthesia, Group M received intravenous magnesium sulfate (40 mg/kg) for 15 min, followed by a continuous infusion (15 mg/kg) until the end of the procedure. In the same manner, Group C received an infusion of the same amount of isotonic saline using the same method as the Group M.

**Results:** Compared with Group C, Group M had significantly better QoR-15 scores on postoperative day 1 (POD<sub>1</sub>) than Group C ( $P < 0.05$ ). Analysis of the dimensions of QoR-15 scores indicated that Group M exhibited notably reduced levels of pain, and higher levels of emotional state and physical comfort than Group C ( $P < 0.05$ ). Furthermore, Group C had significantly higher numerical rating scale (NRS) scores at POD<sub>1</sub> than Group M ( $P < 0.05$ ).

**Conclusion:** For elderly patients undergoing knee arthroplasty, magnesium sulfate can be used as an adjuvant in a multimodal analgesic regimen to reduce early postoperative pain and improve the quality of early postoperative recovery.

**Keywords:** magnesium sulfate, quality of recovery, postoperative pain, multimodal analgesic regimen, total knee arthroplasty

## Introduction

In recent years, there has been an increasing focus on enhancing postoperative recovery to improve the quality of life for patients and facilitate their return to normal life functions. Especially in geriatric patients, total knee arthroplasty (TKA) is one of the most prevalent orthopedic procedures. During the initial postoperative phase following TKA, an estimated 60% of patients experience severe pain while 30% endure moderate pain,<sup>1</sup> which dramatically reduces the quality of recovery (QoR), extends the duration of hospitalization and functional immobility and increases the risk of postoperative

complications.<sup>2–5</sup> To enhance recovery after surgery (ERAS), enhancing the quality of recovery and a more favorable recovery experience mitigates complications and alleviates patient anxiety.<sup>6</sup>

Historically, opioids have been used as the first-line medication for postoperative analgesia following TKA. However, they may impede early postoperative recovery and diminish the quality of life of patients due to various adverse effects. Consequently, anesthesiologists are facing the challenge of minimizing intraoperative and postoperative opioid use while establishing an efficient strategy for pain management. It is important to note that opioids continue to play an essential role in the multimodal analgesia regimen for perioperative pain management. We aspire to achieve our vision of exploring different approaches in order to establish multimodal analgesic strategies.

Magnesium sulfate exerts antinociceptive effects by blocking N-methyl-D-aspartate (NMDA) receptors and related ion channels. It has been proposed as a potential adjunct to multimodal analgesic regimens. A continuous intraoperative infusion of magnesium sulfate can reduce postoperative pain, suppress nociceptive sensitization to some extent, and reduce the use of opioids.<sup>7–9</sup> However, no research has been conducted regarding the quality of postoperative recovery and the effectiveness of postoperative analgesia in elderly patients receiving intravenous magnesium sulfate infusion during TKA. This research aimed to examine the impact of postoperative recovery and analgesic effects in patients undergoing TKA using intravenous infusion of magnesium sulfate. The findings of this study offer novel insights for the development of multimodal analgesic regimens and enhancements to the quality of postoperative recovery for patients undergoing TKA.

## Materials and Methods

### Study Design

This study is a double-blind, prospective, randomized controlled trial, which was approved by the Institutional Review Board (Approval No. KY-20220404001-01, Approval Date: April 23, 2022) at Lianyungang Hospital and was registered with the Chinese Clinical Trials Registry (Registration No. ChiCTR2200065940, registration date: November 18, 2022) using <http://www.chictr.org.cn>. The study strictly adhered to the protocol outlined in the CONSORT and the Declaration of Helsinki. Written informed consent was obtained from all patients.

### Participants

Patients were enrolled in the study if they fulfilled following inclusion criteria: (1) Voluntary participation with a clear understanding of the study and signed an informed consent form; (2) Between 60 and 85 years of age; (3) Physical status I–III as defined by the American Society of Anesthesiologists (ASA); (4) Proposed elective knee replacement surgery; (5) Consciousness and absence of cognitive impairment and other psychiatric disorders; (6) Stable condition and ability to cooperate to complete the study. The following exclusion criteria were included: (1) Body mass index (BMI) less than 18 or greater than 30 kg/m<sup>2</sup>; (2) Documented allergy to one of the study drugs; (3) Severe hepatic, renal, or cardiac dysfunction; (4) Preoperative bradycardia accompanied by atrioventricular block; (5) Prior use of opioid and calcium channel blocker medications; (6) Patients with acute and critical illnesses (eg, acute heart failure, acute stroke, acute myocardial infarction, and severe infection). Patients were excluded for the following reasons: (1) Unplanned admission to the Intensive Care Unit (ICU); (2) Patients who failed to complete a quality postoperative recovery assessment; (3) Death within three days after surgery; (4) Severe intraoperative adverse events, such as allergic reactions, and cardiac arrest.

### Randomization and Blinding

Patients included in this study were randomly allocated to one of the two groups with a 1:1 ratio: the control group (Group C) and the magnesium group (Group M), using a web-based randomized system (<http://www.random.org>). The regimen for Group M was given intravenous magnesium sulfate (40 mg/kg) for 15 min before induction of anesthesia, followed by a continuous infusion of magnesium sulfate (15 mg/kg) during the procedure until the skin incision was sutured. Group C infused the same amount of isotonic saline using the same method. The assignments and details of each patient's anesthetic regimen were kept in an opaque sealed envelope, and only investigators could open them before induction of anesthesia. The medicines used in this study were prepared by a particular researcher and labeled as a “research drug”, where both solutions appear identical. Patients, surgeons, nurses, anesthesiologists, and outcome investigators were blinded to the randomization and medicines delivered to the individual groups throughout the trial period.

## Procedures

The study implemented a standardized approach for all anesthesia procedures. Prior to surgery, the participants did not receive any pre-medication and were instructed to fast for 8 h and abstain from drinking for 4 h before surgery. Once in the operating room, the patient underwent standard monitoring, including an electrocardiogram, non-invasive blood pressure, and pulse oxygen saturation measurement. Furthermore, we inserted a radial artery catheter to monitor arterial blood pressure after opening venous access to the upper limb. While monitoring the depth of anesthesia with the BIS, we prepared oxygen for pre-storage.

The anesthesia team induced by administering sequential slow intravenous injections of 0.3–0.5 µg/kg sufentanil, 1.5–2.0 mg/kg propofol, and 0.15–0.2 mg/kg cis-atracurium. Tracheal intubation was performed when BIS was less than 60, and the cuff pressure was adjusted to 20–25 cmH<sub>2</sub>O with a manometer. After tracheal intubation, the anesthesia machine was connected, and mechanical ventilation was performed using the pressure-controlled volume guaranteed ventilation mode (PCV-VG) with a tidal volume of 6–8 mL/kg, a respiratory rate of 12–14 breaths/min, a fresh gas flow rate of 2.0 L/min, an inhaled oxygen concentration of 60%, an inspiratory-expiratory ratio of 1:2, a positive end-expiratory pressure (PEEP) value of 5 cmH<sub>2</sub>O, and intraoperative maintenance of end-tidal partial pressure of carbon dioxide between 35–45 mmHg. During maintenance of anesthesia, intravenous propofol (4–12 mg/kg/h) and remifentanyl (0.1–0.3 µg/kg/min) were administered to regulate the BIS value to 40–60 and the mean arterial pressure (MAP) within 30% of the baseline value. The rate of infusion of propofol or remifentanyl was adjusted as needed during the intraoperative period. When the MAP deviated from the target value, the depth of anesthesia and infusion rate were adjusted first for observation. While MAP was still below target, norepinephrine tartrate was administered as needed based on the situation.

During the procedure, our team administered a Ringer's lactate solution at a rate of 6 mL/kg/h to maintain fluid volume. Intraoperative arterial blood samples were intermittently collected for blood gas analysis and to ensure electrolyte balance was maintained. The same group of experienced orthopedic surgeons (unknown to the study protocol) performed the surgery using the same surgical technique and type of prosthesis for all patients. Post-operative rehabilitation was performed following standard protocol. To prevent postoperative nausea and vomiting, the medical team administered 2 mg of intravenous Tropisetron hydrochloride 15 minutes before completing the procedure and discontinued all maintenance medications while suturing the skin incision. The time elapsed between the end of the procedure and the removal of the tracheal tube is referred to as the extubation time. After the patient's spontaneous breathing was fully restored, the tracheal tube was removed, and the patient was admitted to the post-anesthesia care unit (PACU) for continued observation. Specific anesthesia care providers assessed and recorded the quality of awakening indicators. The patient was returned to the ward with a Steward arousal score greater than 4. The femoral nerve block was administered in the PACU as soon as the patient was awake and able to cooperate. All patients received femoral nerve block (regimen: an experienced anesthesiologist performed an ultrasound-guided injection of 20 mL of 0.25% ropivacaine around the femoral nerve). Moreover, intravenous patient-controlled analgesia (PCA) was performed (regimen: 2 µg/kg Fentanyl in 0.9% saline at a total volume of 100 mL with a pressurized dose of 2 mL, no background dose, and a lockout interval of 20 min), which was discontinued on day three postoperatively. The time of the PCA administration was calculated from when the patient transferred from the PACU to the ward. The patient determined the timing of the administration based on their pain level.

## Data Collection and Outcome Assessment

During data collection, we used standardized forms to obtain baseline characteristics from the clinical record, including demographic and morphologic characteristics, preoperative comorbidities, and history of smoking and alcohol abuse. For data accuracy and consistency, we provided preoperative education to patients and families by a specific investigator unaware of the study subgroups at the preoperative visit. During the education process, the investigator explained the rules of the scoring questionnaire in detail to all subjects, ensuring that all questions were answered. Pre- or postoperative data were uniformly collected in the ward between 6 and 8 p.m. on the same day to ensure timeliness and consistency of data.

The primary outcome of this study was the QoR-15 scores on postoperative day 1 (POD<sub>1</sub>).<sup>10</sup> The QoR-15, which comprises 15 items in five dimensions (pain (2 items), emotional state (4 items), physical comfort (5 items), psychological support (2 items), and physical independence (2 items)), is a patient-reported outcome measure (PROM). The items

are assessed using a ten-point scale from 1 to 10, with a total score of 150 (optimal quality of recovery). A higher score indicates a better quality of postoperative recovery. High-quality evidence supports the QoR-15 as a unidimensional measure for the quality of recovery; the minimum clinically important difference (MCID) was revised to 6.0.<sup>10–12</sup> The secondary outcomes included the following: numerical rating scale (NRS) scores at 3 days postoperatively; propofol and remifentanyl dosage; hemodynamic profile (vasoactive drug dosage); number of first PCA administrations, total PCA administrations, and remedial analgesia frequency within 24 h; time of the first ambulation; QoR-15 score on POD<sub>2</sub> and POD<sub>3</sub>; postoperative adverse effects, and length of hospital stay.

During the procedure, our team diligently monitored the hemodynamics, oxygenation index, and EEG dual-frequency index at 11-time points: after entering the operating room (T<sub>0</sub>), 1 minute after induction (T<sub>1</sub>), after intubation (T<sub>2</sub>), at skin incision (T<sub>3</sub>), 15 min after tourniquet inflation (T<sub>4</sub>), 30 min (T<sub>5</sub>), 45 min (T<sub>6</sub>), 60 min (T<sub>7</sub>), 5 min before deflation (T<sub>8</sub>), 5 min after deflation (T<sub>9</sub>) and after extubation (T<sub>10</sub>). We consistently recorded these parameters throughout the procedure. Furthermore, we have documented relevant information, such as the duration of the operation, anesthesia time, extubation time, PACU stay, medication dosage, and rehydration volume.

## Sample Size Calculation

In the preliminary study, the QoR-15 score was assessed in 30 patients undergoing elective TKA to increase the accuracy of sample size calculation. The results of the QoR-15 score for both groups were Group M ( $119.33 \pm 10.74$ ) and Group C ( $114.87 \pm 8.71$ ). Assuming an  $\alpha$  of 0.05 and 80% power, with GPower 3.1.1.lik, it was concluded that the maximum sample size for this trial was 61 patients per group. Considering the 20% shedding rate, it was concluded that 74 patients per group were needed.

## Statistical Analysis

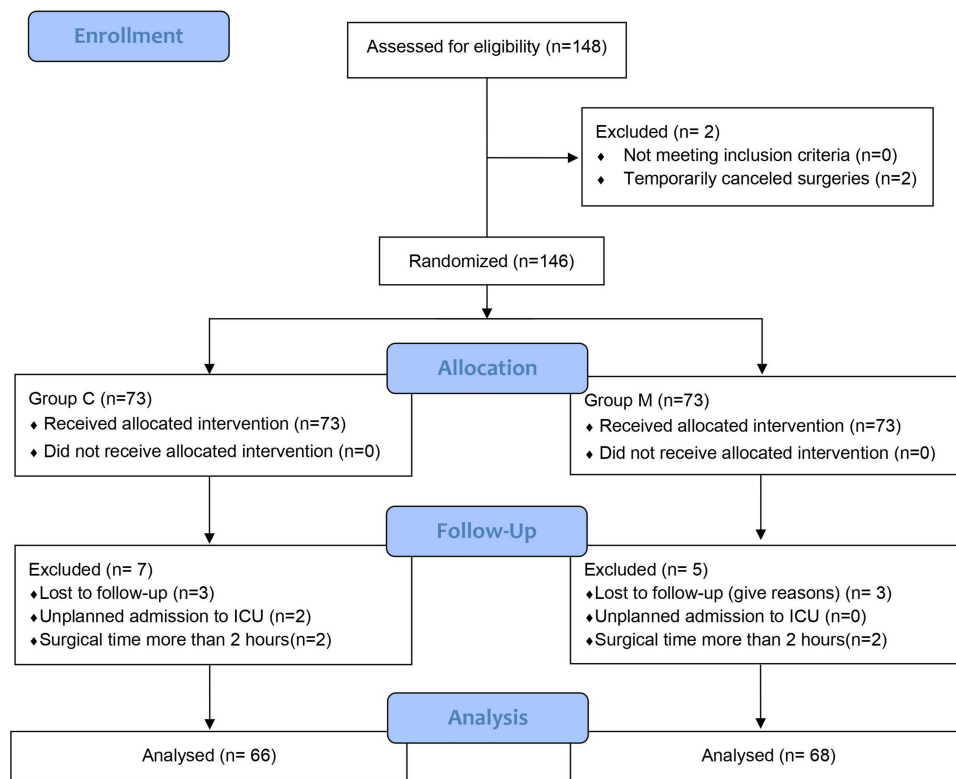
Whether the quantitative data adhered to a normal distribution was ascertained using the Shapiro–Wilk test. The measures were expressed as mean  $\pm$  standard deviation for a normal distribution, with within-group comparisons at different time points using repeated measures ANOVA and between-group comparisons using independent samples *t*-tests. For non-normal distribution, they were expressed as median and interquartile range (IQR), using independent samples nonparametric test (Mann–Whitney *U*-test). The counts and categorical variables were compared using the chi-square test or Fisher's exact probability method, where categorical variables were expressed as numbers (%). The statistical analysis was conducted using the SPSS statistical software (version 25.0; SPSS Inc, IBM, Chicago, IL, USA).  $P < 0.05$  was considered a statistically significant difference.

## Results

The eligibility of 148 patients slated to undergo TKA was evaluated; 14 were subsequently excluded for the subsequent rationales. Four patients were excluded because the duration of surgery was longer than 2 h after receiving the study intervention. Two patients canceled surgery temporarily; six failed to complete the postoperative evaluation due to losing follow-up, and two were unexpectedly admitted to the intensive care unit. In the final analysis, 134 patients were incorporated (Figure 1), with Group M comprising 68 patients and Group C comprising 66. The two groups had no clinically significant differences in baseline characteristics such as age, gender, BMI, ASA classification, past medical history etc (Table 1).

Group M exhibited substantially higher QoR-15 scores at POD<sub>1</sub> and POD<sub>2</sub> compared to Group C, and the difference was statistically significant ( $P < 0.001$ ;  $P = 0.013$ , respectively) (Table 2). Group M had lower pain levels than Group C ( $P < 0.001$ ), as determined by an analysis of the dimensions of QoR-15 scores on the POD<sub>1</sub>; Group M had higher emotional state and physical comfort than Group C ( $P < 0.001$ ;  $P < 0.001$ , respectively) (Figure 2). The NRS score of POD<sub>1</sub> in Group C was significantly above that of Group M ( $P < 0.001$ ). No statistically significant difference was observed in NRS scores between the two groups when patients were discharged from the PACU and on the POD<sub>2</sub> and POD<sub>3</sub> ( $P = 0.683$ ;  $P = 0.217$ ;  $P = 0.200$ , respectively) (Table 2).

Compared to Group C, Group M had a significant decrease in remifentanyl usage and a significant increase in norepinephrine consumption ( $P < 0.001$ ;  $P < 0.001$ , respectively) (Table 3). However, no statistically significant difference



**Figure 1** The CONSORT flow chart for the recruitment of patients.

was observed between the two groups regarding the medication used for anesthesia induction and maintenance dosage of propofol during the surgery ( $P > 0.05$ ). In contrast to patients in Group C, Group M exhibited notable advantages, as evidenced by a substantial delay in the Initial PCA administrations and reduced total number of postoperative administrations ( $P < 0.001$ ;  $P < 0.001$ , respectively). However, no significant differences were observed between the two groups in terms of extubation time, PACU residence time, first ground activity time, hospital stay, and remedial analgesia frequency within 24h ( $P > 0.05$ ) (Table 3).

**Table 1** Baseline Characteristics of the Patients in the Two Groups

Characteristic	Group C (n=66)	Group M (n=68)	P-value
Age, years	66.00 (62.00–71.00)	67.00 (64.00–70.00)	0.970
Male/Female, n	16/50	14/54	0.612
Weight, kg	65.56 ± 9.21	66.31 ± 6.92	0.597
BMI, kg/m <sup>2</sup>	25.50 (23.75–28.00)	25.00 (24.00–27.00)	0.900
ASA, classification, n (%)			0.589
I	0	0	
II	54 (81.82%)	58 (85.29%)	
III	12 (18.18%)	10 (14.71%)	
Pre-MAP, mmHg	102.79 ± 9.19	101.88 ± 10.12	0.589
Pre-QoR-15	146.00 (146.00–148.00)	146.00 (144.00–148.00)	0.381
Pre-NRS			0.909
0	28 (42.42%)	31 (45.59%)	
1	23 (34.85%)	19 (27.94%)	
2	8 (12.12%)	12 (17.65%)	
3	6 (9.09%)	5 (7.35%)	
4	1 (1.52%)	1 (1.47%)	

(Continued)

**Table 1** (Continued).

Characteristic	Group C (n=66)	Group M (n=68)	P-value
Diabetes, n (%)	11 (16.67%)	10 (14.71%)	0.755
Drinking, n (%)	6 (9.10%)	2 (2.94%)	0.582
Smoking, n (%)	5 (7.58%)	7 (10.29%)	0.255
Anesthetic duration, min	92.50 (86.00–105.00)	92.00 (82.50–101.50)	0.267
Surgical duration, min	71.32 ± 11.24	68.53 ± 15.20	0.228
Infusion volume, l	1.44 (1.23–1.50)	1.47 (1.35–1.51)	0.236

**Notes:** Data are presented as mean ± SD, median (interquartile range), or number (percentage).

**Abbreviations:** Group C, control group; Group M, magnesium sulfate group; ASA, the American Society of Anesthesiologists; BMI, Body Mass Index; Pre, preoperative; QoR, quality of recovery; NRS, numerical rating scale.

**Table 2** QoR-15 Scores and NRS Scores

Scores	Group C (n=66)	Group M (n=68)	P-value
QoR-15 scores			
POD1 QoR-15	116.00 (112.00–118.00)	126.00 (122.00–128.00)**	<0.001
POD2 QoR-15	128.00 (126.00–128.00)	128.00 (126.00–130.00)*	0.013
POD3 QoR-15	136.00 (135.00–136.00)	136.00 (135.00–136.00)	0.725
NRS scores			
PACU NRS	0.05 (0.00–1.00)	1.00 (0.00–1.00)	0.683
POD1 NRS	4.00 (3.00–4.25)	2.00 (2.00–3.00)**	<0.001
POD2 NRS	3.00 (3.00–4.00)	3.00 (3.00–4.00)	0.217
POD3 NRS	1.00 (1.00–2.00)	1.00 (0.00–2.00)	0.200

**Notes:** \* $P < 0.05$  compared with Group C; \*\* $P < 0.001$  compared with Group C. Data are presented as median (interquartile range).

**Abbreviations:** Group C, control group; Group M, magnesium sulfate group; QoR, quality of recovery; POD, postoperative day; PACU, Post-anesthesia care unit; NRS, numerical rating scale.

The BIS values were significantly higher in Group M compared to Group C at time points  $T_5$ ,  $T_6$ , and  $T_7$  ( $P = 0.024$ ,  $P = 0.009$ ,  $P = 0.013$ , respectively). However, at  $T_{10}$ , Group C had a higher BIS value than Group M, and the difference was statistically significant ( $P = 0.025$ ) (Figure 3). In addition, Group M exhibited MAP values at  $T_2$ ,  $T_3$ ,  $T_5$ ,  $T_6$ ,  $T_7$ ,  $T_8$ , and  $T_{10}$  that were considerably lower than that of Group C, and this difference was statistically significant ( $P = 0.006$ ;  $P < 0.001$ ;  $P = 0.042$ ;  $P = 0.032$ ;  $P < 0.001$ ;  $P < 0.001$ ;  $P < 0.001$ ;  $P < 0.001$ , respectively). According to repeated measures ANOVA at different time points, the difference in MAP changes between Groups M and C was statistically significant, implying that the stability of the trend of MAP changes in Group M was greater than that in Group C ( $P < 0.001$ ) (Figure 4).

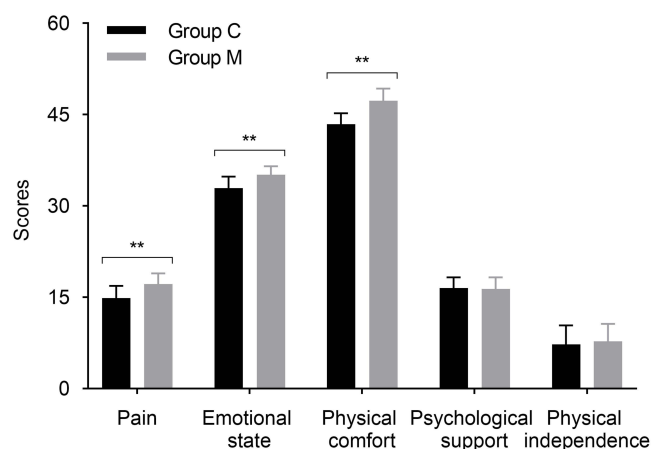
Furthermore, no statistically significant difference was noticed in the incidence of total postoperative adverse events in Group M compared to Group C. Similarly, the incidence of postoperative nausea, bradycardia, postoperative agitation, and chills was not statistically different between the two groups ( $P > 0.05$ ). However, we found that the incidence of vomiting events was lower in Group M than in Group C, and this difference was statistically significant ( $P = 0.016$ ) (Figure 5).

## Discussion

In this randomized clinical trial involving knee arthroplasty, we found that continuous intraoperative intravenous magnesium sulfate improved the quality of recovery and reduced postoperative pain. No serious adverse events associated with the study drug were observed at the doses selected for this trial.

In the early postoperative phase, the QoR score is an invaluable indicator of the patient's health status. The classic QoR-15 and QoR-40 are the most frequently used indicators for clinical assessment of postoperative recovery quality. In





**Figure 2** Inter-dimensional comparison of QoR-15 on POD<sub>1</sub>.

**Notes:** \*\* $P < 0.001$  compared with group C. Data are presented as means (bars) and standard deviations (error bars) within groups. Different colors indicate different groups.

contrast to the more extensive and marginally intricate QoR-40, the QoR-15 minimizes the time to train staff, increases feasibility, and reduces the potential for jeopardizing trial conduct and disrupting clinical care due to overburdening staff.<sup>13</sup> The efficacy of postoperative recovery is positively correlated with the postoperative QoR-15 score.

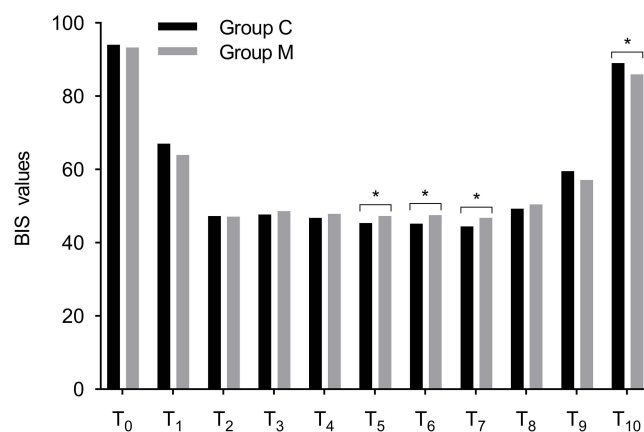
We evaluated the effects of intraoperative intravenous magnesium sulfate infusion on postoperative quality of recovery using the QoR-15 survey. The results of the study demonstrated that the mean QoR-15 score at POD<sub>1</sub> was 8.72 points higher in Group M (123.74) than in Group C (115.02). According to a previous study, perioperative interventions that led to a shift of 8.0 on the QoR-15 score indicated a clinically significant improvement or deterioration.<sup>14</sup> Therefore, the difference in QoR-15 scores on POD<sub>1</sub> between Groups M and C in this study was greater

**Table 3** Intraoperative and Postoperative Indicators

Indicators	Group C (n=66)	Group M (n=68)	P-value
Anesthesia induction			
Sufentanil (ug)	30.00 (25.00–35.00)	30.00 (25.00–35.00)	0.900
Propofol (mg)	120.00 (110.00–140.00)	130.0 (120.00–140.00)	0.192
Cis-atracurium (mg)	10.00 (9.00–12.00)	10.00 (9.00–11.88)	0.580
Anesthesia maintenance			
Propofol (mg)	501.71 ± 117.89	495.02 ± 127.01	0.752
Remifentanyl (ug)	909.65 ± 223.15	657.56 ± 182.80**	<0.001
Vasoactive drugs			
Norepinephrine (mg)	0.00 (0.00–8.00)	10.00 (0.00–60.00) **	<0.001
Recovery time			
Extubation time (min)	13.76 ± 3.11	14.49 ± 2.84	0.159
Duration of PACU stay (min)	23.50 (21.00–25.00)	25.00 (22.00–26.00)	0.068
First ground activity time (h)	23.00 (19.00–26.00)	23.00 (19.00–27.00)	0.846
Duration of hospital stay (d)	9.00 (9.00–11.00)	9.00 (9.00–11.00)	0.773
Analgesic indicators			
PCA first administration time (h)	16.29 ± 3.42	19.43 ± 3.89**	<0.001
Total PCA administrations (n)	2.00 (1.00–4.00)	1.00 (0.00–2.00) **	<0.001
Remedial analgesia frequency(n)	26.00 (39.39%)	17.00 (25.00%)	0.075

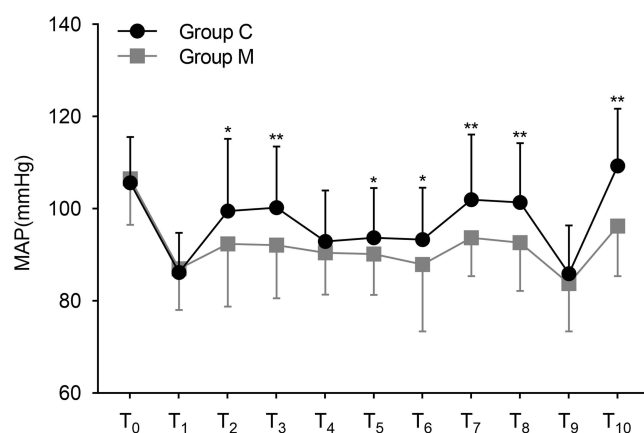
**Notes:** \*\* $P < 0.001$  compared with Group C. Data are presented as mean ± SD, median (interquartile range), or number (percentage).

**Abbreviations:** Group C, control group; Group M, magnesium sulfate group; PACU, Post-anesthesia care unit; PCA, patient-controlled analgesia.



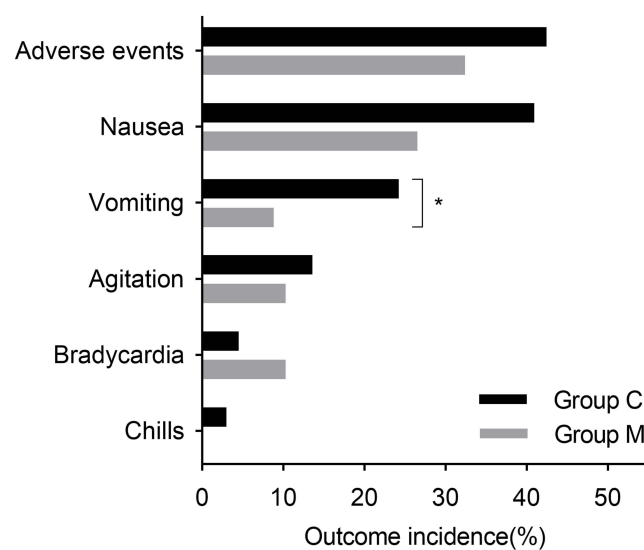
**Figure 3** The BIS values of different time points.

**Notes:** \* $P < 0.05$  compared with group C. Data are presented as means (bars) within groups. Different colors indicate different groups.



**Figure 4** The MAP values of different time points.

**Notes:** \* $P < 0.05$  compared with Group C; \*\* $P < 0.001$  compared with Group C. Data were analyzed using repeated-measures ANOVA and are presented as means (bars) and standard deviations (error bars) within groups. Different colors or shapes indicate different groups.



**Figure 5** The incidence of adverse events after surgery.

**Notes:** \* $P < 0.05$  compared with group C. Data are presented as component ratios (bars); Different colors indicate different groups.



than the minimal clinically important difference, suggesting that intravenous magnesium sulfate prevents physiologic deterioration related to anesthesia and surgery and improves the quality of recovery, which is clinically significant.

Furthermore, we performed additional statistical analyses on each dimension of the QoR-15 score of POD<sub>1</sub> to assess which recovery component improved or deteriorated as a result of treatment, thus providing valuable information. We found that patients treated with magnesium sulfate scored higher on the pain dimension, emotional state, and physical comfort dimensions. Therefore, we believe that improved quality of recovery may involve other factors besides good analgesia. Previous studies showed that intravenous magnesium sulfate during general anesthesia significantly reduces the incidence of postoperative pain, nausea, and vomiting.<sup>6,15,16</sup> The present results indicated that postoperative vomiting incidence was significantly reduced in patients in the magnesium sulfate group. Combined with the above findings, we believe that improving physical comfort and emotional state using magnesium sulfate may be related to its reduction in the incidence of nausea and vomiting. The potential significance of these non-analgesic effects of the beneficial effects of magnesium sulfate on recovery quality should not be ignored. Furthermore, it was found that the difference in QoR-15 scores on POD<sub>2</sub> between the two groups was statistically significant but less than MCID; therefore, it was not clinically significant. This may be related to the level of postoperative pain and side effects of anesthetic drugs after TKA gradually decreased at POD<sub>2</sub>, thereby reducing the difference in scores between the two groups. However, it is unclear whether it is worth expanding the patient sample size to test for clinical significance at POD<sub>2</sub>.

Magnesium sulfate is a natural NMDA receptor blocker and calcium channel blocker with antispasmodic and analgesic properties, decreasing stress response and inhibiting central sensitization.<sup>8,17,18</sup> Several studies demonstrated that magnesium sulfate can be used as part of a balanced analgesic strategy, and that it interacts with other analgesic drugs to alleviate postoperative pain and associated complications.<sup>6,19</sup> In this experiment, the magnesium sulfate group had a significantly better NRS score on POD<sub>1</sub> than the control group, and the amount of intraoperative analgesic medication and the number of postoperative PCA administrations were significantly reduced, further validating the postoperative analgesic effect of magnesium sulfate. Simultaneously, this study identified a relative delay in initiating the first postoperative PCA administration in the magnesium sulfate group. It was hypothesized that the observed outcome could be attributed to the inhibitory effect of magnesium sulfate on rebound pain after nerve block surgery. It has been suggested that postoperative rebound pain may be related to central sensitization, and activation of NMDA receptors is necessary to induce and maintain central sensitization.<sup>20–22</sup> Therefore, magnesium sulfate might be advantageous in mitigating postoperative rebound pain, although further research is required to confirm this speculation.

Based on the results, we hypothesize that magnesium sulfate may improve the QoR-15 score through two mechanisms. Firstly, it acts as an NMDA receptor blocker, reducing pain signals and creating synergistic analgesic effects, ultimately alleviating pain and enhancing the pain dimension score of QoR-15. Additionally, magnesium sulfate can regulate intra- and extracellular ion concentrations, promoting organismal stability. This characteristic reduces perioperative medication dosage, minimizing drug-related adverse effects, resulting in improved patient comfort and other related dimension scores, leading to an overall better quality of recovery.

Interestingly, in the statistical data analysis, we found relatively high BIS values in the magnesium sulfate group at several specific intraoperative time points, which differed from the previous findings by Lee et al.<sup>23</sup> We speculated that the finding might be related to using a tourniquet. Although tourniquets can effectively control bleeding and improve the surgical field of view during orthopedic surgery, ensuing tourniquet reactions can lead to elevated blood pressure and associated pain.<sup>24,25</sup> In such cases, anesthesiologists often deepen the anesthesia or use antihypertensive medications to alleviate these reactions, which usually decreases BIS values. However, we observed that in the magnesium sulfate group of patients, the need to suppress the tourniquet response was correspondingly reduced due to less fluctuation in MAP in this group, which may help to explain the relatively high BIS values in this group of patients.

Regarding the safety of the intervention in this trial, we used a commonly used dose based on previous studies and calculated strictly based on patient body weight. Currently, the favored intravenous protocol for magnesium sulfate entails administering a loading dose ranging from 30 to 50 mg/kg, followed by a continuous intravenous drip of 6–25 mg/kg/h.<sup>26</sup> The potential improvement in QoR-15 and NRS scores with escalating doses of the experimental drug could not be ascertained. Further research and analyses are required to explore the relationship between drug dose and patient prognosis.

All patients in this study did not experience any serious postoperative complications, and none of the patients treated with magnesium sulfate experienced any drug-related adverse effects, consistent with the study by Weber et al.<sup>27</sup> However, there are some limitations to this study. First, the absence of muscle relaxation monitoring prevented a more in-depth examination of the correlation between magnesium sulfate and neuromuscular blocking effects. Second, serum  $Mg^{2+}$  concentration, which could have guided the safe application of magnesium sulfate, was not monitored; however, based on previous research, the dose utilized in this experiment was adequate. Third, the patients were only followed up for three days postoperatively and were not followed up at a later stage. The incidence of chronic persistent pain after knee surgery is likely to be high; thus, conducting further research into a possible strategy for managing this issue would be beneficial. Fourth, only patients undergoing knee replacement surgery were included in the study, which may restrict the applicability of the results to other patients.

## Conclusion

This research indicated that magnesium sulfate enhances the quality of early postoperative recovery in elderly patients undergoing knee arthroplasty. Furthermore, when combined with general anesthesia in a multimodal analgesic approach, magnesium sulfate exhibits considerable analgesic potential while maintaining a favorable safety profile. It can be effectively used as an agent in a multimodal analgesic regimen. Future research could build on this work by examining the potential of magnesium sulfate in conjunction with other complementary therapies and evaluating its effectiveness in various demographics.

## Data Sharing Statement

All data and materials generated or used in this study are available upon request to the corresponding author. For any other questions regarding the data set, reasonable requests to the corresponding author are welcome.

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## Disclosure

The authors report no conflicts of interest in this work.

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