ANESTHESIOLOGY

Magnesium and Bladder Discomfort after Transurethral Resection of Bladder Tumor

A Randomized, Double-blind, Placebo-controlled Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Catheter-related bladder discomfort results from involuntary muscle contraction
- Magnesium relaxes smooth muscle and may therefore relieve bladder discomfort

What This Article Tells Us That Is New

- In a randomized trial of 120 patients recovering from transurethral resection of bladder tumor, intravenous magnesium substantially reduced discomfort with a number needed to treat of only 2
- Intravenous magnesium is a simple and inexpensive way to reduce bladder discomfort

ABSTRACT

Background: Catheter-related bladder discomfort occurs because of involuntary contractions of the bladder smooth muscle after urinary catheterization. Magnesium is associated with smooth muscle relaxation. This study hypothesized that among patients having transurethral resection of bladder tumor, magnesium will reduce the incidence of postoperative moderate-to-severe catheter-related bladder discomfort.

Methods: In this double-blind, randomized study, patients were randomly allocated to the magnesium group ($n = 60$) or the control group ($n = 60$). In magnesium group, a 50 mg/kg loading dose of intravenous magnesium sulfate was administered for 15 min, followed by an intravenous infusion of $15\,mg \cdot kg^{-1} \cdot h^{-1}$ during the intraoperative period. Patients in the control group similarly received normal saline. The primary outcome was the incidence of catheter-related bladder discomfort above a moderate grade at 0 h postoperatively. None, mild, moderate, and severe catheter-related bladder discomfort at 1, 2, and 6 h postoperatively, patient satisfaction, and magnesium-related adverse effects were also assessed.

Results: The incidence of catheter-related bladder discomfort above a moderate grade at 0 h postoperatively was significantly lower in the magnesium group than in the control group (13 [22%] *vs.* 46 [77%]; $P < 0.001$; relative risk = 0.283; 95% CI, 0.171 to 0.467; absolute risk reduction = 0.55; number needed to treat = 2); similar results were observed for catheter-related bladder discomfort above a moderate grade at 1 and 2 h postoperatively (5 [8%] *vs.* 17 [28%]; $P = 0.005$; relative risk = 0.294; 95% CI, 0.116 to 0.746; and 1 [2%] *vs.* 14 [23%]; $P < 0.001$; relative risk = 0.071; 95% CI, 0.010 to 0.526, respectively). Patient satisfaction on a scale from 1 to 7 was significantly higher in the magnesium group than in the control group (5.1 ± 0.8 *vs.* 3.5 ± 1.0; $P < 0.001$; 95% CI, 1.281 to 1.919). Magnesium-related adverse effects were not significantly different between groups.

Conclusions: Magnesium reduced the incidence of catheter-related bladder discomfort above a moderate grade and increased patient satisfaction among patients having transurethral resection of bladder tumor.

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Transurethral resection of bladder tumor is the treatment of choice for noninvasive bladder tumors.[1,2] Patients having transurethral resection of bladder tumor require large–diameter urinary catheters postoperatively,[3] which can induce catheter–related bladder discomfort. Catheter-related bladder discomfort is characterized by discomfort in the suprapubic region and manifests as urinary urgency and frequency with or without urge incontinence after urinary catheterization.[3] The incidence rate of catheter–related bladder discomfort is 47 to 90% among patients who have undergone general surgery.[4] Particularly, catheter–related bladder discomfort above a moderate grade, which

is frequently intolerable and requires treatment,[5] is reported among 38 to 57% of patients with urinary bladder catheters *in situ* at the postanesthesia care unit (PACU).[6] Therefore, appropriate treatment or prevention of catheter–related bladder discomfort is essential for the improvement of post–operative outcomes among patients having transurethral resection of bladder tumor who require large–diameter urinary catheters because catheter–related bladder discomfort can be accompanied by poor patient satisfaction, increased postoperative agitation, prolonged hospital stay, and increased workload for medical staff.[4] Various agents such as ketamine, tramadol, butylscopolamine, and lidocaine have been studied for the prevention of catheter–related bladder

discomfort.[7–10] Despite the availability of these various agents, sufficient evidence for effective treatment without adverse reaction such as nausea, vomiting, hallucinations, respiratory depression, sedation, dry mouth, and neurologic and cardiac complications are lacking.[4,7–10]

Magnesium is the fourth most abundant cation in the body.[11] Magnesium is related to diverse biochemical reactions, such as signal transduction in cell membranes, protein synthesis, muscle and nerve transmission, neuromuscular conduction, blood pressure regulation, and blood glucose control.[11] Moreover, magnesium is important for the reduction and stabilization of smooth muscle contraction because it plays a key role in the active transport of calcium ions across cell membranes.[11] Based on these considerations, magnesium is thought to influence the occurrence of catheter–related bladder discomfort. However, its effect on the prevention of postoperative catheter-related bladder discomfort has not yet been studied. We therefore tested the hypothesis that intraoperative magnesium reduces moderate-to-severe catheter-related bladder discomfort in patients recovering from transurethral resection of bladder tumor.

Materials and Methods

This prospective, randomized, double-blind, placebo-controlled study was conducted at the Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. The study protocol was approved by the institutional review board of the Asan Medical Center (2019-0586). Before enrollment of any patients, the study protocol was registered at the Clinical Research Information Service (KCT 0003915, Principal Investigator: Young-Kug Kim, registration date: May 14, 2019). All participants provided written informed consent before participating in the study. The trial was conducted in accordance with the original protocol.

Study Population

All patients were enrolled between July 2019 and October 2019. The inclusion criteria were age 20 to 79 yr, American Society of Anesthesiologists (ASA) Physical Status I or II, scheduled transurethral resection of bladder tumor under general anesthesia, and voluntary participation in this clinical study. The exclusion criteria were: change in surgical plans, chronic kidney disease, atrioventricular block, neuromuscular disease, hypermagnesemia (serum magnesium concentration greater than 3.0 mg/dl), hypocalcemia (serum calcium concentration less than 8.6 mg/dl), analgesic overuse, psychiatric disorders, or taking medications known to interact with magnesium (appendix 1). Patients with a preexisting bladder disease such as an overactive bladder, bladder outflow obstruction, and neurogenic bladder were also excluded.

Randomization, Concealment, and Blinding

Patients enrolled in the present study were randomized. Before initiation of patient recruitment, the first investigator

produced a random number table using a web-based randomization software (Random Allocation Software version 1.0; Isfahan University of Medical Sciences, Isfahan, Iran). Randomization was performed with block sizes of four and an allocation ratio of 1:1. Eligible participants were assigned to receive either intravenous magnesium sulfate (magnesium group) or intravenous normal saline as control (control group) according to a computer-generated randomization schedule.

The randomization codes were enclosed in sequentially numbered, identical, opaque, and sealed envelopes. The envelopes were kept in a closed box during the entire study period. The codes were concealed by the first principal investigator and delivered to the second investigator. The second investigator prepared a 50-ml volume of either magnesium sulfate or normal saline in identical syringes and labeled them with the patients' names and hospital registration numbers. All syringes and tubes did not require wrapping for masking purposes because both drugs were transparent and visually similar. After induction of anesthesia, the medications were administered by the third investigator, who was blinded to the allocation groups. The fourth investigator, who was also blinded to the allocation groups, assessed the outcomes of the study in the PACU or general ward. To avoid potential biases, the predetermined random allocation codes were strictly applied to all consecutive patients during the entire study period. Compliance with the order was confirmed by another investigator at the end of data collection. All other investigators and participants, except the first and second investigators, were blinded to the group allocation until data analyses were completed.

Anesthesia and Monitoring

Preoperatively, patients were educated on symptoms of catheter–related bladder discomfort (*i.e.*, a burning sensation with an urge to void or discomfort in the suprapubic area). No premedication was administered before the induction of general anesthesia.

On arrival at the operating room, the patients were monitored according to our institutional standards. Anesthesia was induced using 2 mg/kg propofol. Subsequently, 0.6 mg/kg rocuronium bromide was administered. Once the patient was unconscious, the LMA Supreme (Teleflex, Ireland) was inserted. Anesthesia was maintained with 2 to 3 vol% sevoflurane in a mixture of 50% nitrous oxide and 50% oxygen. The depth of anesthesia was monitored using the bispectral index (A-1050 monitor; Aspect Medical Systems, USA), which was maintained between 40 and 60. Sevoflurane administration was intermittently adjusted intraoperatively according to the bispectral index and hemodynamic parameters. Train-of-four monitoring was used to measure the degree of neuromuscular blockade. Rocuronium bromide was administered intermittently to maintain train-of-four count of at most 2 throughout surgery to prevent bladder perforation caused by unexpected thigh adduction.

Postoperative nausea and vomiting were prevented by administering 0.3 mg of ramosetron (Nasea; Yamanouchi Pharmaceutical Co. Ltd., Japan) 15 min before the end of the procedure. At the end of the procedure, 2 mg/kg of sugammadex (Bridion; MSD, The Netherlands) was used for rapid and complete reversal of neuromuscular blockade if the train-of-four count was 2 or higher at the end of surgery. A 20 Fr urinary catheter was inserted, and the balloon was inflated with 10 ml of distilled water. The urinary catheter was lubricated using 2% lidocaine gel and fixed in the suprapubic area with adhesive tape. Normal saline was infused continuously through the urinary catheter to irrigate the bladder. After confirming that the patient was fully conscious (bispectral index of at least 90) and had recovered from neuromuscular blockade (train-of-four ratio of at least 90%), the LMA Supreme was removed, and the patient was transferred to the PACU.

Study Protocol

The dosage of the magnesium regimen was determined based on previous studies.[12] In magnesium group, a 50 mg/kg (0.5 ml/kg) loading dose of intravenous magnesium sulfate (0.2 mmol/kg Mg^{2+}) was administered for 15 min just after the induction of anesthesia, followed by an intravenous infusion of $15\,mg \cdot kg^{-1} \cdot h^{-1}$ ($0.15\,ml \cdot kg^{-1} \cdot h^{-1}$) of intravenous magnesium sulfate ($0.06\,mmol \cdot kg^{-1} \cdot h^{-1}\ Mg^{2+}$) during the intraoperative period. At the end of the procedure, intravenous magnesium sulfate infusion was stopped. Patients in the control group received normal saline in the same manner as those in magnesium group.

Tramadol and fentanyl were used as rescue medications in the PACU. Tramadol (1 mg/kg) was administered only when catheter-related bladder discomfort above a moderate grade was identified; fentanyl (1 μg/kg) was administered to the patients only if the degree of postoperative pain (superficial, sharp, and definite pain at the surgical site), assessed using a numeric rating scale, was 4 or higher. Patients who complained of both catheter-related bladder discomfort and postoperative pain were treated with either tramadol or fentanyl based on their chief complaint and then reassessed. The same protocol for analgesia was maintained after transfer to the general ward, except for ketorolac administration. After transfer to the general ward, 30 mg of ketorolac was administered, up to two times per day, instead of tramadol to treat catheter-related bladder discomfort above a moderate grade. Patients received tramadol (1 mg/kg) if they had contraindications to nonsteroidal antiinflammatory drugs or experienced no response to nonsteroidal antiinflammatory drugs.

Assessments

Patients' characteristics assessed were age, sex, body mass index, ASA Physical Status, hypertension, diabetes mellitus, serum magnesium concentration, serum calcium concentration, and estimated glomerular filtration rate. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Intraoperative variables included anesthesia duration, operation duration, amount of crystalloid, urethral stricture, tumor stage, tumor size, tumor multiplicity, and tumor location.

Catheter-related bladder discomfort grade was assessed at 0, 1, 2, and 6 h postoperatively. The catheter-related bladder discomfort grade at 0 h postoperatively was assessed just after the patients were transferred to the PACU. The severity of catheter-related bladder discomfort was considered "mild" when reported by patients only on questioning, "moderate" when reported by patients on their own without questioning and not accompanied by any behavioral response, and "severe" when reported by patients on their own with accompanying behavioral responses, such as flailing limbs, a strong vocal response, or an attempt to remove the catheter.[8]

Patient satisfaction was assessed using a seven-point Likert scale (1 = strongly dissatisfied, 2 = moderately dissatisfied, 3 = slightly dissatisfied, 4 = neutral, 5 = slightly satisfied, 6 = moderately satisfied, 7 = extremely satisfied) at 6 h postoperatively.[13] Serum magnesium concentrations were measured before and immediately after surgery. Magnesium-related adverse effects, such as nausea/vomiting, headache, lethargy, flushing, hypotension, and respiratory depression, were assessed at the PACU or general ward.[14,15] Hypotension, defined as a decrease in systolic blood pressure less than 80 mmHg for more than 10 min was assessed intraoperatively and on postoperative day 1.[16] Respiratory depression was assessed, until postoperative day 1, by desaturation events defined as events of saturation less than 90%.[17] Postoperative pain was assessed using a numeric rating scale (0 = no pain to 10 = worst imaginable pain) at 0, 1, 2, and 6 h postoperatively.[18] Opioid requirement was summed up as all opioids, tramadol, and nonsteroidal antiinflammatory drugs administered to patients during the 24 h after surgery. Dosages of opioids, tramadol, and nonsteroidal antiinflammatory drugs were converted to intravenous fentanyl equianalgesic doses according to published conversion factors (100 μg of fentanyl = 100 mg of tramadol = 30 mg of ketorolac).[19,20] Postoperative delirium was assessed using the confusion assessment method score.[21] The confusion assessment method score was determined by examining the patient for (1) acute and fluctuating changes in mental status, (2) inattention, (3) disorganized or incoherent thinking, and (4) altered level of consciousness. Patients who displayed (1), (2), and (3); or (1), (2), and (4); or (1), (2), (3), and (4) were considered to have postoperative delirium. Postoperative delirium was investigated until 6 h postoperatively. Hospitalization duration was defined as the period from the day before surgery to the day of discharge.

Primary and Secondary Outcomes

The primary outcome was the incidence of catheter-related bladder discomfort above a moderate grade at 0 h

postoperatively. The secondary outcomes were the incidences of catheter-related bladder discomfort levels above a moderate grade at 1, 2, and 6 h postoperatively. The severity of catheter-related bladder discomfort at 0, 1, 2, and 6 h postoperatively, incidence of catheter-related bladder discomfort above a moderate grade according to sex, preoperative concentrations of magnesium according to catheter-related bladder discomfort occurrence above a moderate grade at 0 h postoperatively, patient satisfaction, magnesium-related adverse effects, postoperative pain, postoperative opioid requirement, postoperative delirium, and hospitalization duration were also assessed.

Statistical Analysis

The study was designed as a superiority trial to evaluate the effect of magnesium in preventing postoperative catheter-related bladder discomfort among patients having transurethral resection of bladder tumor. Based on our unpublished data, 67% of patients experienced catheter-related bladder discomfort above a moderate grade at 0 h after transurethral resection of bladder tumor. We assumed that magnesium might decrease the incidence of catheter-related bladder discomfort above a moderate grade by 40% (67.0% vs. 40.2%). Based on this assumption, our calculation showed that 54 patients in each group would be necessary to acquire statistical significance, with a two-sided $\alpha = 0.05$ and $\beta = 0.20$. Considering a 10% dropout rate, 60 patients were included in each group.

Enrollment ceased when the target sample size was obtained. The analyses were performed on an intention-to-treat basis. All patients who were enrolled and randomly allocated for treatment were included in the analysis. The data are expressed as means ± SD, number (proportion), relative risk, 95% CI, absolute risk reduction, or number needed to treat. We focused the primary outcome as the incidence of catheter-related bladder discomfort above a moderate grade at 0 h postoperatively. Therefore, our primary outcome was compared using the chi-square test. The secondary outcomes of the incidences of catheter-related bladder discomfort levels above a moderate grade at 1, 2, and 6 h postoperatively were also compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. We performed the post hoc subgroup analyses regarding the incidence of catheter-related bladder discomfort above a moderate grade according to sex and preoperative magnesium concentration according to catheter-related bladder discomfort above a moderate grade at 0 h postoperatively. All P values were two-sided, and a value of $P < 0.05$ was considered statistically significant. Otherwise, the comparisons of postoperative pain between the two groups at each time point were analyzed using the Mann–Whitney U test and performed at an adjusted significance level of 0.0125 (0.05/4) after post

hoc analysis using the Bonferroni method. Statistical analyses were performed using MedCalc version 11.3.3.0 (MedCalc Software bvba, Belgium) and SPSS version 21.0.0 for Windows (IBM Corporation, USA).

Results

The study flowchart is presented in figure 1. During the enrollment process, 160 patients were assessed for eligibility, and 40 patients were excluded. All remaining 120 randomized patients were included in the final analysis because none were lost to follow-up in both groups. The patient and intraoperative characteristics in this study are shown in tables 1 and 2. In magnesium group, 4.1 ± 0.6 g of magnesium sulfate was administered during transurethral resection of bladder tumor. The postoperative magnesium concentration was significantly higher in magnesium group than in control group (1.6 ± 0.2 mM vs. 0.9 ± 0.1 mM; $P < 0.001$). Figure 2 shows the comparison of the serum magnesium concentrations at the preoperative and immediate postoperative periods between control and magnesium groups.

Magnesium administration resulted in a lower catheter-related bladder discomfort incidence above a moderate grade at 0 h postoperatively than normal saline administration, which was statistically significant and clinically important (13 [22%] vs. 46 [77%]; $P < 0.001$; relative risk = 0.283; 95% CI, 0.171 to 0.467; absolute risk reduction = 0.55; number needed to treat = 2; fig. 3). In addition, the magnesium group had lower incidences of catheter-related bladder discomfort above a moderate grade at 1 and 2 h postoperatively than did the control group, which were statistically significant and clinically important (5 [8%] vs. 17 [28%]; $P = 0.005$; relative risk = 0.294; 95% CI, 0.116 to 0.746; and 1 [2%] vs. 14 [23%]; $P < 0.001$; relative risk = 0.071; 95% CI, 0.010 to 0.526, respectively). The incidence of catheter-related bladder discomfort above a moderate grade at 6 h postoperatively was not significantly different between the magnesium and control groups (0 [0%] vs. 2 [3%]; $P = 0.496$). The severity of catheter-related bladder discomfort at 0, 1, 2, and 6 h postoperatively was significantly lower in the magnesium group than in the control group ($P < 0.001$, $P = 0.007$, $P < 0.001$, and $P < 0.001$, respectively; fig. 4).

The incidence of catheter-related bladder discomfort above a moderate grade according to sex was assessed. In male patients, the incidence of catheter-related bladder discomfort above a moderate grade at 0 h postoperatively was significantly lower in magnesium group than in control group (12 [24%] vs. 43 [80%]; $P < 0.001$; relative risk = 0.296; 95% CI, 0.177 to 0.494; absolute risk reduction = 0.56; number needed to treat = 2; table 3). In female patients, the incidence of catheter-related bladder discomfort above a moderate grade at 0 h postoperatively was not significantly different between the magnesium and control groups (1 [11%] vs. 3 [50%]; $P = 0.235$; relative risk = 0.222; 95% CI, 0.030 to 1.665; absolute risk
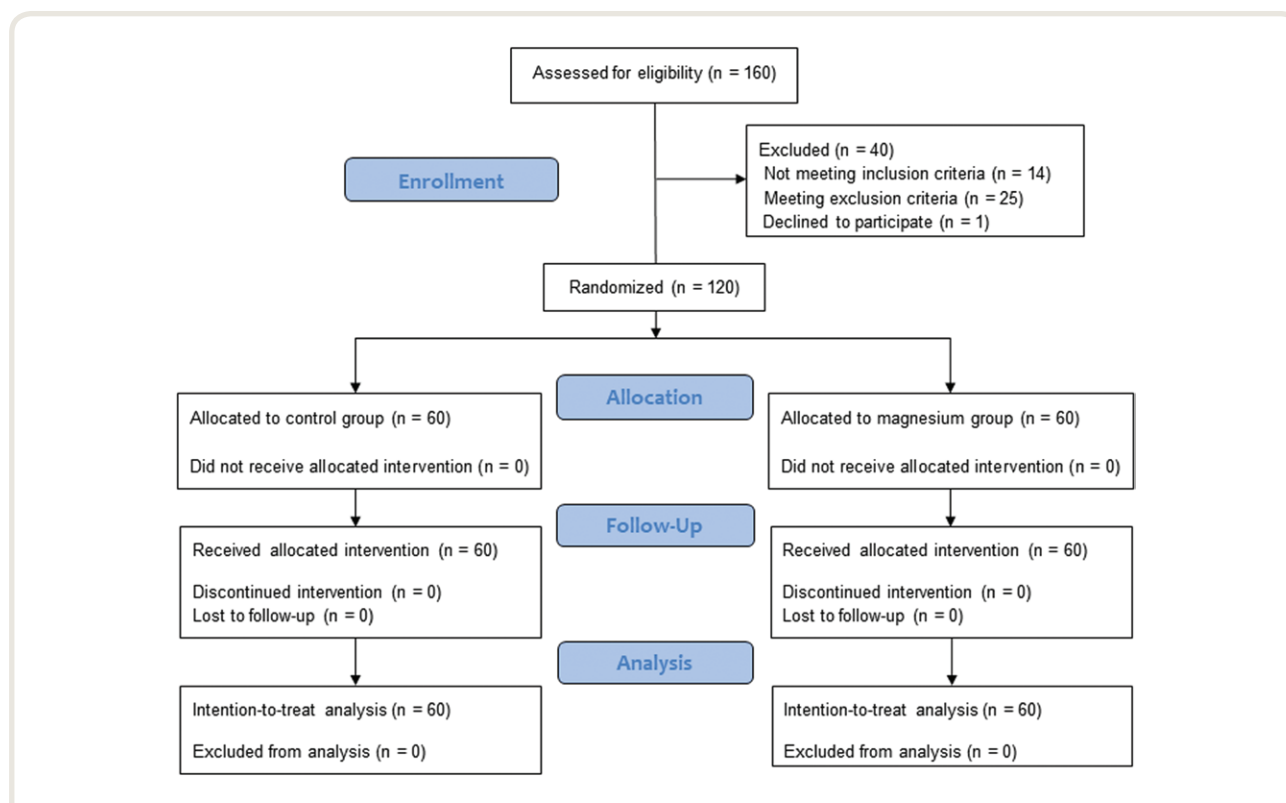
Fig. 1. Study flow diagram of patient inclusion and exclusion. The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium.

reduction = 0.389; number needed to treat = 3; table 3). There was no significant interaction between patients' sex and magnesium on the incidence of catheter–related bladder discomfort above a moderate grade at 0 h postoperatively ($P = 0.745$). Preoperative magnesium concentrations according to catheter–related bladder discomfort grade were assessed. In the control group, there was no difference in the preoperative concentration of magnesium between catheter–related bladder discomfort below

a mild grade and catheter–related bladder discomfort above a moderate grade at 0 h postoperatively (0.87 ± 0.06 vs. 0.90 ± 0.06; $P = 0.196$; 95% CI, -0.063 to 0.013; table 4). In magnesium group, there was also no difference in the preoperative concentration of magnesium between catheter–related bladder discomfort below a mild grade and catheter–related bladder discomfort above a moderate grade at 0 h postoperatively (0.89 ± 0.07 vs. 0.90 ± 0.05; $P = 0.872$; 95% CI, -0.048 to 0.032; table 4).

Table 1. Patient Characteristics

| Characteristics	Control Group (n = 60)	Magnesium Group (n = 60)	Absolute Standardized Difference
Age, yr	65 ± 10	65 ± 7	0.080
Sex, male/female	54 (90)/6 (10)	51 (85)/9 (15)	0.152
Body mass index, kg/m^2	25.5 ± 3.2	25.0 ± 3.2	0.156
ASA Physical Status, class I/II	12 (20)/48 (80)	10 (17)/50 (83)	0.085
Hypertension	38 (63)	34 (57)	0.135
Diabetes mellitus	16 (27)	19 (32)	0.110
Serum Mg^{2+} concentration, mM	0.9 ± 0.1	0.9 ± 0.1	0.006
Serum Ca^{2+} concentration, mg/dl	9.3 ± 0.5	9.3 ± 0.4	0.061
Glomerular filtration rate, ml · min^{-1} · 1.73 m^{-2}	83.1 ± 11.7	81.7 ± 13.2	0.112

The data are expressed as means ± SD or number (%). The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium.

ASA, American Society of Anesthesiologists.

Table 2. Intraoperative Variables

| Variables	Control Group (n = 60)	Magnesium Group (n = 60)	Absolute Standardized Difference
Anesthesia duration, min	70 ± 28	67 ± 22	0.107
Operation duration, min	49 ± 28	46 ± 22	0.006
Amount of crystalloid, ml	174 ± 106	167 ± 52	0.003
Urethral stricture	9 (15.0)	9 (15.0)	0.000
Tumor stage			0.170
No evidence of primary tumor	6 (10)	7 (12)	
Noninvasive papillary carcinoma	19 (31)	23 (38)	
Carcinoma *in situ*	14 (23)	12 (20)	
Tumor invading the lamina propria	19 (32)	16 (27)	
Tumor invading the muscularis propria	2 (3)	2 (3)	
Tumor size			0.191
< 1 cm	17 (28)	13 (22)	
1–3 cm	22 (37)	21 (35)	
3–5 cm	11 (18)	14 (23)	
> 5 cm	10 (17)	12 (20)	
Tumor multiplicity, single/multiple	21 (35)/39 (65)	22 (37)/38 (63)	0.035
Tumor location			
Dome	20 (33)	16 (27)	0.144
Anterior	18 (30)	13 (22)	0.190
Posterior	26 (43)	23 (38)	0.102
Right	27 (45)	23 (38)	0.136
Left	21 (35)	17 (28)	0.144
Trigon	18 (30)	13 (22)	0.190
Neck	16 (27)	12 (20)	0.159
Urethra	2 (3)	4 (7)	0.156

The data are expressed as means ± SD or number (%). The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium.
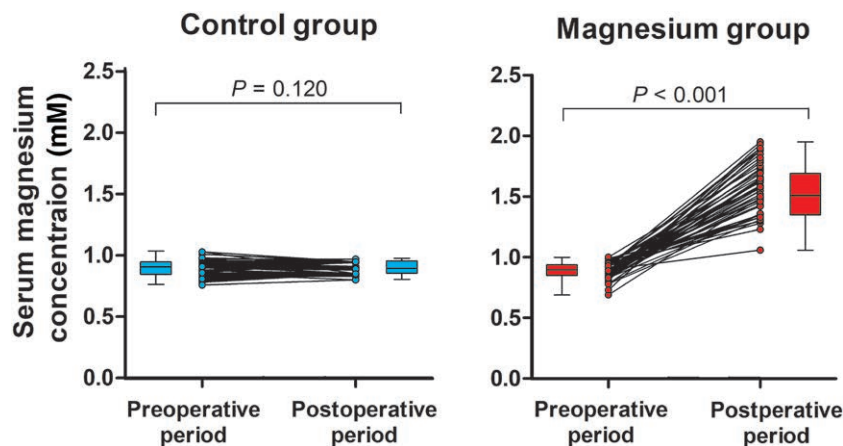
Fig. 2. Comparison of serum magnesium concentrations at the preoperative and immediate postoperative periods between the control group (*blue*) and the magnesium group (*red*). The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium. Each *circle* indicates the serum magnesium concentration of an individual patient. The *horizontal lines* inside the *box plots* indicate median values; the *upper* and *lower edges* of the *box* represent the third and first quartiles, respectively.

Patient satisfaction was significantly higher in the magnesium group than in the control group (5.1 ± 0.8 *vs.* 3.5 ± 1.0; $P < 0.001$; 95% CI, 1.281 to 1.919; fig. 5). There were no significant differences in magnesium-related adverse effects, postoperative pain, postoperative opioid requirement, postoperative delirium, and hospitalization duration between the two groups (table 5).
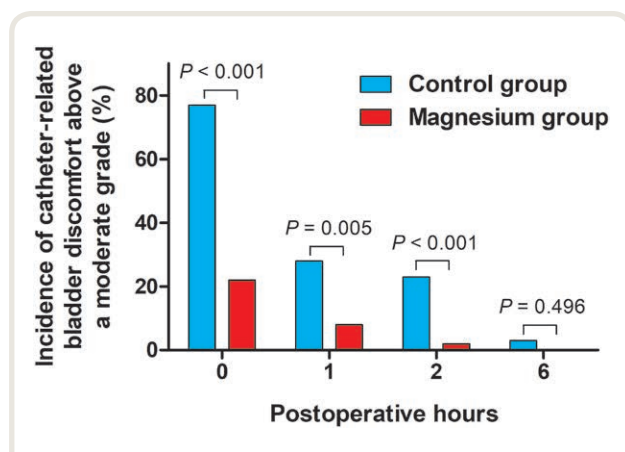
Fig. 3. Comparison of the incidence of catheter-related bladder discomfort above a moderate grade between the control group (*blue bar*) and the magnesium group (*red bar*) at 0, 1, 2, and 6 h postoperatively. The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium. Each *column* indicates the incidence of catheter-related bladder discomfort above a moderate grade. All catheter-related bladder discomfort above a moderate grade was started at postoperative 0 h and was recorded when symptoms were reported by patients on their own without questioning at postoperative 0, 1, 2, and 6 h. The incidence of catheter-related bladder discomfort above a moderate grade at 0, 1, and 2 h postoperatively was significantly lower in the magnesium group than in the control group. Postoperative 0 h was set upon admission to the postanesthetic care unit.

Discussion

In this study, we found that magnesium administration significantly decreased the incidence of catheter-related bladder discomfort above a moderate grade at postoperative 0, 1, and 2 h among patients having transurethral resection of bladder tumor who required large-diameter urinary catheters. The severity of catheter-related bladder discomfort above a moderate grade at 0, 1, 2, and 6 h postoperatively was also significantly lower after magnesium administration. Moreover, patient satisfaction was significantly higher after intravenous magnesium administration. There were no significant differences in magnesium-related adverse effects, postoperative pain, postoperative opioid requirement, and postoperative delirium between control and magnesium groups.

Urinary bladder catheterization can induce catheter-related bladder discomfort in the postoperative period.[22] Catheter-related bladder discomfort was more frequent and more severe in the early postoperative period than in the late postoperative period. Therefore, catheter-related bladder discomfort is an important issue in the PACU after surgery because patients who undergo urinary bladder catheterization usually stay in the PACU during the first postoperative hour.[7,23] Among patients with urinary

catheterization, catheter-related bladder discomfort is a well known risk factor for emergence agitation after awakening from general anesthesia,[24] increasing the workload of the medical staff.[4] In particular, rescue treatments are needed for patients who experience catheter-related bladder discomfort above a moderate grade, which occurs in 38 to 57% of patients in the PACU.[4,25,26] Unlike postoperative somatic pain, opioid administration may be regarded as ineffective to manage catheter-related bladder discomfort considering the mechanisms underlying catheter-related bladder discomfort.[27] One mechanism underlying the occurrence of catheter-related bladder discomfort is the activation of muscarinic acetylcholine receptors by the simulation of the urinary bladder catheter.[3] Therefore, antimuscarinic agents such as tramadol and gabapentin are known to be effective in the management of postoperative catheter-related bladder discomfort (table 6).[8–10,26–31] Another mechanism underlying the occurrence of catheter-related bladder discomfort was found to be mediated by an increased urinary concentration of prostaglandin.[30,31] Urinary catheter and mucosal injury could induce local inflammation with activation of the cyclooxygenase pathway and release of prostaglandin.[32,33] Antiinflammatory agents such as paracetamol and ketorolac are known to be effective in the management of postoperative catheter-related bladder discomfort (table 6).[10,30–32] However, although such interventions were done, the incidence of postoperative catheter-related bladder discomfort still varies.[3] Moreover, many adverse reactions including postoperative nausea and vomiting, hallucinations, respiratory depression, sedation, dry mouth, acute kidney injury, gastrointestinal bleeding, bleeding diathesis, and neurologic and cardiac complications were reported.[4,7–10,30]

In our study, magnesium administration effectively reduced the incidence of catheter-related bladder discomfort above a moderate grade after transurethral resection of bladder tumor. In preference to other anticonvulsants, magnesium is widely used clinically such as in the prevention of eclampsia in women with severe preeclampsia.[34] In patients with ventricular or supraventricular arrhythmia, it can also be used effectively. Intravenous magnesium can improve the quality of anesthesia and analgesia when compared with lidocaine only.[35] Acute postoperative pain is relieved by intravenous magnesium administration.[36] Particularly, in patients with sensory urgency or detrusor instability, magnesium administration improves subjective urinary symptoms.[37] Moreover, low magnesium concentrations can lead to bladder spasm and urinary frequency.[38] High extracellular magnesium concentrations reduced the magnitude of the electrically-induced phasic contractions, as well as spontaneous contractions of the human detrusor smooth muscle *in vitro*.[39] Furthermore, increased blood magnesium concentration reduced inward Ca^{2+} currents in the human detrusor smooth muscle. Therefore, increased detrusor muscle contraction might be effectively regulated by magnesium administration.[39] It is possible that the decrease in
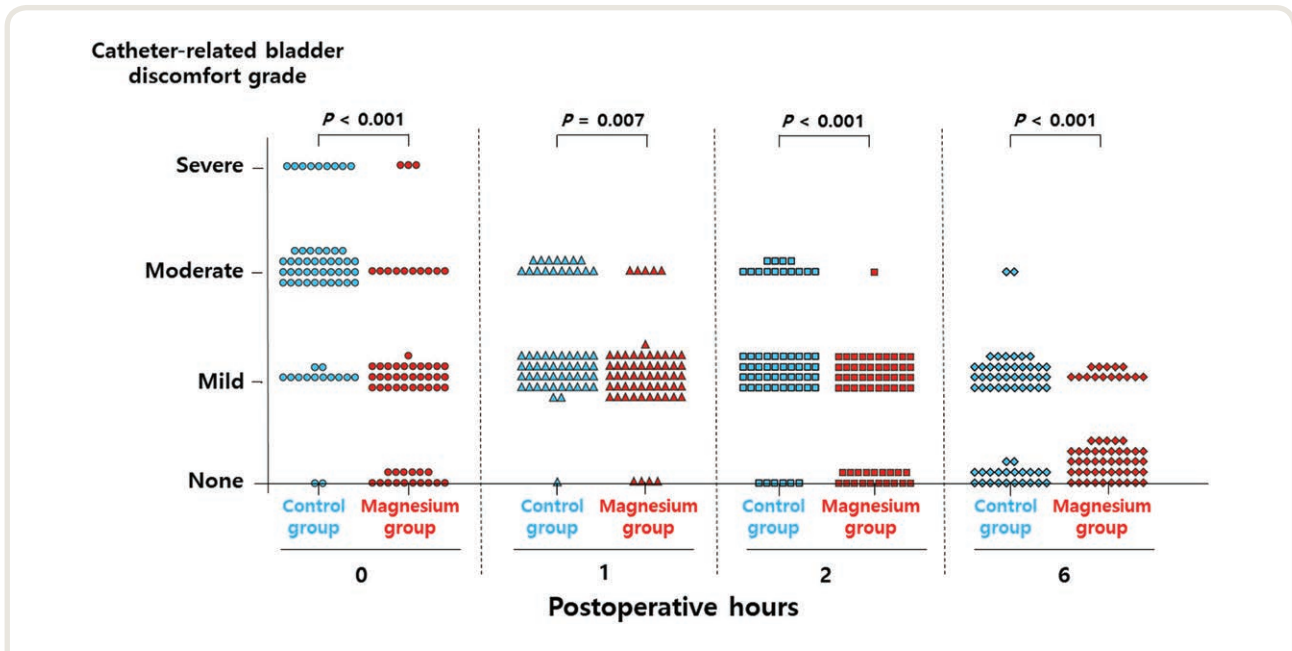
Fig. 4. Comparison of the catheter-related bladder discomfort grade between the control group (*blue symbols*) and the magnesium group (*red symbols*) at 0, 1, 2, and 6 h postoperatively. The catheter-related bladder discomfort grades between control and magnesium groups at 0, 1, 2, and 6 h postoperatively were compared using the chi-square test or Fisher's exact test as appropriate. The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium. Each *circle*, *triangle*, *square*, and *diamond* indicates the catheter-related bladder discomfort grade of an individual patient. Postoperative 0 h was set upon admission to the postanesthetic care unit.

Table 3. Comparison of the Incidence of Postoperative Catheter-related Bladder Discomfort above a Moderate Grade according to Sex

Postoperative Time	Male (n = 105)			Female (n = 15)		
	Control Group (n = 54)	Magnesium Group (n = 51)	P Value	Control Group (n = 6)	Magnesium Group (n = 9)	P Value
0 h	43 (80)	12 (24)	< 0.001	3 (50)	1 (11)	0.235
1 h	17 (32)	4 (8)	0.002	0 (0)	1 (11)	0.999
2 h	12 (22)	1 (2)	0.002	2 (33)	0 (0)	0.143
6 h	2 (4)	0 (0)	0.496	0 (0)	0 (0)	> 0.999

The data are expressed as numbers (%). The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium.

catheter–related bladder discomfort by magnesium admin–istration is mediated by the mitigation of abnormal detrusor muscle instability caused by urinary bladder catheterization.

In the present study, patient satisfaction, assessed on a seven-point Likert scale, was significantly higher after magnesium administration. This can be explained by the reduction in catheter-related bladder discomfort above a moderate grade during the early postoperative period after transurethral resection of bladder tumor by administering magnesium. Because patient satisfaction is related to post-operative outcomes,[40,41] the increase in patient satisfac-tion after magnesium administration may be a significant

benefit, along with a reduction in catheter-related bladder discomfort above a moderate grade. Therefore, we consider that patient satisfaction should be monitored as long as a large-diameter urinary catheter is inserted during the post–operative period.

We did not observe any serious complications attributed to magnesium administration. However, given our relatively small trial size, we have limited ability to judge the frequency of rare but potentially serious events. Magnesium–related adverse effects such as nausea or vomiting, headache, leth–argy, flushing, hypotension, and respiratory depression may occur at higher blood concentrations of magnesium.[14,15]

Table 4. Preoperative Concentrations of Magnesium according to Catheter-related Bladder Discomfort Occurrence above a Moderate Grade at 0 h Postoperatively

	Control Group (n = 60)			Magnesium Group (n = 60)		
	Catheter-related Bladder Discomfort below a Mild Grade at 0 h Postoperatively (n = 14)	Catheter-related Bladder Discomfort above a Moderate Grade at 0 h Postoperatively (n = 46)	P Value	Catheter-related Bladder Discomfort below a Mild Grade at 0 h Postoperatively (n = 47)	Catheter-related Bladder Discomfort above a Moderate Grade at 0 h Postoperatively (n = 13)	P Value
Preoperative serum Mg^{2+} concentration, mM	0.87 ± 0.06	0.90 ± 0.06	0.196	0.89 ± 0.07	0.90 ± 0.05	0.872

The data are expressed as means ± SD. The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium.
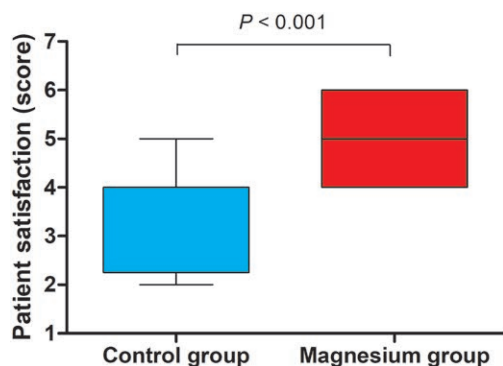
Fig. 5. Comparison of patient satisfaction between the control group (*blue*) and the magnesium group (*red*). Patient satisfaction was assessed on a seven-point Likert scale (1 = strongly dissatisfied, 2 = moderately dissatisfied, 3 = slightly dissatisfied, 4 = neutral, 5 = slightly satisfied, 6 = moderately satisfied, and 7 = extremely satisfied) at 6 h postoperatively. The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium. The *horizontal lines* inside the *boxes* indicate median values; the *upper* and *lower edges* of the *boxes* represent the third and first quartiles, respectively.

Table 5. Magnesium-related Adverse Effects, Postoperative Pain, Postoperative Opioid Requirement, Postoperative Delirium, and Hospitalization Duration among Patients Having Transurethral Resection of Bladder Tumor

Variables	Control Group (n = 60)	Magnesium Group (n = 60)	P Value
Magnesium-related adverse effects			
Nausea/vomiting	3 (5)	1 (2)	0.619
Headache	2 (3)	1 (2)	0.999
Lethargy	0 (0)	0 (0)	> 0.999
Flushing	0 (0)	0 (0)	> 0.999
Hypotension	7 (12)	9 (15)	0.591
Respiratory depression	0 (0)	0 (0)	> 0.999
Postoperative pain, numeric rating scale			
Postoperative 0 h	4.0 ± 1.5	3.9 ± 1.5	0.730
Postoperative 1 h	2.3 ± 1.0	2.3 ± 0.8	0.431
Postoperative 2 h	2.9 ± 2.0	2.9 ± 1.8	0.883
Postoperative 6 h	1.3 ± 1.2	1.2 ± 1.0	0.622
Postoperative opioid requirement, µg	15.7 ± 4.6	14.4 ± 5.7	0.148
Postoperative delirium	0 (0)	0 (0)	> 0.999
Hospitalization duration, days	4.4 ± 1.5	4.2 ± 1.6	0.362

The data are expressed as means ± SD or numbers (%). The control group included patients who received intravenous normal saline as control. The magnesium group included patients who received intravenous magnesium. Postoperative hour 0 was set upon admission to the postanesthetic care unit.

The most prominent clinical manifestations of mild hypermagnesemia of 2 to 3 mM are nausea, flushing, headache, lethargy, drowsiness, and decreased deep tendon reflexes. Plasma magnesium concentration of 3 to 5 mM may cause somnolence, hypocalcemia, absent deep tendon reflexes, hypotension, and bradycardia. Plasma magnesium concentration above 5 mM may cause muscle paralysis leading to flaccid quadriplegia, apnea and respiratory failure, complete heart block, and cardiac arrest.[14,15] Infusion of 4 g of magnesium sulfate resulted in a blood magnesium concentration of less than 1.8 mM.[42] In the present study, 4.1 ± 0.6 g of magnesium sulfate was administered during transurethral resection of bladder tumor in magnesium group, and the serum magnesium concentration at the immediate postoperative period was 1.6 ± 0.2 mM in this group. Therefore, the dose of magnesium administered in this study may be safely used to manage catheter-related bladder discomfort after transurethral resection of bladder tumor. However, it may not be powered enough to detect the difference in magnesium-related adverse effects between control and magnesium groups because this study was designed for the assessment of catheter-related bladder discomfort above a

Table 6. Comparison of Previous Studies Regarding the Prevention of Postoperative Catheter-related Bladder Discomfort

Author, Date	Group, Sample Size	Study Design	Surgery	Mechanism of Action	Results	Adverse Effects
Agarwal *et al.*, 2007[28]	Control, 54 Gabapentin, 54	Randomized controlled trial	Percutaneous nephrolithotomy	Antiepileptic	The incidence of catheter-related bladder discomfort: control group (80%) *vs.* gabapentin group (50%; $P < 0.05$)	Sedation, postoperative nausea and vomiting, light-headedness, and headache: no significant differences between the two groups
Agarwal *et al.*, 2008[8]	Control, 27 Tramdol, 27	Randomized controlled trial	Percutaneous nephrolithotomy	Antimuscarinic	The incidence and severity of catheter-related bladder discomfort was reduced in tramadol group compared with control group at all time points ($P < 0.05$)	Control group *vs.* tramadol group: sedation, 16% *vs.* 56% ($P < 0.05$); vomiting, 12% *vs.* 40% ($P < 0.05$); nausea, 16% *vs.* 60% ($P < 0.05$)
Ergenoglu *et al.*, 2012[31]	Control, 32 Paracetamol, 32	Randomized controlled trial	Percutaneous nephrolithotomy	Antiinflammatory	Scores of catheter-related bladder discomfort were less in paracetamol group compared with control group at all time points except at postoperative 12 h ($P < 0.05$)	No paracetamol-related adverse effects
Kim *et al.*, 2014[26]	Control, 57 Dexmedetomidine, 57	Randomized controlled trial	Transurethral resection of bladder tumor	Antimuscarinic	The incidence of catheter-related bladder discomfort was less in dexmedetomidine group compared with control group at postoperative 0 and 1 h ($P < 0.05$)	Control group *vs.* dexmedetomidine group: hypotension, 22% *vs.* 33% ($P = 0.203$); bradycardia, 9% *vs.* 11% ($P = 0.761$); nausea, 7% *vs.* 9% ($P = 0.742$); dry mouth, 4% *vs.* 6% ($P = 0.679$)
Kim *et al.*, 2017[27]	Sevoflurane, 41 Propofol, 41	Randomized controlled trial	Transurethral resection of bladder tumor	Antimuscarinic	The incidence of catheter-related bladder discomfort: sevoflurane group (59%) *vs.* propofol group (85%) at postoperative 1 h ($P = 0.007$)	Sevoflurane group *vs.* propofol group: nausea, 7% *vs.* 5% ($P = 1.000$); vomiting, 2% *vs.* 5% ($P = 1.000$); dry mouth, 5% *vs.* 5% ($P = 1.000$)
Park *et al.*, 2019[30]	Control, 65 Ketorolac, 65	Randomized controlled trial	Robot-assisted laparoscopic radical prostatectomy	Antiinflammatory	Catheter-related bladder discomfort above a moderate grade at postoperative 0 h: control group (51%) *vs.* ketorolac group (21%; $P = 0.001$)	Control group *vs.* ketorolac group: acute kidney injury, 4% *vs.* 2% ($P > 0.999$); gastrointestinal bleeding, none; desaturation events, 2% *vs.* 0% ($P > 0.999$)
Kim *et al.*, 2019[10]	Control, 45 Lidocaine, 45	Randomized controlled trial	Transurethral resection of bladder tumor	Antimuscarinic, antiinflammatory	Catheter-related bladder discomfort above a moderate grade at postoperative 0 h: control group (67%) *vs.* lidocaine group (26%; $P < 0.001$)	No lidocaine-related adverse effects

moderate grade at 0 h postoperatively as a primary outcome. In addition, it is important to confirm the concentration of magnesium after intravenous infusion of magnesium was stopped. However, we measured the concentration of magnesium only once after magnesium administration. Therefore, the safety concern of magnesium administration needs to be interpreted cautiously.

We found that there were no significant differences in postoperative pain and opioid requirement during postoperative 24 h between the two groups. This result may be, at least in part, because of the surgical characteristic of transurethral resection of bladder tumor. The postoperative pain that occurs in patients after transurethral resection of bladder tumor is not severe because transurethral resection of bladder tumor is a relatively shorter and less invasive form of endoscopic surgery. Although magnesium reduced acute postoperative pain and opioid requirements on the first

postoperative day among patients after lower limb surgery,[36] magnesium administration did not significantly reduce postoperative pain and opioid requirement in the present study.

None of the patients in either group experienced postoperative delirium or magnesium–induced lethargy. The hyperactive type of postoperative delirium may be difficult to distinguish from severe catheter-related bladder discomfort–related agitation, whereas the hypoactive type of postoperative delirium may be difficult to distinguish from magnesium–related lethargy. Both hypoactive delirium and magnesium–related lethargy can have an influence on the catheter-related bladder discomfort scores. Therefore, we used the confusion assessment method score to determine the presence of postoperative delirium.[43] In addition, we assessed the events of magnesium–induced lethargy. In this study, there was no postoperative delirium

and magnesium–induced lethargy. Delirium is defined as an acute or fluctuating course of mental status change combined with inattention and either an altered level of consciousness or disorganized thinking.[43] Postoperative delirium or acute cognitive dysfunction is also a postoperative complication that has a varying incidence of 1.4 to 19.3%.[44,45] The risk factors of postoperative delirium are reported to be ASA Physical Status III or IV, increased surgical duration, usage of opioid, critical illness, malnutrition, and need of mechanical ventilation.[44,46,47] The participants of this study had few risk factors because we enrolled only those with ASA Physical Status of I or II. Furthermore, operation duration and opioid requirements are relatively shorter and smaller in transurethral resection of bladder tumor than in other general surgical procedures. Moreover, at postoperative 0 h, only 12 patients experienced severe catheter-related bladder discomfort in the present study; these cases were resolved within 10 min by administering tramadol. In terms of magnesium–induced lethargy, the participants of this study were administered relatively small-to-moderate doses of magnesium sulfate. In addition, the postoperative magnesium concentration was less than 2 mM in magnesium group. Based on these considerations, the influence of postoperative delirium and magnesium–induced lethargy on postoperative catheter-related bladder discomfort scores were likely insignificant.

In the present study, we assessed the incidence of catheter-related bladder discomfort above a moderate grade according to sex. The incidence of catheter-related bladder discomfort above a moderate grade at 0 h postoperatively was significantly lower in the magnesium group than in the control group in male patients. However, the incidence of catheter-related bladder discomfort above a moderate grade at 0 h postoperatively was not significantly different between the two groups in female patients, although it was much lower in the magnesium group than in the control group. Nonetheless, sex does not seem to influence the effect of magnesium administration on catheter-related bladder discomfort because there was no significant interaction between sex and magnesium on the incidence of catheter-related bladder discomfort. However, we consider that subgroup analyses are prone to replicate poorly and should be interpreted with caution.

Unlike routine perioperative pain management, postoperative catheter-related bladder discomfort might have been relatively overlooked. Many studies have been done with the aim to prevent or treat catheter-related bladder discomfort. Although antimuscarinic agents and antiinflammatory agents were studied in catheter-related bladder discomfort, postoperative catheter-related bladder discomfort has not been sufficiently prevented and remains a burden on patients and medical staff.[3] Moreover, these managements may have some limitations such as postoperative nausea and vomiting, hallucinations, respiratory depression, sedation, dry mouth,

acute kidney injury, gastrointestinal bleeding, bleeding diathesis, and neurologic and cardiac complications.[4,7–10,30,48] Magnesium has various pharmacologic effects associated with smooth muscle relaxation. In this study, magnesium effectively and safely reduced the incidence of catheter-related bladder discomfort above a moderate grade in patients having transurethral resection of bladder tumor. To the best of our knowledge, this is the first study to evaluate the association of magnesium administration and postoperative catheter-related bladder discomfort.

Our study has several limitations. First, we administered magnesium sulfate at a 50 mg/h loading dose for 15 min just after the induction of anesthesia and at $15 \, mg \cdot kg^{-1} \cdot h^{-1}$ continuous infusion during the intraoperative period. Although this loading dose and continuous infusion of magnesium had a beneficial effect on the prevention of catheter-related bladder discomfort above a moderate grade, we did not confirm whether this dose was optimum for preventing catheter-related bladder discomfort. Therefore, further studies are needed to evaluate the optimal magnesium dose required for the prevention of catheter-related bladder discomfort among patients who required a large-diameter urinary catheter. Second, we administered magnesium just after the completion of anesthesia induction and until the completion of the procedure. We did not confirm whether this timing of magnesium administration was optimum for preventing postoperative catheter-related bladder discomfort. Accordingly, further studies are needed to determine the optimal timing required for magnesium administration for the prevention of postoperative catheter-related bladder discomfort. Third, although the qualitative method for assessing catheter-related bladder discomfort has been used in various previous studies,[5,7,8,23,26,28,29,48] the difference between mild grade and moderate grade catheter-related bladder discomfort can be subjective, and the treatment effect estimation may, at least in part, be influenced by the differential distributions of these two categories in magnesium and control groups. Last, this study was conducted in a single center. In addition, we excluded the patients with ASA Physical Status of III or IV. In patients with renal impairment or heart disease, magnesium needs to be administered cautiously because magnesium–related complications may increase.[49] Thus, these limitations may affect the generalizability of our study.

Conclusions

Magnesium reduced the incidence of catheter-related bladder discomfort above a moderate grade and increased patient satisfaction in patients having transurethral resection of bladder tumor. These results suggest that magnesium administration is an effective option for the prevention of catheter-related bladder discomfort among patients having transurethral resection of bladder tumor who required a large-diameter urinary catheter.

Research Support

Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: kyk@amc.seoul.kr. Raw data available at: kyk@amc.seoul.kr.

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Appendix 1. Magnesium Can Affect the Absorption of the Following Drugs[50]

1. Tetracycline
2. Gentamycin
3. Foscarnet
4. Amphotericin B
5. Thiazides
6. Loop diuretics
7. Omeprazole
8. Imipramine
9. Digoxin
10. Pamidronate

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