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# 비뇨기과 수술 후 도뇨관 삽입과 연관된 방광 불편감을 예방하기 위한 새로운 방법: 케토로락 혹은 마그네슘 투여

New approaches to prevent catheter-related bladder discomfort after urologic surgery: ketorolac or magnesium administration

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2020년 12월

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2020년 12월

# ABSTRACT

**Introduction**

Catheter-related bladder discomfort (CRBD) is common in patients with urinary bladder catheters and is accompanied by postoperative agitation, poor patient satisfaction, extended hospital stays, and increased workload for medical staff. CRBD occurs because of the involuntary bladder smooth muscle contractions caused by various factors such as muscarinic receptor activation or inflammation-induced prostaglandin (PG) production. Ketorolac is an anti-inflammatory drug that decreases PG by cyclooxygenase inhibition. Moreover, magnesium can decrease smooth muscle contraction by the active transport of calcium ions across the cell membranes. Thus, ketorolac or magnesium administration is believed to prevent CRBD. However, the preventive effect of ketorolac or magnesium on postoperative CRBD has not been studied. Therefore, the author aimed to evaluate new approaches to prevent CRBD after urologic surgery by ketorolac or magnesium administration, as explained in the following two parts

**Part I**

**Objective:** The author evaluated the effect of ketorolac on the prevention of CRBD in patients undergoing robot-assisted laparoscopic radical prostatectomy (RALP).

**Methods:** All patients were randomly allocated to the ketorolac group (n = 66) or the control group (n = 66). The primary outcome was CRBD above a moderate grade at 0 hours postoperatively. CRBD above a moderate grade at 1, 2, and 6 hours was also assessed. Postoperative pain, opioid requirement, ketorolac-related complications, patient satisfaction, and hospitalization duration were also assessed.

**Results:** The incidence of CRBD above a moderate grade at 0 hours postoperatively was significantly lower in the ketorolac group (14 [21.5%] vs. 33 [50.8%], $P = 0.001$, relative risk [RR] = 0.424, 95% CI: 0.252–0.715, absolute risk reduction [ARR] = 0.29, number needed to treat [NNT] = 3) as were those at 1, 2, and 6 hours. Pain scores at 0 and 1 hours and opioid requirement over 24 hours were significantly lower in the ketorolac group, while patient satisfaction scores were significantly higher in the ketorolac group. Ketorolac-related complications and hospitalization duration were not significantly different between the two groups.

**Conclusion:** This study shows ketorolac can reduce postoperative CRBD above a moderate grade and increase patient satisfaction in patients undergoing RALP, suggesting it is a useful option to prevent postoperative CRBD.

**Part II**

**Objective:** The author evaluated that among patients having transurethral resection of bladder tumor (TURB), magnesium will reduce the incidence of postoperative moderate-to-severe CRBD.

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

**Results:** The incidence of CRBD above a moderate grade at 0 hours postoperatively was significantly lower in the magnesium group than in the control group (13 [22%] vs. 46 [77%], $P$ <0.001, RR = 0.283, 95% CI: 0.171–0.467, ARR = 0.55, NNT = 2); similar results were observed for CRBD above a moderate grade at 1 and 2 hours postoperatively (5 [8%] vs. 17 [28%], $P$ = 0.005, RR = 0.294, 95% CI = 0.116–0.746, and 1 [2%] vs. 14 [23%], $P$ <0.001, RR = 0.071, 95% CI = 0.010–0.526, respectively). Patient satisfaction on a scale from 1–7 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 = 1.281–1.919). Magnesium-related adverse effects were not significantly different between the groups.

**Conclusion:** Magnesium reduced the incidence of CRBD above a moderate grade and increased patient satisfaction among patients having transurethral resection of bladder tumor.

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# INTRODUCTION

Catheter-related bladder discomfort (CRBD) occurs because of the involuntary bladder smooth muscle contractions after catheterization during various surgeries.[1-7] CRBD is characterized by discomfort in the suprapubic region, manifesting as urinary urgency and frequency with or without urge incontinence.[8] The mechanism of CRBD is similar to that of overactive bladder syndrome, in which the urinary bladder smooth muscle contraction is caused by various factors such as type 3 muscarinic receptor activation or inflammation-induced prostaglandin (PG) production.[9-11] The CRBD incidence is 47%–90% in patients with urinary bladder catheters.[9] Especially, CRBD above a moderate grade, which was reported in 38%–57% of patients who had undergone general surgery with urinary bladder catheters at the post-anesthesia care unit (PACU), is challenging to treat and frequently requires active treatment.[4,12] CRBD is usually accompanied by behavioral responses, such as flailing limbs, strong vocal response, and attempting to pull out the urinary catheter.[9] In addition, CRBD can be accompanied by postoperative agitation, poor patient satisfaction, extended hospital stays, and increased workload of medical staff.[9] Therefore, adequate CRBD prevention or treatment is important in patients requiring urinary catheters.

Unlike postoperative pain management, CRBD has been under-evaluated and likely to be resistant to usual pain management owing to different mechanisms between postoperative pain and CRBD.[9] CRBD is induced by the involuntary urinary bladder smooth muscle contractions mediated by type 3 muscarinic receptor activation.[4] Various agents, such as anti-muscarinic agents, have been studied for CRBD prevention.[2,5,13,14] Furthermore, PG increases with the occurrence of inflammation, obstruction, and mucosal injury in the urinary bladder.[15] Inflammation-induced PG production can induce detrusor muscle contraction and consequently induce CRBD.[10] Agents associated with anti-inflammatory effects, have been also used to prevent and treat CRBD by PG inhibition. Despite the availability of these agents, sufficient evidence for effective treatment without adverse reactions, such as nausea, vomiting, mouth dryness, hallucinations, sedation, respiratory depression, and neurologic and cardiac complications, is lacking.[2,5,9,13,14]

Ketorolac, as an anti-inflammatory agent, decreases PG by cyclooxygenase inhibition.[13] It is widely used as an analgesic in various clinical circumstances.[16,17] In particular, multimodal analgesia, including ketorolac, is recommended for effective postoperative pain management.[18] However, the preventive effect of ketorolac on postoperative CRBD has not been studied.

Magnesium is the fourth most abundant cation.[19] It is associated with various physiologic responses, such as signal transduction, protein synthesis, neuromuscular conduction, blood pressure

regulation, and blood glucose control.[19] Moreover, magnesium is important in decreasing and stabilizing smooth muscle contraction because it plays a significant role in the active transport of calcium ions across the cell membranes.[19] In this regard, magnesium is believed to influence CRBD occurrence. However, its effect on postoperative CRBD prevention has not been studied.

Therefore, the author evaluated the hypothesis that new approaches, such as ketorolac or magnesium administration, would reduce postoperative CRBD in patients undergoing urologic surgery. Consequently, the author evaluated the e□ect of ketorolac on CRBD prevention after robot-assisted laparoscopic radical prostatectomy (RALP) in part I. In addition, the author evaluated the e□ect of magnesium on CRBD prevention after transurethral resection of bladder tumor (TURB) in part II.

# PART I

E□ect of Ketorolac on the Prevention of Postoperative Catheter-Related Bladder Discomfort in Patients Undergoing Robot-Assisted Laparoscopic Radical Prostatectomy: A Randomized, Double-Blinded, Placebo-Controlled Study

This part was published in Journal of Clinical Medicine[20]

## 1.1 INTRODUCTION

Urinary catheterization is generally used during surgery, although it can cause postoperative CRBD.[9] CRBD is characterized by discomfort in the suprapubic region, manifesting as urinary urgency and frequency with or without urge incontinence.[8] The incidence of CRBD is 47–90% in patients who have undergone elective surgery.[9] CRBD that is above a moderate grade, which is often intolerable and requires treatment,[4,21] occurs in 38–57% of patients with a urinary bladder catheter in a PACU.[7,12] Indwelling urinary catheter size and male gender are known independent predictors of CRBD above a moderate grade in the PACU.[22] CRBD can be so disturbing to patients that it is accompanied by postoperative agitation, poor satisfaction of a hospital day, extension of hospital stay, and an increased workload for medical staff.[9]

For postoperative pain management, multimodal techniques that include administration of two or more drugs of different mechanisms have been used.[23] Nonsteroidal anti-inflammatory drugs (NSAID), cyclooxygenase-2 selective NSAID, and opioids should be individualized for the multimodal technique.[23] Opioid and non-opioid analgesics have been administered to 58.9% and 96.5% of patients to manage postoperative pain in general surgery, respectively.[24] However, in contrast to postoperative pain, CRBD has been under-treated and may be resistant to conventional pain management such as opioids because different mechanisms are involved in developing postoperative pain and CRBD.[9] CRBD is induced by involuntary contractions of the urinary bladder mediated by type 3 muscarinic receptor activation.[4] Agents associated with anti-muscarinic effects have been used to prevent and manage CRBD, with varying degrees of success.[3,4] However, these agents are limited because of various adverse effects, including dry mouth, postoperative nausea and vomiting, facial flushing, and blurred vision.[9]

Ketorolac tromethamine, an NSAID, induces a decrease in PG levels driven by the inhibition of cyclooxygenase.[13] Ketorolac is widely used as an analgesic in various clinical practices.[16,17] In particular, multimodal analgesia including ketorolac is recommended for effective postoperative pain management.[18] However, the preventive effect of ketorolac on postoperative CRBD has not been studied. Based on these considerations, the author hypothesized that ketorolac could prevent CRBD after surgery in male patients requiring urinary catheterization. The author evaluated the effect of ketorolac on the prevention of postoperative CRBD above a moderate grade in patients undergoing RALP.

## 1.2 MATERIALS AND METHODS

This prospective, randomized, double-blinded, placebo-controlled study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (2018-0749). This study was registered at the Clinical Research Information Service (KCT0003064).

### Patients

Patients aged 20–79 years of age with an American Society of Anesthesiologists physical status (ASA PS) ≤II, who were scheduled to undergo elective RALP and voluntarily agreed to this clinical study, were enrolled as participants. Patients with chronic kidney disease, uncontrolled hypertension, morbid obesity, psychiatric disorders, a history of preexisting bladder disease, gastrointestinal ulcers or perforation, hemorrhage, coagulopathy, or asthma were excluded. Those with a history of ketorolac allergy were also excluded.

### Randomization, Concealment, and Blinding

Patients enrolled in the present study were randomized. For the randomization, a web-based randomization software (Random Allocation Software version 1.0, Isfahan University of Medical Sciences, Isfahan, Iran) was used. Randomization was determined with block sizes of four and an allocation ratio of 1:1. Eligible participants were allocated to be given either intravenous ketorolac (ketorolac group) or intravenous normal saline as a placebo (control group) by a computer-generated randomization schedule.

The randomization codes were enclosed in sequentially numbered, identical, opaque, and sealed envelopes. The envelope was kept in a closed box during the study period. The codes were concealed by the first investigator and were given to the second investigator, who prepared the medications of either ketorolac or normal saline. These medications were prepared in identical syringes with a volume of 2 mL, and labelled with the patients' names and hospital registration numbers. After the completion of urethrovesical anastomosis during surgery, 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. All other investigators and participants, except the first and second investigators, did not know the group allocation until the data analyses were completed.

**Anesthetic and Surgical Techniques**

Before surgery, patients were instructed on symptoms of CRBD (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 to the operating room, patient monitoring was performed according to institutional standards. Intraoperative monitoring included electrocardiography, intra-arterial blood pressure, end-tidal carbon dioxide concentration, and peripheral oxygen saturation. Anesthesia was induced with 5 mg/kg thiopental sodium and target-controlled infusion of remifentanil (Orchestra Base Primea; Fresenius Kabi, Bad Homburg, Germany) with an effect site concentration of 2 ng/mL. Subsequently, 0.6 mg/kg rocuronium bromide was given to facilitate tracheal intubation. Anesthesia was maintained with 2 to 3 vol% sevoflurane and 50% oxygen in medical air. Also, the effect site concentration of remifentanil target-controlled infusion was adjusted to between 2 and 5 ng/mL. The depth of anesthesia was monitored using the bispectral index (A-1050 Monitor; Aspect Medical Systems, Newton, MA, USA), which was maintained between 40 and 60. Systolic blood pressure was maintained at 80–130 mmHg and heart rate was maintained at 60–100 beat/min. Sevoflurane administration and remifentanil target-controlled infusion were intermittently adjusted during surgery according to the bispectral index and hemodynamic parameters. Train-of-four monitoring was used for neuromuscular blockade monitoring. Rocuronium bromide was administered intermittently to maintain train-of-four $\leq 2$ throughout surgery. Mechanical ventilation using an anesthetic machine (Primus; Dräger, Lübeck, Germany) was performed using a fixed tidal volume of 8 mL/kg (ideal body weight) and a respiratory rate of 10–16 frequency/min to maintain an end-tidal carbon dioxide concentration of 35–40 mmHg. A positive end-expiratory pressure of 5 cm $H_2O$ was applied. The maintenance infusion rate of Plasma Solution A (CJ Pharmaceutical, Seoul, Korea) as a crystalloid fluid was 2–4 mL/kg/h. A colloid fluid was not used during RALP.

The RALP was performed according to standard protocols using the da Vinci robot system (Intuitive Surgical, Inc., Sunnyvale, CA, USA). During surgery, all patients were placed in the Trendelenburg position and pneumoperitoneum, which was achieved by continuous carbon dioxide insufflation maintaining an intra-abdominal pressure of 12 cm $H_2O$. After skin sterilization for surgery, urinary bladder catheterization was performed with a 16 to 20-Fr Foley catheter after lubrication with lidocaine jelly, and its balloon was inflated with 10 mL of normal saline. To access the space of Retzius, bladder mobilization was performed. A transperitoneal antegrade approach was used to dissect the prostate, and nerve sparing was carried out on all patients on sides that were not suspected for extension of cancer. Pelvis lymph node dissection was performed in intermediate- to

high-risk groups as designated by the D'Amico criteria.[25] Urethrovesical anastomosis was performed with a continuous suture.

Patients were given either ketorolac (30 mg) or an equivalent volume of placebo (0.9% normal saline) intravenously just after urethrovesical anastomosis. At the end of the procedure, sugammadex 2 mg/kg was administered to antagonize residual neuromuscular block after confirming that train-of-four count was ≥2. In the PACU, when the patient reported CRBD above a moderate grade, 50 mg tramadol was administered intravenously as rescue therapy to decrease CRBD as tramadol has a potent anti-muscarinic effect.[5] Postoperative pain, defined as sharp pain at the surgical site, was assessed using a numerical rating scale (0 = no pain to 10 = worst imaginable pain). In case of postoperative pain without urgency or suprapubic discomfort like CRBD, 50 μg fentanyl was administered as rescue therapy when pain scores were ≥4 on a numeric rating scale. If the patient complained of both CRBD and postoperative pain, the author treated the main chief complaint by either tramadol or fentanyl, and then reassessed the patient.

**Assessments**

Patient characteristics assessed were age, sex, body mass index, American Society of Anesthesiologists physical status, underlying disease (diabetes mellitus and hypertension), Gleason score, and tumor category. Gleason score was assessed by adding the numeric value of the two most prevalent differentiation patterns on histology obtained during preoperative transrectal ultrasound-guided needle biopsy.[26] Gleason scores were categorized into three groups: under 7, equal to 7, and above 7.[27-29] Tumor category was assessed by digital rectal exam, transrectal ultrasound-guided biopsy, and imaging studies performed preoperatively.[30] Tumor category was classified by the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[31] Intraoperative variables included operation time, intraoperative fluid administered, and urinary catheter size used.

CRBD above a moderate grade was assessed at 0, 1, 2, and 6 hours postoperatively. Especially, CRBD above a moderate grade at 0 hours postoperatively was assessed just after the patients were transferred to the PACU. The severity of CRBD 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.[4]

Postoperative pain was assessed using a numerical rating scale at 0, 1, 2, and 6 hours postoperatively. Doses of all opioids and tramadol administered to patients during the 24 hours

following surgery were converted to intravenous fentanyl equianalgesic doses according to published conversion factors (intravenous fentanyl 100 μg = intravenous tramadol 100 mg).[32,33] Patient satisfaction was assessed with 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)[34] at 6 hours postoperatively.

Ketorolac-related complications included acute kidney injury, hemoglobin changes, gastrointestinal bleeding, and desaturation events. Acute kidney injury was assessed by Kidney Disease: Improving Global Outcomes (KDIGO) criteria. According to KDIGO criteria, acute kidney injury is defined as an increase in serum creatinine by 0.3 mg/dL or more within 48 h, or an increase in serum creatinine of 1.5 times or more within the prior 7 days. However, the urine output criterion was not included because of the inconsistency in urine output measurements [21]. Hemoglobin changes, calculated by subtracting preoperative hemoglobin levels from hemoglobin levels at postoperative day 1, were evaluated. Gastrointestinal bleeding during hospitalization was evaluated according to criteria fulfilling one or more of the following conditions: physician-documented frank hematemesis, physician-documented frank melena, heme-positive stool associated with a documented upper gastrointestinal lesion judged to be the source of the bleeding, and active upper gastrointestinal bleeding documented by endoscopy or angiography [35]. Desaturation events, defined as events of saturation below 90%, were assessed in the PACU or general ward until postoperative day 1 [36].

**Primary and Secondary Outcomes**

The primary outcome was CRBD above a moderate grade at 0 hours postoperatively. The secondary outcomes were CRBD levels above a moderate grade at 1, 2, and 6 hours postoperatively. Postoperative pain, postoperative opioid requirement, ketorolac-related complications, patient satisfaction, and hospitalization duration were also assessed.

**Statistical Analysis**

From the pilot study, 48% of patients complained of CRBD above a moderate grade at 0 hours after RALP. The author assumed that ketorolac might decrease the incidence of CRBD above a moderate grade by 50% (i.e., 48% vs. 24%). The author calculated that 59 patients would be necessary for each group to acquire statistical significance, with $\alpha = 0.05$ and $\beta = 0.20$. Considering a 10% dropout rate, 66 patients were included in each group.

The analyses were performed on a modified intention-to-treat basis, which included all randomly assigned participants with all eligible criteria, who performed the study intervention and did not withdraw consent to participate in this study. Data are expressed as mean ± standard deviation, median (interquartile range), number (%), relative risk (RR), 95% confidence interval (CI), absolute risk reduction (ARR), or number needed to treat (NNT) as appropriate. Normality was assessed using the Kolmogorov–Smirnov test. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the independent t-test or Mann–Whitney U test as appropriate. The comparisons of postoperative pain scores between the two groups at each time point were analyzed by independent t-test and a p value $<0.0125$ (0.05/4) was considered significant after using Bonferroni correction. Otherwise, a p value $<0.05$ was considered significant. Statistical analysis was conducted using MedCalc (version 11.3.3.0; MedCalc Software bvba, Mariakerke, Belgium) and SPSS 21 for Windows (version 21.0.0; IBM Corporation, Chicago, IL, USA).

## 1.3 RESULTS

The CONSORT flowchart of this study is presented in Figure 1-1. During the enrollment process, 143 patients were assessed for eligibility, and 11 patients were excluded. Therefore, a total of 132 patients were included in the present study. Two patients did not receive an intervention, as their surgeries were converted to open prostatectomies. Finally, 130 patients were included in the analysis. All patients were Asian. There were no significant differences in age, gender, body mass index, American Society of Anesthesiologists physical status, underlying disease, Gleason score, tumor category, operation time, intraoperative fluid, and urinary catheter size between the two groups (Table 1-1).

Incidences of CRBD at 0, 1, 2, and 6 hours postoperatively are shown in Table 1-2. The incidence of CRBD above a moderate grade at 0 hours postoperatively was significantly lower in the ketorolac group compared with the control group (14 [21.5%] vs. 33 [50.8%], $P = 0.001$, RR = 0.424, 95% CI: 0.252–0.715, ARR = 0.29, NNT = 3) (Figure 1-2). In addition, incidences of CRBD above a moderate grade were significantly lower in the ketorolac group compared with the control group at 1, 2, and 6 hours postoperatively (5 [7.7%] vs. 26 [40.0%], $P < 0.001$, RR 0.192, 95% CI: 0.078–0.470; 7 [10.8%] vs. 38 [58.5%], $P < 0.001$, RR = 0.184, 95% C: 0.089–0.382; 8 [12.3%] vs. 24 [36.9%], $P = 0.001$, RR = 0.333, 95% CI: 0.162–0.687; respectively) (Figure 1-2).

Pain scores at 0 and 1 hours postoperatively were significantly lower in the ketorolac group than in the control group ($P = 0.012$, $P = 0.007$, respectively) (Table 1-3). However, pain scores at 2 and 6 hours postoperatively did not significantly differ between the two groups ($P = 0.766$, $P = 0.132$, respectively). Opioid requirement during the 24 hours following surgery was significantly lower in the ketorolac group than in the control group (100.0 (75.0–125.0) μg vs. 125.0 (87.5–175.0) μg, $P < 0.001$) (Figure 1-3). There were no significant differences in acute kidney injury, hemoglobin changes, gastrointestinal bleeding, and desaturation events between the two groups (Table 1-3). Patient satisfaction scores were significantly higher in the ketorolac group than in the control group (5.0 [4.0–6.0] vs. 4.0 [4.0–4.0], $P < 0.001$) (Table 1-3). There was no significant difference in hospitalization duration between the two groups (7.0 [5.0–7.0] days vs. 7.0 days [5.0–7.0] days, $P = 0.722$) (Table 1-3).

## 1.4 DISCUSSION

In the present study, the author found that ketorolac administration significantly decreased the incidences of CRBD above a moderate grade, not only at 0 hours postoperatively, but also at 1, 2, and 6 hours in male patients undergoing RALP. In addition, pain scores were significantly lower in the ketorolac group than in the control group at 0 and 1 hours, but not at 2 and 6 hours. The opioid requirement during the 24 hours following surgery was significantly lower in the ketorolac group compared with the control group. There were no significant differences in ketorolac-related complications between the two groups. Patient satisfaction scores were significantly higher in the ketorolac group compared with the control group.

Bladder urinary catheterization may induce CRBD after awakening from general anesthesia in the postoperative period.[9] CRBD is a known risk factor for emergence agitation occurring during anesthetic recovery.[37] The incidence of CRBD was higher in the early postoperative period compared with the late postoperative period. Therefore, CRBD is an important issue in the PACU, as patients who receive urinary catheterization usually stay in the PACU for about 1 hour postoperatively.[6,38,39] In particular, urgent treatment may be needed for patients experiencing CRBD above a moderate grade, which occurs in 38–57% of patients in the PACU.[7,12,21] Unlike routine perioperative pain management, opioid administration may be regarded as ineffective for CRBD because of the difference between mechanisms of postoperative pain and CRBD.[7,39] For the mechanism of CRBD, the anti-muscarinic actions, particularly type 3 muscarinic receptor blockade, are considered to be responsible for the effective management of postoperative CRBD. Therefore, anti-muscarinic agents, such as tolterodine,[40] oxybutynin,[41] butylscopolamine,[8] ketamine,[4] glycopyrrolate,[38] dexmedetomidine,[7] and lidocaine[2] have been evaluated for either treatment or prevention of CRBD. However, even if such medications are used, the incidence of postoperative CRBD is reported to be high.[4]

In this study, ketorolac effectively reduced the incidence of CRBD above a moderate grade after RALP. Ketorolac, an NSAID and cyclooxygenase inhibitor, inhibits PG synthesis.[42] PG in the bladder, which increase with the occurrence of obstruction, inflammation, and mucosal injury in the urinary bladder,[15] induce detrusor muscle contraction. In addition, capsaicin-sensitive C fibers activated by PG contract the bladder detrusor muscle.[43-45] Therefore, ketorolac is thought to reduce CRBD induced by the contraction of the detrusor muscle from the secretion of inflammatory substances and the synthesis of PG resulting from urinary catheterization. Similarly, paracetamol, which is not an NSAID but is another cyclooxygenase inhibitor, is reported to reduce CRBD scores 0.5, 1, 2, and 6 hours after percutaneous nephrolithotomy.[11] However, paracetamol has various adverse effects.[11] Most importantly, paracetamol overdose is a common cause of acute liver failure.[46] Severe liver impairment

or hepatic necrosis may occur when the maximum amount of the recommended dose is administered.[47-49] In patients with weakened hepatic function, paracetamol can more easily lead to hepatic impairment.[47] Renal impairment not associated with hepatic failure has also been reported.[50]

The author found that ketorolac decreased pain scores at 0 and 1 hours postoperatively, but not at 2 and 6 hours. This result may be, at least in part, because of the analgesic characteristics of ketorolac. It is known that 30 mg ketorolac is equivalent to 10 mg morphine sulfate or 100 μg fentanyl.[32,33] The peak effect of intravenous ketorolac tromethamine occurs at 75–150 minutes.[17] In the present study, ketorolac was administered just after the completion of urethrovesical anastomosis, with the surgery ending 30–60 minutes after ketorolac administration. Therefore, ketorolac administration may influence the postoperative pain score, especially at 0 and 1 hours postoperatively.

NSAIDs such as ketorolac may uncommonly induce renal impairment, peptic ulceration, bleeding diathesis, gastrointestinal bleeding, respiratory distress, and asthma exacerbation.[17] Incidences of these side effects are reported to be 0.17% for renal failure, 1.04% for surgical bleeding, and 0.04% for gastrointestinal bleeding in patients intravenously administered 90 mg ketorolac tromethamine daily for 7 days after surgery.[51,52] Ketorolac is related with an increased risk of gastrointestinal bleeding and renal insufficiency in elderly patients with use exceeding 5 days and higher than 105 mg/day.[17] In the present study, there were no significant differences in acute kidney injury, hemoglobin changes, gastrointestinal bleeding, or desaturation events between the ketorolac group and control group. Therefore, the author found that a single administration of 30 mg ketorolac tromethamine does not induce adverse effects associated with NSAID regimens postoperatively.

Unlike postoperative pain, CRBD might not be managed properly by clinicians. This seems to be partly because clinicians pay less attention to CRBD than postoperative pain. Moreover, conventional analgesics such as opioids may not manage CRBD effectively.[9] In this study, ketorolac reduced postoperative CRBD above a moderate grade and increased patient satisfaction in patients who underwent RALP. In addition, postoperative complications related to ketorolac were not significantly different between the two groups. Therefore, the author assume that all patients requiring urinary catheterization can be administered ketorolac for preventing postoperative CRBD when there are no risk factors of side effects associated with NSAIDs, such as renal disease, gastrointestinal ulcers, coagulopathy, and asthma.

In the present study, patient satisfaction scores were significantly higher in the ketorolac group than in the control group. This may be explained by the reduction of CRBD above a moderate grade within 6 hours after RALP in the ketorolac group. In addition, higher patient satisfaction scores are thought to be related to the reduction of pain scores at 0 and 1 hours after surgery in the ketorolac group. Therefore, it seems feasible to administer ketorolac to prevent CRBD after RALP.

This study has several limitations. First, the author administered 30 mg ketorolac only once in the present study. Although this single dose of ketorolac had a beneficial effect on the prevention of CRBD above a moderate grade, the author did not confirm whether this dose of ketorolac was the optimal dose to prevent CRBD. Therefore, further studies are needed to evaluate optimal doses of ketorolac to prevent CRBD in patients requiring urinary catheterization during surgery. Second, the author administered ketorolac just after the completion of urethrovesical anastomosis, and the author did not confirm whether this timing of ketorolac administration was optimal to prevent postoperative CRBD. Accordingly, further studies are needed to determine the optimal timing of ketorolac to prevent postoperative CRBD. Third, urinary urgency and urge incontinence are unique characteristics of CRBD, unlike nociceptive postoperative pain. However, it may be difficult to distinguish CRBD and postoperative pain by asking a patient about suprapubic pain after RALP. Therefore, further study will be needed to evaluate the effect of ketorolac on CRBD in patients undergoing surgery in another surgical site. Lastly, the author assessed CRBD until 6 hours postoperatively in this study. It might be better to assess CRBD until 12 or 24 hours postoperatively. However, many studies assessed CRBD until only 6 hours postoperatively because the incidence of CRBD above moderate grade significantly reduced after 6 hours postoperatively.[1,2,5,13,14,53-55] Furthermore, CRBD above moderate grade required treatment occur frequently 1 hour postoperatively.[7,12,27] Therefore, it could be reasonable to assess CRBD until 6 hours postoperatively.

## 1.5 CONCLUSION

Ketorolac reduced the incidence of CRBD above a moderate grade in male patients undergoing RALP. In addition, 30 mg ketorolac administered intravenously during RALP was not associated with any adverse effects. These results suggest that ketorolac administration is an effective and safe option to prevent CRBD above a moderate grade in male patients undergoing RALP who require urinary catheterization.

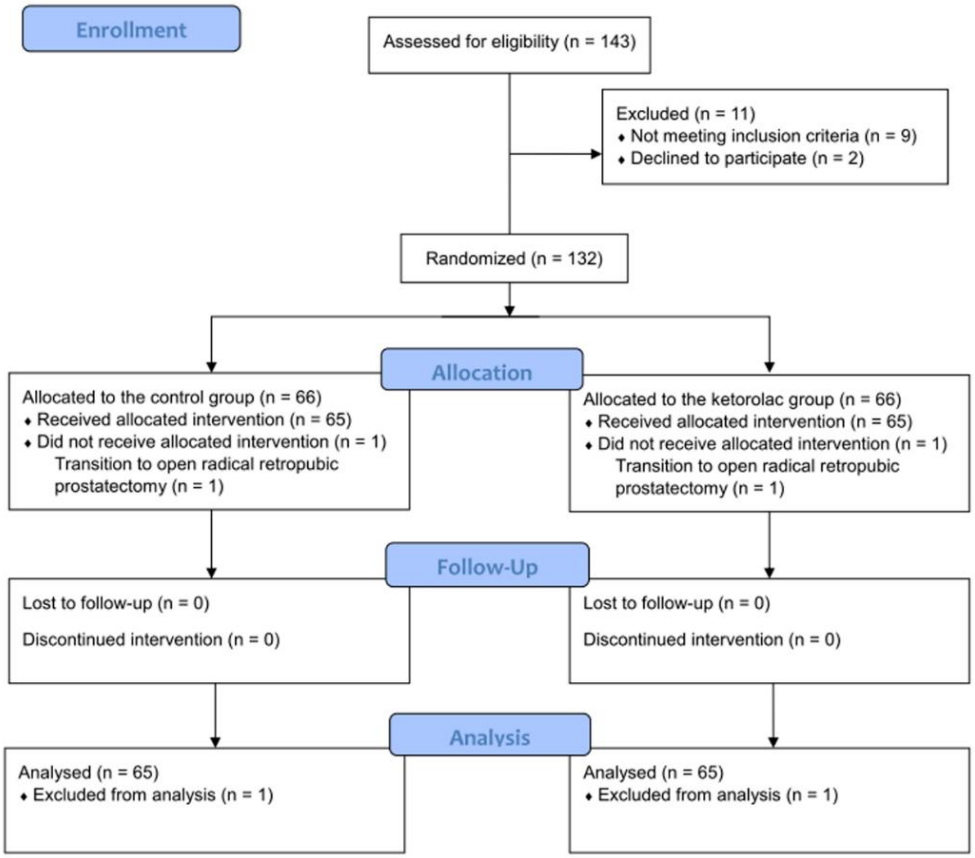


**Figure 1-1.** A CONSORT flow chart.

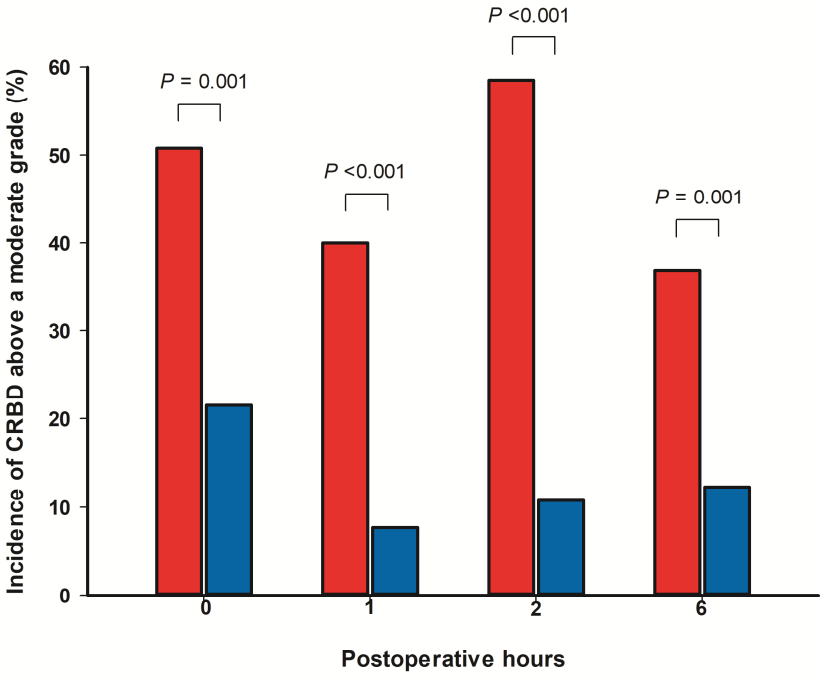


**Figure 1-2.** Comparisons of incidences of CRBD above a moderate grade between the control group (red bar) and the ketorolac group (blue bar) at 0, 1, 2, and 6 hours postoperatively. Each column indicates the incidence of CRBD above a moderate grade. CRBD = catheter-related bladder discomfort; Postoperative hour 0 = upon admission to the postanesthetic care unit.

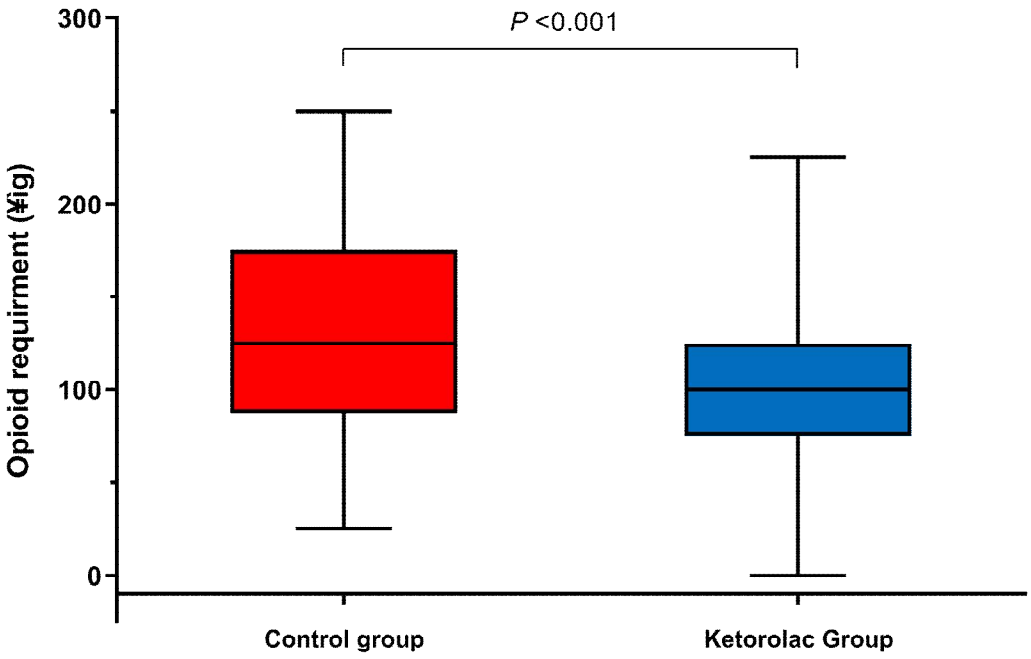


**Figure 1-3.** Comparison of opioid requirements within 24 hours after surgery between the control group (red box) and ketorolac group (blue box). The line inside the rectangle shows the median. The upper and lower ends of the box indicate the third quartile and first quartile, respectively. Whiskers above and below the box designate 90% and 10%, respectively.

**Table 1-1.** Characteristics of study participants.

| Variables | Control group (n = 65) | Ketorolac group (n = 65) | *P* |
|---|---|---|---|
| Age, yr | 66.7 ± 6.5 | 65.4 ± 7.0 | 0.282 |
| Sex, male/female | 65(100)/0(0) | 65(100)/0(0) | 1.000 |
| BMI, kg/m$^2$ | 24.5 (23.0–26.6) | 24.2 (22.4–25.8) | 0.329 |
| ASA PS | | | |
| Class I/II | 2/63 (3.1/96.9) | 5/60 (7.7/92.3) | 0.440 |
| Diabetes mellitus | 9 (13.8) | 9 (13.8) | 1.000 |
| Hypertension | 27 (41.5) | 30 (46.2) | 0.596 |
| Gleason score, points | | | 0.940 |
| ≤6/7/>7 | 15 (23.1)/33 (50.8)/17 (26.2) | 16 (24.6)/31 (47.7)/18 (27.7) | |
| T category | | | 0.720 |
| T2/T3a/T3b/T4 | 38 (58.5)/24 (36.9)/2 (3.1)/1 (1.5) | 40 (61.5)/18 (27.7)/6 (4.0)/1 (1.5) | |
| Operation time, minutes | 168.0 (156.5–186.5) | 167.0 (150.0–184.0) | 0.373 |
| Intraoperative fluid, mL | 1100.0 (900.0–1325.0) | 1150.0 (800.0–1325.0) | 0.393 |
| Urinary catheter size, F | | | 0.387 |
| 16/18/20 | 32 (49.2)/5 (7.7)/28 (43.1) | 30 (46.2)/10 (15.4)/25 (38.5) | |

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) as appropriate. Control group; patients who received intravenous normal saline as control. Ketorolac group; patients who received intravenous Ketorolac. BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status; T category, tumor category.

**Table 1-2.** Postoperative CRBD in patients undergoing RALP.

| CRBD | Control group (n = 65) | Ketorolac group (n = 65) | *P* |
|---|---|---|---|
| Postoperative 0 hours | | | <0.001 |
| None | 12 (18.5) | 20 (30.8) | |
| Mild | 20 (30.8) | 31 (47.7) | |
| Moderate | 17 (26.2) | 14 (21.5) | |
| Severe | 16 (24.6) | 0 (0.0) | |
| Postoperative 1 hour | | | <0.001 |
| None | 5 (7.7) | 9 (13.8) | |
| Mild | 34 (52.3) | 51 (78.5) | |
| Moderate | 25 (38.5) | 5 (7.7) | |
| Severe | 1 (1.5) | 0 (0.0) | |
| Postoperative 2 hours | | | <0.001 |
| None | 0 (0.0) | 1 (1.5) | |
| Mild | 27 (41.5) | 57 (87.7) | |
| Moderate | 38 (58.5) | 7 (10.8) | |
| Severe | 0 (0.0) | 0 (0.0) | |
| Postoperative 6 hours | | | <0.001 |
| None | 0 (0.0) | 16 (24.6) | |
| Mild | 41 (63.1) | 41 (63.1) | |
| Moderate | 24 (36.9) | 8 (12.3) | |
| Severe | 0 (0.0) | 0 (0.0) | |

Data are presented as number (%). Control group; patients who received intravenous normal saline as control. Ketorolac group; patients who received intravenous Ketorolac. Postoperative 0 hours, upon admission to the postanesthetic care unit. CRBD, catheter-related bladder discomfort; RALP, robot-assisted laparoscopic radical prostatectomy.

**Table 1-3.** Postoperative pain score, opioid requirement, ketorolac-related complications, patient satisfaction score, and hospitalization duration in patients undergoing RALP.

| Variables | Control group (n = 65) | Ketorolac group (n = 65) | *P* |
|---|---|---|---|
| Postoperative pain score | | | |
| Postoperative 0 hours | 5.4 ± 1.1 | 4.8 ± 1.5 | 0.012* |
| Postoperative 1 hour | 3.0 ± 1.3 | 2.5 ± 0.7 | 0.007* |
| Postoperative 2 hours | 4.5 ± 1.5 | 4.4 ± 1.5 | 0.766 |
| Postoperative 6 hours | 2.9 ± 1.0 | 2.7 ± 0.9 | 0.132 |
| Opioid requirement during 24 hours after surgery, μg | 125.0 (87.5–175.0) | 100 (75.0–125.0) | <0.001 |
| Ketorolac-related complications | | | |
| Acute kidney injury | 2 (3.7) | 1 (2.2) | >0.999 |
| Hemoglobin changes, mg/dL | −1.7 ± 1.2 | −2.0 ± 1.1 | 0.148 |
| Gastrointestinal bleeding | 0 (0.0) | 0 (0.0) | 1.000 |
| Desaturation events | 1 (1.5) | 0 (0.0) | >0.999 |
| Patient satisfaction score | 4.0 (4.0–4.0) | 5.0 (4.0–6.0) | <0.001 |
| Hospitalization duration, days | 7.0 (5.0–7.0) | 7.0 (5.0–7.0) | 0.722 |

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) as appropriate. Control group; patients who received intravenous normal saline as control. Ketorolac group; patients who received intravenous Ketorolac. Hemoglobin change is calculated by subtracting preoperative hemoglobin levels from hemoglobin levels at postoperative day 1. Desaturation events are defined as events of saturation below 90% confirmed in the post-anesthesia care unit or in the general ward until postoperative day 1. Postoperative 0 hours, upon admission to the postanesthetic care unit. *p <0.0125 (Bonferroni-corrected significance level). RALP, robot-assisted laparoscopic radical prostatectomy.

# PART II

Magnesium and Bladder Discomfort after Transurethral Resection of Bladder Tumor:

A Randomized, Double-blind, Placebo-controlled Study

This part was published in Anesthesiology[1]

## 2.1 INTRODUCTION

TURB is the treatment of choice for non-invasive bladder tumors.[56,57] Patients having transurethral resection of bladder tumor require large diameter urinary catheters postoperatively,[58] which can induce CRBD. CRBD is characterized by discomfort in the suprapubic region and manifests as urinary urgency and frequency with or without urge incontinence after urinary catheterization.[58] The incidence rate of CRBD is 47–90% among patients who have undergone general surgery.[9] Particularly, CRBD above a moderate grade, which is frequently intolerable and requires treatment,[4] is reported among 38–57% of patients with urinary bladder catheters in situ at the PACU.[12] Therefore, appropriate treatment or prevention of CRBD is essential for the improvement of postoperative outcomes among patients having TURB who require large diameter urinary catheters because CRBD can be accompanied by poor patient satisfaction, increased postoperative agitation, prolonged hospital stay, and increased workload for medical staff.[9] Various agents such as have been studied for the prevention of CRBD.[2,5,13,14] 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.[2,5,9,13,14]

Magnesium is the fourth most abundant cation in the body.[19] Magnesium is related to diverse biochemical reactions.[19] Moreover, magnesium is important for the reduction and stabilization of smooth muscle contraction.[19] Based on these considerations, magnesium is thought to influence the occurrence of CRBD. However, its effect on the prevention of postoperative CRBD has not yet been studied.

The author therefore tested the hypothesis that intraoperative magnesium reduces moderate-to-severe CRBD in patients recovering from TURB.

## 2.2 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, 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 20–79 years, ASA PS ≤II, scheduled TURB 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 >3.0 mg/dL), hypocalcemia (serum calcium concentration <8.6 mg/dL), analgesic overuse, psychiatric disorders, or taking medications known to interact with magnesium. 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 as 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 pre-determined 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 CRBD (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 Laryngeal Mask Airway Supreme™ (LMA Teleflex, Athlone, Co Westmeath, Ireland) was inserted. Anesthesia was maintained with 2–3 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, Newton, MA, 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 $\leq 2$ 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, Tokyo, Japan) 15 minutes before the end of the procedure. At the end of the procedure, 2 mg/kg of sugammadex (Bridion®; MSD, Oss, the Netherlands) was used for rapid and complete reversal of neuromuscular blockade if the train-of-four count was $\geq 2$ 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 ≥90) and had recovered from neuromuscular blockade (train-of-four ratio ≥90%), the Laryngeal Mask Airway 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.[59] In the 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 minutes just after the induction of anesthesia, followed by an intravenous infusion of 15 mg/kg/h (0.15 ml/kg/h) of intravenous magnesium sulfate (0.06 mmol/kg/h $Mg^{2+}$) 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 CRBD 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. Patients who complained of both CRBD 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 CRBD above a moderate grade. Patients received tramadol (1 mg/kg) if they had contraindications to nonsteroidal anti-inflammatory drugs or experienced no response to nonsteroidal anti-inflammatory drugs.

**Assessments**

Patients' characteristics assessed were age, sex, body mass index, ASA physical status, hypertension, diabetes mellitus, preoperative administration of calcium channel blocker or aspirin, 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.

CRBD grade was assessed at 0, 1, 2, and 6 hours postoperatively. The CRBD grade at 0 hours postoperatively was assessed just after the patients were transferred to the PACU. The severity of CRBD 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.[5]

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 hours postoperatively.[34] 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.[60,61] Hypotension, defined as a decrease in systolic blood pressure below 80 mmHg for more than 10 minutes was assessed intraoperatively and on postoperative day 1.[62] Respiratory depression was assessed, until postoperative day 1, by desaturation events defined as events of saturation below 90%.[36] Postoperative pain was assessed using a numeric rating scale (0 = no pain to 10 = worst imaginable pain) at 0, 1, 2, and 6 hours postoperatively.[63] Opioid requirement was summed up as all opioids, tramadol, and nonsteroidal anti-inflammatory drugs administered to patients during the 24 hours following surgery. Dosages of opioids, tramadol, and nonsteroidal anti-inflammatory drugs were converted to intravenous fentanyl equianalgesic doses according to published conversion factors (fentanyl 100 μg = tramadol 100 mg = ketorolac 30 mg).[32,33] Postoperative delirium was assessed using the confusion assessment method score.[64] The confusion assessment method score was determined by examining the patient for (a) acute and fluctuating changes in mental status, (b) inattention, (c) disorganized or incoherent thinking, and (d) altered level of consciousness. Patients who displayed a, b, and c, or a, b, and d, or a, b, c, and d were considered to have postoperative delirium. Postoperative delirium was investigated until 6 hours postoperatively. Hospitalization duration was defined as the period from the day before surgery to the day before discharge.

**Primary and Secondary Outcomes**

The primary outcome was the incidence of CRBD above a moderate grade at 0 hours postoperatively. The secondary outcomes were the incidences of CRBD levels above a moderate grade at 1, 2, and 6

hours postoperatively. The severity of CRBD at 0, 1, 2, and 6 hours postoperatively, incidence of CRBD above a moderate grade according to sex, preoperative concentrations of magnesium according to CRBD occurrence above a moderate grade at 0 hours 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 CRBD among patients having TURB. Based on our unpublished data, 67% of patients experienced CRBD above a moderate grade at 0 hours after TURB. The author assumed that magnesium might decrease the incidence of CRBD 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. Data are expressed as mean ± standard deviation, number (proportion), relative risk (RR), 95% confidence interval (CI), absolute risk reduction (ARR), or number needed to treat (NNT). The author focused the primary outcome as the incidence of CRBD above a moderate grade at 0 hours postoperatively. Therefore, our primary outcome was compared using the Chi-square test. The secondary outcomes of the incidences of CRBD levels above a moderate grade at 1, 2, and 6 hours 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. The author performed the post hoc subgroup analyses regarding the incidence of CRBD above a moderate grade according to sex and preoperative magnesium concentration according to CRBD grade. 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, Mariakerke, Belgium) and SPSS version 21.0.0 for Windows (IBM Corporation, Chicago, IL, USA).

## 2.3 RESULTS

The study flowchart is presented in Figure 2-1. 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 as none was lost to follow-up in both groups. The patient and intraoperative characteristics in this study are shown in Tables 2-1 and 2-2. In the magnesium group, 4.1 ± 0.6 g of magnesium sulfate was administered during TURB. The postoperative magnesium concentration was significantly higher in the magnesium group than in the control group (1.6 ± 0.2 mmol/L vs. 0.9 ± 0.1 mmol/L, P <0.001). Figure 2-2 shows the comparison of the serum magnesium concentrations at the preoperative and immediate postoperative periods between the control and the magnesium groups.

Magnesium administration resulted in a lower CRBD incidence above a moderate grade at 0 hours postoperatively than normal saline administration, which was statistically significant and clinically important (13 [22%] vs. 46 [77%], P <0.001, RR = 0.283, 95% CI: 0.171–0.467, ARR = 0.55, NNT = 2) (Figure 2-3). In addition, the magnesium group had lower incidences of CRBD above a moderate grade at 1 and 2 hours postoperatively than did the control group, which were statistically significant and clinically important (5 [8%] vs. 17 [28%], P = 0.005, RR = 0.294, 95% CI = 0.116–0.746, and 1 [2%] vs. 14 [23%], P <0.001, RR = 0.071, 95% CI = 0.010–0.526). The incidence of CRBD above a moderate grade at 6 hours postoperatively was not significantly different between the magnesium and the control groups (2 [3%] vs. 0 [0%], P = 0.496). The severity of CRBD at 0, 1, 2, and 6 hours 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) (Figure 2-4).

The incidence of CRBD above a moderate grade according to sex at 0 hours postoperatively was assessed. In male patients, the incidence of CRBD above a moderate grade at 0 hours postoperatively was significantly lower in the magnesium group than in the control group (12 [24%] vs. 43 [80%], P <0.001, RR = 0.296, 95% CI: 0.177–0.494, ARR = 0.56, NNT = 2) (Table 2-3). In female patients, the incidence of CRBD above a moderate grade at 0 hours postoperatively was not significantly different between the magnesium and the control groups (1 [11%] vs. 3 [50%], P = 0.235, RR = 0.222, 95% CI: 0.030–1.665, ARR = 0.389, NNT = 3) (Table 2-3). There was no significant interaction between patients' sex and magnesium on the incidence of CRBD above a moderate grade at 0 hours postoperatively (P = 0.745).

Preoperative magnesium concentrations according to CRBD grade were assessed. In the control group, there was no difference in the preoperative concentration of magnesium between CRBD below

a mild grade and CRBD above a moderate grade at 0 hours postoperatively (0.87 ± 0.06 vs. 0.90 ± 0.06, P = 0.196, 95% CI: -0.063–0.013) (Table 2-4). In the magnesium group, there was also no difference in the preoperative concentration of magnesium between CRBD below a mild grade and CRBD above a moderate grade at 0 hours postoperatively (0.89 ± 0.07 vs. 0.90 ± 0.05, P = 0.872, 95% CI: -0.048–0.032) (Table 2-4).

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 1.281–1.919) (Figure 2-5). 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 2-5).

## 2.4 DISCUSSIONS

In this study, the author found that magnesium administration significantly decreased the incidence of catheter-related bladder discomfort above a moderate grade at postoperative 0, 1, and 2 hours 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 hours 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 the control and the magnesium groups.

Urinary bladder catheterization can induce CRBD in the postoperative period.[58] CRBD was more frequent and more severe in the early postoperative period than in the late postoperative period. Therefore, CRBD 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.[13] Among patients with urinary catheterization, CRBD is a well-known risk factor for emergence agitation after awakening from general anesthesia,[37] increasing the workload of the medical staff.[9] In particular, rescue treatments should be needed for patients who experience CRBD above a moderate grade, which occurs in 38–57% of patients in the PACU.[7,12] Unlike postoperative somatic pain, opioid administration may be regarded as ineffective to manage CRBD considering the mechanisms underlying CRBD.[39] One mechanism underlying the occurrence of CRBD is the activation of muscarinic acetylcholine receptors by the simulation of the urinary bladder catheter.[58] Therefore, anti-muscarinic agents such as tramadol, and gabapentin are known to be effective in the management of postoperative CRBD [2,5,14,39,65] (Table 2-6). Another mechanism underlying the occurrence of CRBD was found to be mediated by an increased urinary concentration of PG.[11,20] Urinary catheter and mucosal injury could induce local inflammation with activation of the cyclooxygenase pathway and release of PG.[15,66] Anti-inflammatory agents, such as paracetamol, and ketorolac, are known to be effective in the management of postoperative CRBD[2,11,20,66] (Table 2-6). However, although such interventions were done, the incidence of postoperative CRBD sill varies.[58] 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.[2,5,9,13,14,20]

In our study, magnesium administration effectively reduced the incidence of CRBD above a moderate grade after TURB. In preference to other anticonvulsants, magnesium is widely used clinically such as in the prevention of eclampsia in women with severe pre-eclampsia.[67] 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.[68] Acute postoperative pain is relieved by intravenous magnesium administration.[69] Particularly, in patients with sensory urgency or detrusor instability, magnesium administration improves subjective urinary symptoms.[70] Moreover, low magnesium concentrations can lead to bladder spasm and urinary frequency.[71] 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*.[72] 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.[72] It is possible that the decrease in CRBD by magnesium administration 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 CRBD above a moderate grade during the early postoperative period after TURB by administering magnesium. Because patient satisfaction is related to postoperative outcomes,[73,74] the increase in patient satisfaction after magnesium administration may be a significant benefit, along with a reduction in CRBD above a moderate grade. Therefore, the author consider that patient satisfaction should be monitored as long as a large diameter urinary catheter is inserted during the postoperative period.

The author did not observe any serious complications attributed to magnesium administration. But given relatively small trial size of this study, the author have limited ability to judge the frequency of rare but potentially serious events. Magnesium-related adverse effects such as nausea or vomiting, headache, lethargy, flushing, hypotension, and respiratory depression may occur at higher blood concentrations of magnesium.[60,61] The most prominent clinical manifestations of mild hypermagnesemia of 2 to 3 mmol/L are nausea, flushing, headache, lethargy, drowsiness, and decreased deep tendon reflexes. Plasma magnesium concentration of 3–5 mmol/L may cause somnolence, hypocalcemia, absent deep tendon reflexes, hypotension, and bradycardia. Plasma magnesium concentration above 5 mmol/L may cause muscle paralysis leading to flaccid quadriplegia, apnea and respiratory failure, complete heart block, and cardiac arrest.[60,61] Infusion of 4 g of magnesium sulfate resulted in a blood magnesium concentration of <1.8 mmol/L.[75] Moreover, a blood magnesium concentrations decreased after all dose of magnesium continuous infusions were stopped.[75] In the present study, 4.1 ± 0.6 g of magnesium sulfate was administered during TURB in the magnesium group, and the serum magnesium concentration at the immediate postoperative period was 1.6 ± 0.2 mmol/L in this group. Therefore, the dose of magnesium administered in this study may

be safely used to manage CRBD after TURB. However, it may not be powered enough to detect the difference in magnesium-related adverse effects between the control and the magnesium groups because this study was designed for the assessment of CRBD above a moderate grade at 0 hours postoperatively as a primary outcome. In addition, although a magnesium concentrations decreased after magnesium continuous infusions were ceased[75], it may be important to confirm the changes of concentration of magnesium after intravenous infusion of magnesium was stopped. However, the author measured the concentration of magnesium only once after magnesium administration. Therefore, the safety concern of magnesium administration needs to be interpreted cautiously.

The author found that there were no significant differences in postoperative pain and opioid requirement during postoperative 24 hours between the two groups. This result may be, at least in part, due to the surgical characteristic of TURB. The postoperative pain that occurs in patients after TURB is not severe because TURB is 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,[69] magnesium administration did not significantly reduce postoperative pain and opioid requirement in the present study.

None of the patients in both groups experienced postoperative delirium or magnesium-induced lethargy. The hyperactive type of postoperative delirium may be difficult to distinguish from severe CRBD-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 CRBD scores. Therefore, the author used the confusion assessment method score to determine the presence of postoperative delirium.[76] In addition, the author 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.[76] Postoperative delirium or acute cognitive dysfunction is also a postoperative complication that has a varying incidence of 1.4–19.3%.[77,78] 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.[77,79,80] The participants of this study had few risk factors because the author enrolled only those with ASA physical status I or II. Furthermore, operation duration and opioid requirements are relatively shorter and smaller in TURB than in other general surgical procedures. Moreover, at postoperative 0 hours, only 12 patients experienced severe CRBD in the present study; these cases were resolved within 10 minutes by administering tramadol. In terms of magnesium-induced lethargy, the participants of this study were administered relatively small-to-moderate doses of magnesium sulfate. Also, the postoperative magnesium concentration was below 2

mmol/L in the magnesium group. Based on these considerations, the influence of postoperative delirium and magnesium-induced lethargy on postoperative CRBD scores were likely insignificant.

In the present study, the author assessed the incidence of CRBD above a moderate grade according to sex. The incidence of CRBD above a moderate grade at 0 hours postoperatively was significantly lower in the magnesium group than in the control group in male patients. However, the incidence of CRBD above a moderate grade at 0 hours 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 CRBD because there was no significant interaction between sex and magnesium on the incidence of CRBD. However, the author consider that subgroup analyses are prone to replicate poorly and should be interpreted with caution.

Unlike routine perioperative pain management, postoperative CRBD might have been relatively overlooked. Many studies have been done with the aim to prevent or treat CRBD. Although anti-muscarinic agents and anti-inflammatory agents were studied in CRBD, postoperative CRBD has not been sufficiently prevented and remains a burden on patients and medical staff.[58] 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.[2,5,9,13,14,205] Magnesium has various pharmacological effects associated with smooth muscle relaxation. In this study, magnesium reduced the incidence of CRBD above a moderate grade in patients having TURB. To the best of our knowledge, this is the first study to evaluate the association of magnesium administration and postoperative CRBD.

This study has several limitations. First, the author administered magnesium sulfate at a 50 mg/kg loading dose for 15 minutes just after the induction of anesthesia and at 15 mg/kg/h continuous infusion during the intraoperative period. Although this loading dose and continuous infusion of magnesium had a beneficial effect on the prevention of CRBD above a moderate grade, the author did not confirm whether this dose was optimum for preventing CRBD. Therefore, further studies are needed to evaluate the optimal magnesium dose required for the prevention of CRBD among patients who required a large diameter urinary catheter. Second, the author administered magnesium just after the completion of anesthesia induction and until the completion of the procedure. The author did not confirm whether this timing of magnesium administration was optimum for preventing postoperative CRBD. Accordingly, further studies are needed to determine the optimal timing required for magnesium administration for the prevention of postoperative CRBD. Third, although the qualitative method for assessing CRBD has been used in various previous studies,[4,5,13,65] the difference between

mild grade and moderate grade CRBD can be subjective, and the treatment effect estimation may, at least in part, be influenced by the differential distributions of these 2 below mild grade and above moderate grade in the magnesium and the control groups. In addition, the author excluded the patients with ASA physical status III or IV. In patients with renal impairment or heart disease, magnesium needs to be administered cautiously because magnesium-related complications may increase.[81] Thus, these limitations may affect the generalizability of this study. Lastly, the author studied the effect of magnesium on CRBD in terms of dilation of bladder smooth muscle. Considering that the drugs of various mechanism such as anti-muscarinic or anti-inflammatory mechanism have been used to prevent CRBD, further studies of combination drugs will be needed.

## 2.5 CONCLUSION

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

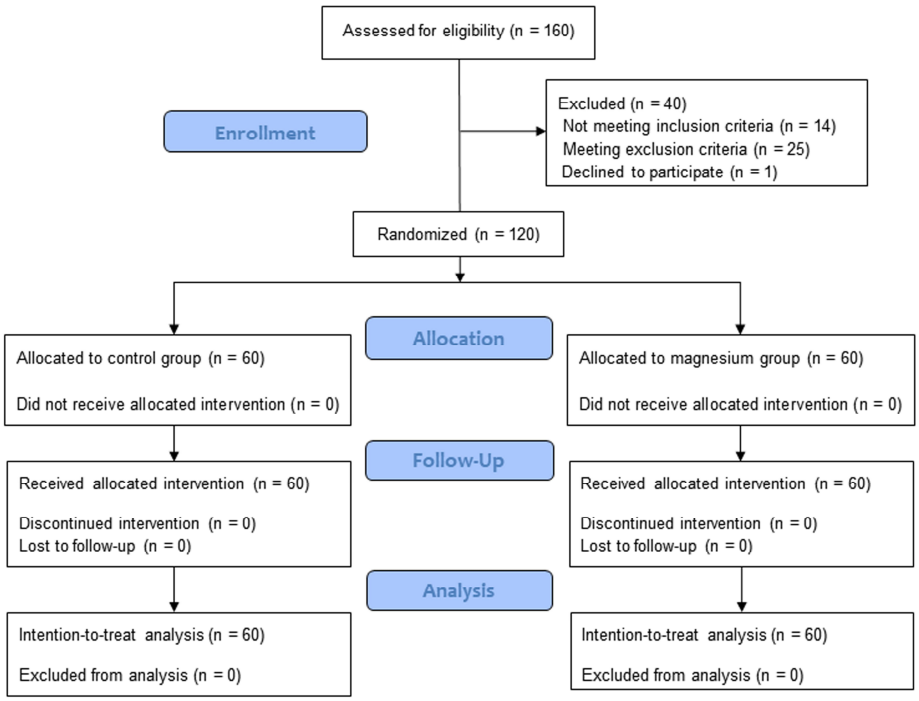


**Figure 2-1.** Study flow diagram of patient inclusion and exclusion. Control group; patients who received intravenous normal saline as control. Magnesium group; patients who received intravenous magnesium.

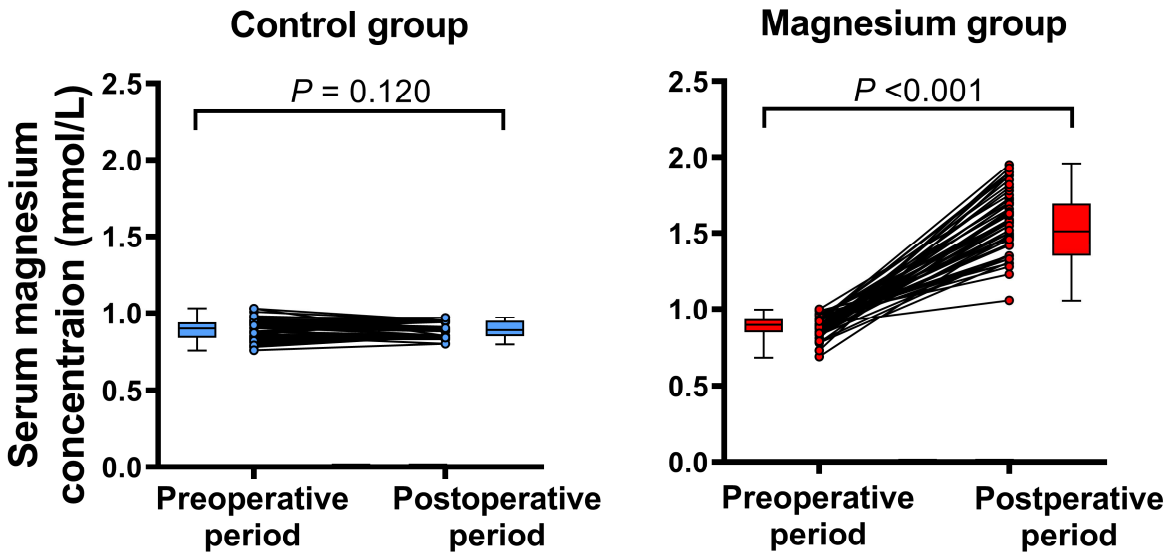


**Figure 2-2.** Comparison of serum magnesium concentrations at the preoperative and immediate postoperative periods between the control group (blue) and the magnesium group (red). Control group; patients who received intravenous normal saline as control. Magnesium group; patients who received intravenous 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.

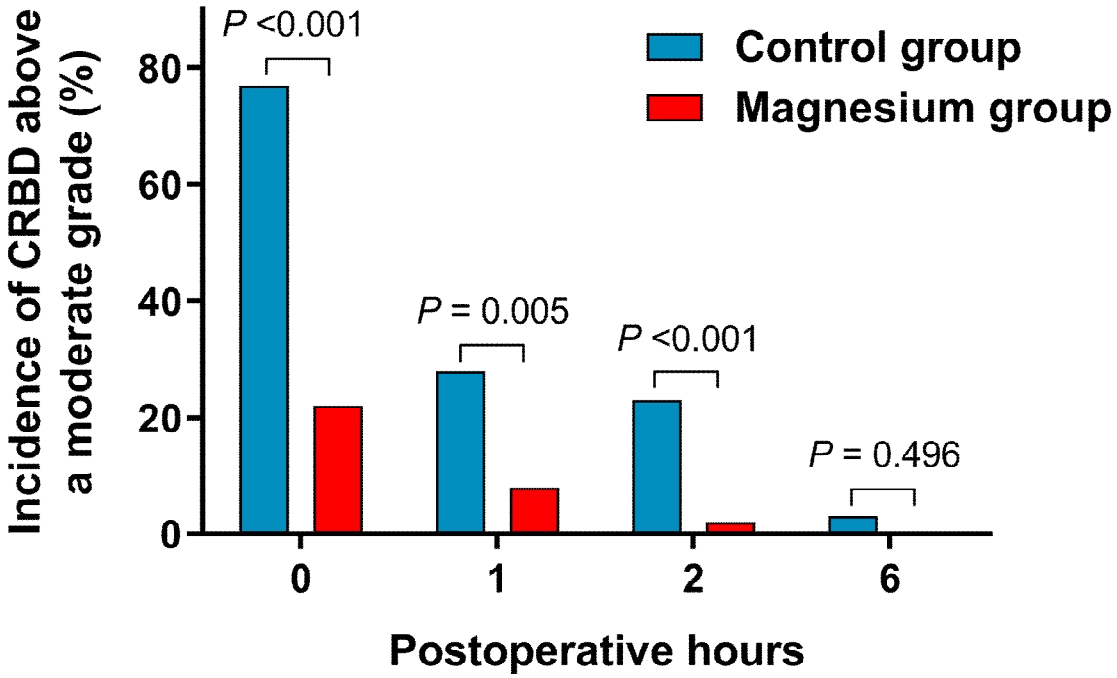


**Figure 2-3.** Comparison of the incidence of CRBD above a moderate grade between the control group (blue bar) and the magnesium group (red bar) at 0, 1, 2, and 6 hours postoperatively. Control group; patients who received intravenous normal saline as control. Magnesium group; patients who received intravenous magnesium. Each column indicates the incidence of CRBD above a moderate grade. All CRBD above a moderate grade was started at postoperative 0 hours and was recorded when symptoms were reported by patients on their own without questioning at postoperative 0, 1, 2, and 6 hours. The incidence of CRBD above a moderate grade at 0, 1, and 2 hours postoperatively was significantly lower in the magnesium group than in the control group. Postoperative 0 hours, upon admission to the postanesthetic care unit. CRBD, catheter-related bladder discomfort.

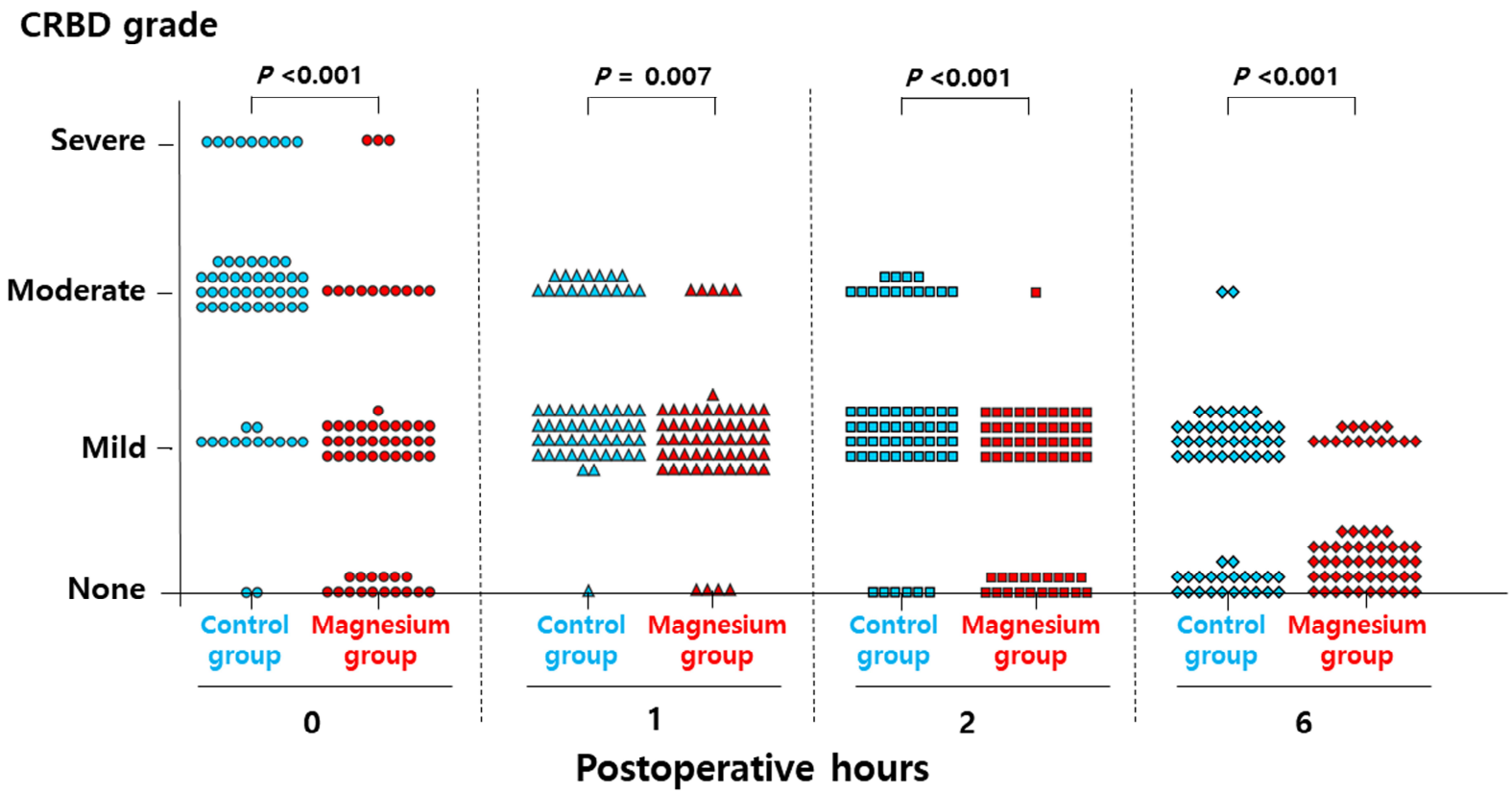


**Figure 2-4.** Comparison of the CRBD grade between the control group (blue circle, triangle, square, and diamond) and the magnesium group (red circle, triangle, square, and diamond) at 0, 1, 2, and 6 hours postoperatively. The CRBD grades between the control and the magnesium groups at 0, 1, 2, and 6 hours postoperatively were compared using the Chi-square test or Fisher's exact test as appropriate. Control group; patients who received intravenous normal saline as control. Magnesium group; patients who received intravenous magnesium. Each circle, triangle, square, and diamond indicates the CRBD grade of an individual patient. Postoperative 0 hours, upon admission to the postanesthetic care unit. CRBD, catheter-related bladder discomfort.

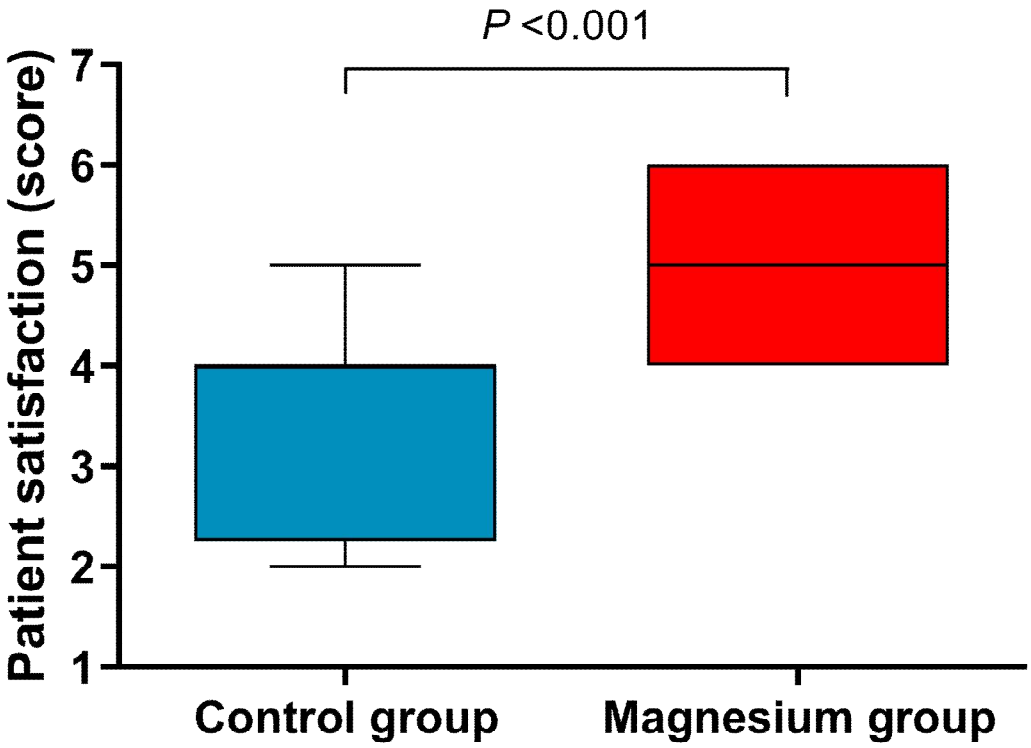


**Figure 2-5.** Comparison of patient satisfaction between the control group (blue) and the magnesium group (red). Patient satisfaction was assessed on a 7-point Likert scale (1 = strongly dissatisfied, 2 = moderately dissatisfied, 3 = slightly dissatisfied, 4 = neutral, 5 = slightly satisfied, 6 = moderately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

**Table 2-1.** Patient characteristics

| | Control group (n = 60) | Magnesium group (n = 60) | Absolute standardized difference |
|---|---|---|---|
| Age, yrs | 65 ± 10 | 65 ± 7 | 0.080 |
| Sex | | | 0.152 |
| Male/female | 54 (90)/6 (10) | 51 (85)/9 (15) | |
| Body mass index, $kg/m^2$ | 25.5 ± 3.2 | 25.0 ± 3.2 | 0.156 |
| ASA PS | | | 0.085 |
| Class I/II | 12 (20)/48 (80) | 10 (17)/50 (83) | |
| Hypertension | 38 (63) | 34 (57) | 0.135 |
| Diabetes mellitus | 16 (27) | 19 (32) | 0.110 |
| Calcium channel blocker | 15 (25) | 12 (20) | 0.120 |
| Aspirin | 3 (5) | 2 (3) | 0.085 |
| Serum $Mg^{2+}$ concentration, mmol/L | 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, $mL/min/1.73\ m^2$ | 83.1 ± 11.7 | 81.7 ± 13.2 | 0.112 |

Data are expressed as mean ± standard deviation or number (%). Control group; patients who received intravenous normal saline as control. Magnesium group; patients who received intravenous magnesium. ASA PS, American Society of Anesthesiologists physical status.

**Table 2-2.** Intraoperative variables

| | Control group (n = 60) | Magnesium group (n = 60) | Absolute standardized difference |
|---|---|---|---|
| Anesthesia duration, minutes | 70 ± 28 | 67 ± 22 | 0.107 |
| Operation duration, minutes | 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 |
| T0 | 6 (10) | 7 (12) | |
| Ta | 19 (31) | 23 (38) | |
| Tis | 14 (23) | 12 (20) | |
| T1 | 19 (32) | 16 (27) | |
| T2 | 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 | | | 0.035 |
| Single/multiple | 21 (35)/39 (65) | 22 (37)/38 (63) | |
| 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 |

Data are expressed as mean ± standard deviation or number (%). Control group; patients who received intravenous normal saline as control. Magnesium group; patients who received intravenous magnesium. T0, no evidence of primary tumor; Ta, noninvasive papillary carcinoma; Tis, carcinoma in situ; T1, tumor invading the lamina propria; T2, tumor invading the muscularis propria.

**Table 2-3.** Comparison of the incidence of postoperative CRBD above a moderate grade according to sex

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

Data are expressed as number (%). Control group; patients who received intravenous normal saline as control. Magnesium group; patients who received intravenous magnesium. Postoperative 0 hours, upon admission to the postanesthetic care unit. CRBD, catheter-related bladder discomfort.

**Table 2-4.** Preoperative concentrations of magnesium according to CRBD occurrence above a moderate grade at 0 hours postoperatively

| | Control group (n = 60) | | | Magnesium group (n = 60) | | |
|---|---|---|---|---|---|---|
| | CRBD below a mild grade at 0 hours postoperatively (n = 14) | CRBD above a moderate grade at 0 hours postoperatively (n = 46) | *P* | CRBD below a mild grade at 0 hours postoperatively (n = 47) | CRBD above a moderate grade at 0 hours postoperatively (n = 13) | *P* |
| Preoperative serum $Mg^{2+}$ concentration, mmol/L | 0.87 ± 0.06 | 0.90 ± 0.06 | 0.196 | 0.89 ± 0.07 | 0.90 ± 0.05 | 0.872 |

Data are expressed as mean ± standard deviation. Control group; patients who received intravenous normal saline as control. Magnesium group; patients who received intravenous magnesium. CRBD, catheter-related bladder discomfort.

**Table 2-5.** Magnesium-related adverse effects, postoperative pain, postoperative opioid requirement, postoperative delirium, and hospitalization duration among patients having TURB.

| Variables | Control group (n = 60) | Magnesium group (n = 60) | *P* |
|---|---|---|---|
| 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, NRS | | | |
| Postoperative 0 hours | 4.0 ± 1.5 | 3.9 ± 1.5 | 0.730 |
| Postoperative 1 hour | 2.3 ± 1.0 | 2.3 ± 0.8 | 0.431 |
| Postoperative 2 hours | 2.9 ± 2.0 | 2.9 ± 1.8 | 0.883 |
| Postoperative 6 hours | 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 |

Data are expressed as mean ± standard deviation or number (%). Control group; patients who received intravenous normal saline as control. Magnesium group; patients who received intravenous magnesium. Postoperative 0 hours, upon admission to the postanesthetic care unit. TURB, transurethral resection of bladder tumor; NRS, numeric rating scale.

**Table 2-6.** Comparison of previous studies regarding the prevention of postoperative CRBD

| Author, date | Group, sample size | Study design | Surgery | Mechanism of action | Results | Adverse effects |
|---|---|---|---|---|---|---|
| Agarwal et al, 2007[3] | Control, 54<br>Gabapentin, 54 | Randomized controlled trial | Percutaneous nephrolithotomy | Anti-epileptic | The incidence of CRBD: 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[5] | Control, 27<br>Tramadol, 27 | Randomized controlled trial | Percutaneous nephrolithotomy | Anti-muscarinic | The incidence and severity of CRBD 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[11] | Control, 32<br>Paracetamol, 32 | Randomized controlled trial | Percutaneous nephrolithotomy | Anti-inflammatory | Scores of CRBD were less in paracetamol group compared with control group at all time points except at postoperative 12 hours ($P$ <0.05). | No paracetamol-related adverse effects |
| Kim et al, 2014[7] | Control, 57<br>Dexmedetomidine, 57 | Randomized controlled trial | Transurethral resection of bladder tumor | Anti-muscarinic | The incidence of CRBD was less in dexmedetomidine group compared with control group at postoperative 0 and 1 hours ($P$ <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[39] | Sevoflurane, 41<br>Propofol, 41 | Randomized controlled trial | Transurethral resection of bladder tumor | Anti-muscarinic | The incidence of CRBD: Sevoflurane group (59%) vs. Propofol group (85%) at postoperative 1 hour (*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[20] | Control, 65<br>Ketorolac, 65 | Randomized controlled trial | Robot-assisted laparoscopic radical prostatectomy | Anti-inflammatory | CRBD above a moderate grade at postoperative 0 hours: 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[2] | Control, 45<br>Lidocaine, 45 | Randomized controlled trial | Transurethral resection of bladder tumor | Anti-muscarinic, Anti-inflammatory | CRBD above a moderate grade at postoperative 0 hours: Control group (67%) vs. Lidocaine group (26%) (*P* <0.001) | No lidocaine-related adverse effects |

CRBD, catheter-related bladder discomfort.

# CONCLUSION

The present study was performed to evaluate new approaches to prevent postoperative CRBD in urologic patients with urinary bladder catheters.

In part I, the author evaluated the effect of ketorolac on CRBD above a moderate grade after RALP. Ketorolac significantly reduced the CRBD incidence above a moderate grade. Moreover, ketorolac decreased pain scores at 0 and 1 h and opioid requirement over 24 h and increased patient satisfaction scores. Additionally, ketorolac was not associated with any adverse effects.

In part II, the author evaluated the effect of magnesium on CRBD above a moderate grade after TURB. Magnesium reduced the CRBD incidence above a moderate grade and increased patient satisfaction scores. Furthermore, magnesium was not associated with any adverse effects.

These results suggest that ketorolac and magnesium administration is an effective and safe option to prevent postoperative CRBD in urologic surgery.

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# ABSTRACT IN KOREAN

# 국문 초록


**서론**

도뇨관 삽입 후 방광 불편감은 도뇨관을 거치한 환자에서 흔히 발생하며, 수술 후 초조가 증가하며, 환자 만족도가 떨어지고. 입원 기간이 연장되며, 의료진의 업무가 늘어난다. 도뇨관 삽입 후 방광 불편감은 무스카린 수용체의 활성화나 염증으로 인한 프로스타글란딘 생산 등 여러가지 요소에 의한 방광 평활근의 불수의적인 수축으로 발생한다.

케토로락은 사이클로옥시네이즈를 억제하여 프로스타글란딘을 감소시키는 항염 약물이다. 마그네슘은 칼슘 이온의 능동 수송에 의한 평활근 수축을 억제한다. 그러므로 케토로락과 마그네슘은 도뇨관 삽입 후 방광 불편감을 예방할 수 있을 것이다. 그러나 케토로락이나 마그네슘의 도뇨관 삽입 후 방광 불편감의 예방 효과는 연구된 적이 없다. 그러므로 저자는 두개의 챕터에서 비뇨기과 수술 이후 발생하는 도뇨관 삽입 후 방광 불편감을 케토로락이나 마그네슘으로 예방하는 새로운 접근에 대해 연구하기로 하였다.

**연구방법**

**Part I**

모든 환자는 케로토락 군 (n = 66)이나 대조군 (n = 66)으로 무작위 배정되었으며, 이중 맹검으로 연구가 수행되었다.

일차 결과 지표는 수술 직후 중등도 이상의 도뇨관 삽입 후 방광 불편감이다. 수술

후 1, 2, 그리고 6 시간의 도뇨관 삽입 후 방광 불편감, 수술 후 통증 점수, 진통제 요구량, 환자 만족도, 케토로락 연관 합병증, 그리고 입원 기간 또한 분석하였다.

**Part II**

모든 환자는 마그네슘 그룹 (n = 60)이나 대조군 (n = 60)으로 무작위 배정되었으며, 이중 맹검으로 연구가 수행되었다. 마그네슘 군에서는 마그네슘을 50mg/kg의 부하용량을 15 분간 정맥으로 정주하였고, 정주가 끝난 후 15mg/kg/h의 속도로 수술 중 투여하였다. 대조군에서는 생리식염수를 비슷한 방법으로 투여하였다

일차 결과 지표는 수술 직후 중등도 이상의 도뇨관 삽입 후 방광 불편감이다. 수술 후 1, 2, 그리고 6 시간의 도뇨관 삽입 후 방광 불편감, 환자 만족도, 그리고 마그네슘 연관 합병증 또한 분석하였다.

## 연구결과

**Part I**

수술 직 후 중등도 이상의 도뇨관 삽입 후 방광 불편감은 케토로락 군에서 유의하게 낮았다 (14 [21.5%] vs. 33 [50.8%], $P$ = 0.001, 상대 위험도 = 0.424, 95% 신뢰 구간: 0.252–0.715, 절대 위험 감소 = 0.29, 치료 필요 수 = 3). 이는 수술 후 1, 2, 그리고 6 시간에도 유의하게 케토로락 군에서 낮았다. 수술 후 0시간, 1시간 통증 점수, 수술 후 24시간 동안 진통제도 케토로락 군에서 유의하게 낮았으며, 환자 만족도는 케토로락 군에서 유의하게 높았다. 케토로락 연관 합병증, 입원기간은 두 군간의 유의한 차이는 없었다.

**Part II**

수술 직후 중등도 이상의 도뇨관 삽입 후 방광 불편감은 마그네슘 군에서 유의하게

낮았다 (13 [22%] vs. 46 [77%], $P$ <0.001, 상대 위험도 = 0.283, 95% 신뢰 구간: 0.171–0.467, 절대 위험 감소 = 0.55, 치료 필요 수 = 2). 수술 후 1, 2시간에도 비슷한 결과가 관찰되었다 (5 [8%] vs. 17 [28%], $P$ = 0.005, 상대 위험도 = 0.294, 95% 신뢰 구간 = 0.116–0.746, and 1 [2%] vs. 14 [23%], $P$ <0.001, 상대 위험도 = 0.071, 95% 신뢰 구간 = 0.010–0.526). 7점 환자 만족도는 마그네슘 군에서 유의하게 높았다. (5.1±0.8 vs. 3.5±1.0, $P$ <0.001, 95% 신뢰 구간 = 1.281–1.919). 마그네슘 연관 합병증은 두 군간 차이는 없었다.

**결론**

케토로락과 마그네슘은 비뇨기과 수술을 받는 환자에서 도뇨관 삽입 후 방광 불편감을 예방하는 데 효과적이고 안전한 방법일 것 같다.