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Intraoperative magnesium sulfate is not associated with improved pain control after urologic procedures

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Abstract

Objective To evaluate effects of intraoperative magnesium sulfate infusion on pain control and analgesic use in the postanesthesia care unit (PACU).

Methods This is a retrospective review of patients undergoing robot-assisted radical prostatectomy (RARP) and endoscopic procedures of the bladder, prostate, and urethra from 2/2021 to 12/2021. Patients receiving Mg infusion (Mg group) received an intravenous 2-g bolus of Mg at anesthesia induction, followed by infusion of 1 g/h until procedure end. Outcomes were compared with patients who underwent similar procedures during this timeframe without Mg (Control). Endpoints were use of anticholinergic (AC) and belladonna and opium suppositories (BO), maximum pain score, and morphine milligram equivalents (MME) in PACU.

Results There were 182 patients, with 89 (48.9%) patients in the Mg group and 93 (51.1%) in the Control. Significantly, fewer patients in the Mg group were given AC/BO in PACU (9.0% vs. 21.7%, $p = 0.02$), with odds of using AC/BO which was 0.36 (95% *CI* 0.14, 0.83). No differences were found in pain score ($p = 0.62$) or MME administration ($p = 0.94$). In subgroup univariate analysis, only those who underwent bladder procedures had a significant difference in use of AC/BO (9.5% vs. 30.2%; $p = 0.02$). Across all surgeries, Mg infusion was associated with decreased use of AC/BO in the PACU (*OR* 0.34, $p = 0.02$); however, stratifying by procedure type did not find a difference in AC/BO use postoperatively.

Conclusion Intravenous infusion of magnesium was found to decrease use of AC/BO in the PACU; however, this significance was lost after multivariable analysis stratifying by procedure type.

Keywords Postoperative pain, Bladder spasm, Anticholinergic, Opioid reduction

Background

Postoperative pain control can be challenging after common urologic procedures. There is an impetus to decrease postoperative opioid prescribe in urology, as continued use and diversion of unused pills prescribed by surgeons have contributed to the current opioid epidemic (Carnes et al. 2022; Robles et al. n.d.; Shah et al. 2017; Ellis et al. 2021; Serna et al. 2020). Multimodal pain management is helpful to limit perioperative narcotic usage, with options including nonsteroidal anti-inflammatory agents, nerve blocks using local anesthetics, and

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anticholinergic medications (AC) such as oxybutynin chloride and belladonna and opium (BO) suppositories (Masilamani et al. 2022; Bai et al. 2015; Li et al. 2021; Iselin et al. 1997; Fetzer et al. 2019; Lukasewycz et al. 2010). While ACs are an appealing choice for managing postoperative detrusor muscle overactivity after urologic instrumentation, they have an often-unacceptable side effect profile, including dry mouth, headache, constipation, and dizziness (Bai et al. 2015; Li et al. 2021; Iselin et al. 1997). Furthermore, the manufacturing of BO suppositories was discontinued due to lack of the raw ingredient necessary for manufacturing of the medication, and the drug only recently began distribution again this year (Wheeler 2024).

Perioperative magnesium infusion is well-studied in the literature as an anesthesia adjunct, and it has also been suggested to have analgesic effects in the perioperative setting (Albrecht et al. 2013; Rodriguez-Rubio et al. 2017; Filho et al. 2021; Park et al. 2020; Kim et al. 2021). The data is sparse regarding its use in urologic procedures (Park et al. 2020; Kim et al. 2021; Tauzin-Fin et al. 2006), but in vitro studies have shown that increased concentration of extracellular magnesium reduces detrusor muscle overactivity (Montgomery et al. 1992; Yu et al. 1995). In that context, this study aims to evaluate the use of magnesium in common urologic surgeries including robot-assisted radical prostatectomy (RARP), transurethral bladder surgery, and endoscopic procedures of the prostate and urethra. We hypothesize that intraoperative infusion of magnesium sulfate will help to reduce postoperative discomfort associated with detrusor overactivity and reduce administration of AC/BO and opioid medications in the PACU after these common urologic procedures.

Methods

We performed an IRB-exempt retrospective review of patients undergoing RARP and endoscopic procedures of the bladder, prostate, and urethra from February 2021 to December 2021. Starting in February 2021, author L. M. partnered with several urologic surgeons at our institution to adopt the intraoperative magnesium infusion protocol as follows: an intravenous 2-g bolus of magnesium sulfate (Mg) administered at time of anesthesia induction, followed by an infusion of 1 g/h until the end of the case. Patients who underwent anesthesia with L. M. were included in the study who were over 18 years old and were undergoing procedures with the surgeons who elected to participate in the protocol. Patients who received this infusion (Mg group) were compared with patients who underwent similar procedures during this timeframe but did not receive the Mg infusion (Control). The groups were further split into procedure type to compare outcomes in patients undergoing RARP, transurethral bladder surgery, and endoscopic procedures of the prostate and urethra.

Postanesthesia care unit (PACU) nursing staff recorded postoperative pain scores and administered analgesic medications as ordered by anesthesia and urology teams. Standardized order sets were used and included anticholinergic and narcotic medications for pain control in both the Mg and Control patients. Intravesical gemcitabine in the PACU was instilled after bladder tumor resection to prevent tumor recurrence and progression (Gontero and Frea 2006), which was ordered per provider discretion according to the patient's clinical history. This chemotherapy administration was recorded, as side effects can include irritative urinary symptoms.

The endpoints of interest were AC or BO use, maximum pain score, and morphine milligram equivalents (MME) in the PACU. Univariate testing was performed to determine differences in demographics and clinical characteristics of the patients between the groups. For continuous variables, mean (SD) was calculated, a linear model ANOVA test was used, count (percentage) was calculated, and Pearson's chi-squared test was used for categorical variables. Multivariable analysis was also performed. Logistic regression was performed for use of AC/B&O in the PACU, and linear regression for pain score and MME in PACU was used to adjust for use of gemcitabine in the PACU, transurethral resection of bladder tumor (TURBT) resection size, and the use of AC pre-procedure. A p-value of less than 0.05 was considered significant. R statistical software version 4.0.3 was used to conduct the analysis.

Results

A total of 182 patients were included in the analysis, with 89 (48.9%) patients in the Mg group and 93 (51.1%) in the control group. The average age at time of surgery was 68, and 91.8% of the patients were male. Table 1 summarizes the demographics and clinical characteristics of the cohort. The percentage of patients who used AC pre-procedure was significantly different between the two groups (Mg 2.2% versus control 11.8%, $p = 0.01$); otherwise, there were no significant differences regarding demographics or clinical characteristics. Table 2 summarizes the types of procedures performed in each group.

Univariate analysis showed the percentage of patients who were given AC/BO in the PACU was significantly lower in the Mg group (9.0% vs. 21.7%, $p = 0.02$). No significant differences were found in maximum pain score (mean 3.5 vs. 3.2, $p = 0.62$) or MME (80.6 mg vs 81.8 mg, $p = 0.94$). These data are summarized in Table 3. The endpoints were then compared between the Mg and control groups for each of the three procedure groups

Table 1 Patient demographics

		Magnesium (*N* = 89)	Control (*N* = 93)	*p*-value
Male sex		83 (93.3%)	84 (90.3%)	0.47
Age at surgery		69.5 (7.8)	67.1 (9.8)	0.07
BMI		27.9 (4.4)	28.7 (5.5)	0.31
ASA		2.3 (0.6)	2.3 (0.6)	0.40
Pre-op AC use		2 (2.2%)	11 (11.8%)	**0.01**
Procedure type	RARP	29 (32.6%)	28 (30.1%)	0.90
	Bladder	42 (47.2%)	44 (47.3%)	
	Endo[a]	18 (20.2%)	21 (22.6%)	

Categorical variables presented as number (percentage). Continuous variables presented as mean (standard deviation)

[a] Endoscopic procedures of prostate and urethra

individually (Table 3). No differences were found in the use of AC/BO, pain scores, or MME in the PACU between the Mg and the control patients for patients undergoing RARP or endoscopic procedures of the prostate and urethra. For those who underwent procedures of the bladder, there was no difference in maximum pain score or MME in the PACU between the Mg and control cohorts; however, there was a statistically significant difference in use of AC/BO in the PACU (9.5% versus 30.2%; $p = 0.02$).

Multivariable logistic regression showed that use of AC/BO in PACU was 66% lower for patients in the Mg group compared with control (*OR* 0.34, $p = 0.02$); however, there was no statistically significant difference in AC/BO use between the Mg and control groups when stratifying by procedure type ($p = 0.19$). Multivariable linear regression for maximum pain score showed no difference in PACU maximum pain scores between the Mg vs control groups ($p = 0.71$), but did show that pain scores were lower for patients who had bladder procedures (−1.42, $p = 0.005$) and endoscopic procedures of the prostate/urethra (−2.71, $p < 0.001$) in comparison with RARP. Multivariable linear regression for MME in the PACU showed no difference between the Mg and control groups ($p = 0.86$), and this again demonstrated decreased MME in the PACU for the bladder (−23.55, $p = 0.20$) and endoscopic procedures (−73.46, $p = 0.001$) compared with patients who underwent RARP.

Further multivariable analyses were performed for only the bladder procedure group, due to the significant difference found in AC/BO usage postoperatively on univariate analysis. Demographics and clinical characteristics of patients who underwent procedures of the bladder are shown in Table 4. Notably, a higher proportion of patients in the control group used AC prior to their procedure (4.8% versus 22.7%, $p = 0.02$), and a greater number of patients in the Mg group received intravesical gemcitabine in the PACU (31.7% versus 11.9%, $p = 0.03$). There was no difference between the groups regarding proportion of patients with TURBT resection size ≥ 2 cm (44.7% versus 48.8%, $p = 0.72$).

Multivariable analysis of use of AC/BO in the PACU between Mg and control groups was performed and adjusted for the use of gemcitabine in the PACU, TURBT resection size, and the use of AC pre-procedure (Table 5).

Table 2 Procedures type by group

Group	Procedure	Magnesium (*N* = 89)	Control (*N* = 93)
RARP*	RARP	29 (100%)	28 (100%)
Bladder*	CBF[a]	30 (71.4%)	31 (70.5%)
	TURBT[b]	11 (26.2%)	13 (29.5%)
	Cystolitholapaxy	1 (2.4%)	0 (0.0%)
Endoscopic procedures of prostate/urethra*	TURP[c]	7 (38.9%)	10 (47.6%)
	Urethral procedure	4 (22.2%)	3 (14.3%)
	TUIP[d]	3 (16.7%)	3 (14.3%)
	TUIBNC[e]	2 (11.1%)	2 (9.5%)
	HoLEP[f]	2 (11.1%)	1 (4.8%)
	DVIU	0 (0.0%)	2 (9.5%)

[*] Categorical variables presented as number (percentage)

[a] Cystoscopy, biopsy, and fulguration

[b] Transurethral resection of bladder tumor

[c] Transurethral resection of prostate

[d] Transurethral incision of prostate

[e] Transurethral incision of bladder neck contracture

[f] Holmium laser enucleation of the prostate

Table 3 Magnesium and control cohort outcomes

	Outcome	Magnesium (*N* = 89)	Control (*N* = 93)	*p*-value
Overall (*N* = 182)	Use of AC/BO in PACU	8 (9.0%)	20 (21.7%)	**0.02**
	Maximum pain score	3.5 (3.0)	3.2 (3.0)	0.62
	MME in PACU — mg	80.6 (113.9)	81.8 (107.6)	0.94
RARP (*N* = 57)	Use of AC/BO in PACU	3 (10.3%)	5 (17.9%)	0.41
	Maximum pain score	5.0 (2.2)	4.2 (2.6)	0.18
	MME in PACU — mg	116.0 (101.6)	99.7 (84.9)	0.52
Bladder (*N* = 86)	Use of AC/BO in PACU	4 (9.5%)	13 (30.2%)	**0.02**
	Maximum pain score	2.9 (3.3)	3.5 (3.5)	0.37
	MME in PACU — mg	72.0 (126.5)	96.4 (127.6)	0.38
Endoscopic procedures of prostate and urethra (*N* = 39)	Use of AC/BO in PACU	1 (5.6%)	2 (9.5%)	0.64
	Maximum pain score	2.4 (2.7)	1.5 (1.8)	0.22
	MME in PACU — mg	43.6 (87.5)	27.0 (66.9)	0.51

Categorical variables presented as number (percentage). Continuous variables presented as mean (standard deviation)

Table 4 Bladder procedure group demographics

		Magnesium (*N* = 42)	Control (*N* = 44)	*p*-value
Male sex		36 (85.7%)	35 (79.5%)	0.45
Age at surgery — years		72.2 (8.3)	68.7 (11.2)	0.10
BMI		27.7 (4.4)	27.5 (5.4)	0.87
ASA		2.3 (0.6)	2.5 (0.5)	0.14
Pre-op AC use		2 (4.8%)	10 (22.7%)	**0.02**
Use of gemcitabine in PACU		13 (31.7%)	5 (11.9%)	**0.03**
Resection size — cm	< 2 cm	21 (55.3%)	21 (51.2%)	0.72
	≥ 2 cm	17 (44.7%)	20 (48.8%)	
Presence of catheter postoperatively		41 (97.6%)	36 (81.8%)	**0.02**

Categorical variables presented as number (percentage). Continuous variables presented as mean (standard deviation)

Table 5 Multivariable analysis of AC/BO usage

	Odds ratio (CI)	*p*-value
Control group — Mg	0.31 (0.07, 1.15)	0.09
Use of gemcitabine in PACU	0.66 (0.09, 3.21)	0.63
TURBT resection size ≥ 2 cm	4.14 (1.21, 16.83)	**0.03**
Pre-op AC use	0.69 (0.09, 3.77)	0.68

There was not a significant difference in the use of AC/BO in the PACU between the Mg and control groups for bladder procedure patients, as the odds of using AC/BO in the PACU for patients in the Mg group compared to patients in control group undergoing bladder procedures were 0.31 (*CI* 0.07–1.15, $p = 0.09$). TURBT resection size ≥ 2 cm was also found to be a significant predictor of the use of AC/BO ($p = 0.03$) and maximum pain score ($p < 0.01$) in the PACU. Multivariable regression found no difference between the Mg and control groups regarding pain scores and MME in the PACU. Due to the small number of patients who did not have a catheter in place after a bladder procedure, we could not control for the presence of catheter in multivariable analysis. Of the 77 patients who had a catheter in place in the PACU, those who did not have the Mg infusion had higher rates of AC/BO usage in the PACU (36.1% vs 9.8%), and none of the patients without a catheter received AC/BO.

Discussion

While multivariable analysis showed decreased use of AC/BO in the PACU after intraoperative magnesium sulfate infusion across the entire patient cohort, this significance was not seen when stratifying by procedure type. Patients who underwent procedures of the bladder and endoscopic surgery of the urethra and prostate were shown to have lower pain scores than those who underwent RARP, and patients who had endoscopic surgery used fewer MME in the PACU than after RARP.

Postoperative pain control is a challenging part of any surgery, and discomfort related to bladder spasms is commonly encountered after many urologic procedures.

Magnesium demonstrated in vitro effect of attenuating overactivity of detrusor muscle cells makes perioperative magnesium infusion an appealing option to help reduce the use of opioids and AC/BO in the PACU (Montgomery et al. 1992; Yu et al. 1995). The present study shows that intraoperative infusion of magnesium sulfate was associated with reduced use of AC/BO medications across the entire cohort. Univariate data suggests that patients benefitted most from Mg infusion if the procedural intervention directly involved the detrusor muscle, as opposed to the bladder neck (RARP, endoscopic prostate procedures) or further distally in the urethra. The decreased use of AC/BO suppositories is clinically meaningful in the context of their side effects and the temporary discontinuation of BO suppository production (Bai et al. 2015; Li et al. 2021; Iselin et al. 1997; Wheeler 2024).

Park et al. performed a prospective, randomized, double-blind, placebo-controlled study evaluating the use of magnesium sulfate to manage postoperative catheter-related pain after transurethral resection of bladder tumors (Park et al. 2020). Sixty patients received a 50 mg/kg bolus of magnesium sulfate (0.2 mmol/kg) followed by an infusion of 15 mg/kg/h (0.06 mmol/kg), and another 60 patients received normal saline in the same fashion. Patients in the intervention group received an average of 4.1 ± 0.6g of magnesium sulfate. The study demonstrated that patients who received Mg infusion had lower incidence and severity of bladder discomfort at 0, 1, and 2 h postoperatively and lower severity at 6 h (Park et al. 2020). They also reported no difference in postoperative pain scores, opioid requirements, or magnesium-related adverse events. Park et al. and much of the anesthesia literature differentiate "catheter-related bladder discomfort" from postoperative pain (Bai et al. 2015; Li et al. 2021; Park et al. 2020; Hu et al. 2016). In the present study, the majority of patients across all surgeries in the present study did have a foley catheter in place postoperatively, so we were unable to make a meaningful comparison between those who did and did not have a catheter postoperatively. However, across all surgeries, we did not find significant difference in maximum pain score or MME in the PACU between the Control and Mg groups, thus challenging the results of the study by Park et al.

This study is not without limitations, as it is a retrospective review of a single institution over the span of a year, limiting generalizability. Additionally, the urologic surgeons, anesthesia, and PACU nursing staff were not blinded to which patients received the Mg infusion. For this reason, provider bias in using certain analgesics cannot be ruled out. Standardization of order sets for PACU pain control was used, but additional medications given on an as-needed basis was per the discretion of the anesthesia and urology providers. Across all procedure types, the patients who underwent bladder procedures had the highest rates of AC/BO use, so this study might have contributed to the significant difference on univariate analysis that was then lost on multivariable statistics.

There are several future directions in which this study can be expanded. Continuing the magnesium infusion into the PACU is the logical next step to examine its continued postoperative effects to determine if there is added benefit in pain control after the patient emerges from anesthesia. Intravesical infusion to bring the magnesium ions directly to the source of the detrusor overactivity is also an appealing concept to be explored. Furthermore, mixture with other medications such as lidocaine and heparin for additional pain relief can be investigated, as "bladder cocktails" are commonly used in the treatment of interstitial cystitis/bladder pain syndrome in the outpatient and ambulatory surgical (Colemeadow et al. 2020; Henry et al. 2015). Additionally, this study did not investigate serum levels of magnesium in the perioperative setting. Perhaps patients who are hypomagnesemic prior to their bladder surgery benefit more from the intraoperative infusion in comparison with those who have normal Mg levels before their procedure.

Conclusions

While intravenous infusion of magnesium sulfate during urologic procedures was found to improve AC/BO use in the PACU across all urologic surgeries investigated, stratification by procedure type and multivariable analysis did not show improvement in AC/BO use, maximum pain scores, or MME received postoperatively. While intraoperative IV magnesium sulfate infusion may be a helpful tool in the management of postoperative discomfort in patients undergoing endoscopic procedures of the bladder, more studies are necessary to help elucidate this further.

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Authors' contributions
DS and KO responsible for writing of manuscript; MK performed statistical analysis; DS, KO, MT, MH, and LM responsible for development of study

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Availability of data and materials
Data is available by request of the first author, D. S.
No datasets were generated or analysed during the current study.

Declarations

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This was an IRB exempt retrospective study, and consent was waived.

Consent for publication
All authors consent to publication.

Competing interests
The authors declare no competing interests.

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