Identifying predictors of antispasmodic use following robotic assisted simple prostatectomy

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Introduction: *Anticholinergic or ß-3 agonist use following robotic simple prostatectomy (RASP) is not well described. We describe rates of antispasmodic use following RASP and identify potential predictors of medication use.*

Materials and methods: *A retrospective review of all RASP patients from 2/2016 - 1/2020 was conducted. Patients with no preoperative International Prostate Symptom Score (IPSS) were excluded. Demographics, clinical data, and postoperative medication use were collected by electronic medical record review. Multivariable logistic regression analysis using a priori variables was performed to identify independent factors associated with antispasmodic use.*

Results: *A total of 255 patients underwent RASP at a mean age of 70.0 years ± 7.3 and mean body mass index (BMI) of 28.6 kg/m^2 ± 5.0. Median preoperative prostate volume was 132.3 cc ± 45.0. Rates of preoperative diabetes, obstructive sleep apnea (OSA), smoking and alcohol use were 19.6%, 6.3%, 3.1%, and 11.8% respectively; 8.6% of patients (n = 22) initiated antispasmodics at a median of 2.5 months (IQR 1.3-4.2) postoperatively. Median duration of antispasmodic use was 6.5 months (IQR 1.7-14.7). Mirabegron was most commonly prescribed (31.8%). On multivariable logistic regression analysis, OSA was independently associated with postoperative antispasmodic use (OR 8.13, 95% CI 2.02-32.67, p = 0.003); 68.8% of OSA patients were treated with continuous positive airway pressure (CPAP). Treatment was not significantly associated with postoperative antispasmodic use (p = 0.61).*

Conclusion: *Patients with OSA are over 8 times more likely to require antispasmodic medications following RASP in the short term. These patients may benefit from more tailored preoperative counseling.*

Key Words: robotic simple prostatectomy, BPH, anticholinergic, LUTS, irritative, medication

Introduction

Between 20%-50% of men experience persistent lower urinary tract symptoms (LUTS) following a de-obstructing procedure for benign prostatic hyperplasia (BPH).[1,2] Such bothersome symptoms may be significant enough to warrant initiation of antispasmodic medications such as anticholinergics, ß3-agonists, or other bladder relaxants in 10%-15% of patients following transurethral resection of the prostate (TURP) or open simple prostatectomy.[3,4] As the decision to proceed with a surgical de-obstructing procedure may be largely influenced by desire to wean off of medication for management of LUTS, patients must be carefully counseled regarding

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this possibility. Additionally, given the associated cognitive risks associated with anticholinergic exposure and significant side effects, efforts to identify and appropriately counsel these patients before surgery are paramount.[5]

The development of alternative surgical strategies to open simple prostatectomy, such as holmium laser enucleation of the prostate (HoLEP) or robotic simple prostatectomy (RASP), have provided more efficient means of addressing large gland BPH. However, the rate of de-novo antispasmodic medication use following RASP has not been previously described and remains unknown. Moreover, though systemic comorbidities such as diabetes, cardiovascular disease, obesity, neurologic disorders, anxiety or depression, and sleep apnea have been associated with medication use after de-obstructing prostate procedures, specific clinical risk factors for antispasmodic use after RASP are unknown.[6]

Identifying the rates of postoperative antispasmodic use after RASP and the associated clinical factors would therefore help provide more tailored patient counseling. Thus, we describe rates of antispasmodic use following RASP at our institution and identify potential predictors of postoperative medication initiation. We hypothesize that rates of postoperative antispasmodic use in this population are lower than historically reported rates for TURP, and likely similar to those following open simple prostatectomy.

Methods and methods

Patient population

At our institution, patients with large prostate glands routinely undergo RASP rather than HoLEP. After receiving institutional review board approval, a retrospective review was performed of all patients at a tertiary care academic institution undergoing RASP from 2/2016 - 1/2020. Patients with no preoperative International Prostate Symptom Score (IPSS) were excluded. Demographic data, and preoperative clinical characteristics were collected for all patients. De novo postoperative antispasmodic use was determined through electronic medical record review and was defined as ≥ 1 week of medication use. Duration of antispasmodic use and number of medications trialed were also recorded for each patient. Antispasmodic agents were defined as anticholinergics, ß3- agonists, or other bladder relaxants such flavoxate or hyoscyamine. Patients were considered to have "treated" obstructive sleep apnea (OSA) if continuous positive airway pressure (CPAP) use was documented at the time of surgery.

Robotic simple prostatectomy

At our institution, RASP was performed by one of four surgeons. All surgeons perform the procedure in a similar fashion through a transvesical suprapubic approach. Briefly, a cystotomy is made within the bladder, and enucleation is carried out using blunt dissection and electrocautery. Hemostasis is achieved with running 3-0 barbed polyglyconate sutures and trigonalization of the prostatic fossa is also performed using the same suture. The bladder mucosa is then brought down to the prostatic capsule with 3-0 barbed polyglyconate suture in a running fashion. Use of hemostatic agents is at the discretion of the provider on a case-by-case basis. Cystorrhaphy is performed in two layers using a 3-0 barbed polyglyconate suture. A 20 Fr 3-way foley catheter is placed for 3-7 days depending on provider, and a JP drain is typically left in place and removed prior to discharge. A belladonna and opium suppository is administered intraoperatively, and antispasmodics are used as needed during postoperative admission. Patients are instructed to stop α-antagonists and 5α-reductase inhibitors post-operatively and are not routinely discharged with antispasmodic medication.

Statistical analysis

Means and medians were used to perform analysis of demographic and clinical data. Patients requiring antispasmodic use postoperatively were compared to those who did not, using chi-square or Fisher's exact test as appropriate. A multivariable logistic regression model was performed using a priori defined variables, including age, body mass index (BMI), preoperative IPSS score, preoperative history of OSA, history of diabetes, active smoking history, and heavy alcohol use (≥ 7 drinks/week) to identify independent risk factors associated with postoperative antispasmodic use. All analyses were performed using SPSS version 25 (IBM; Armonk, NY, USA).

Results

A total of 255 patients underwent RASP at a mean age of 70.0 years ± 7.3 and mean BMI of 28.6 kg/m^2 ± 5.0. Mean preoperative prostate volume was 132.3 cc ± 45.0. Rates of preoperative diabetes, heavy alcohol use, obstructive sleep apnea (OSA), and smoking were 19.6%, 11.8%, 6.3%, and 3.1%, respectively. Eleven patients with OSA (68.8%) were treated with CPAP at time of RASP. Mean preoperative IPSS and quality of life scores were 17.6 ± 7.8 and 3.6 ±1.6, respectively. Median preoperative post-void residual was 118 cc (IQR 61-225 cc) and median Qmax was 8.3 cc/sec (IQR

6.2-11.8 cc/sec). Additional patient demographic and clinical characteristics are summarized in Table 1.

Average operative time was 147.4 minutes ± 38.7 and mean estimated blood loss was 216.5 cc ± 133.4. The transfusion rate was 2.4%. On average, 85.0 ± 37.9 grams of prostate tissue was removed. Mean duration of foley catheterization time was 4.6 ± 3.3 days. Among those with postoperative PSA (n = 195), median postoperative PSA was 0.6 (IQR 0.4-1.0). Complications occurred in 19.2% (n = 49, Table 2). The most common postoperative complication was the development of urethral stricture requiring urethral

TABLE 1. **Demographic and clinical characteristics of patients undergoing robotic simple prostatectomy**

	All patients (n = 255)	**No postoperative antispasmodic use (n = 233)**	**Requiring postoperative antispasmodics (n = 22)**	***p value**
Mean age (years)	70 ± 7.3	69.9 ± 7.5	71.5 ± 5.1	0.19
Race/ethnicity				0.76
White	80.8% (n = 206)	80.7% (n = 188)	81.8% (n = 18)	
Black	9.0% (n = 23)	9.0% (n = 21)	9.1% (n = 2)	
Hispanic	6.3% (n = 16)	6.0% (n = 14)	9.1% (n = 2)	
Other	3.5% (n = 9)	3.9% (n = 9)	0% (n = 0)	
Not reported	0.4% (n = 1)	0.4% (n = 1)	0% (n = 0)	
History of diabetes mellitus	19.6% (n = 50)	20.2% (n = 47)	13.6% (n = 3)	0.58
History of OSA	6.3% (n = 16)	4.7% (n = 11)	22.7% (n = 5)	0.007
Treated (CPAP)	68.8% (n = 11)	72.7% (n = 8)	60% (n = 3)	1
Untreated	31.3% (n = 5)	27.3% (n = 3)	40% (n = 2)	
Active smoker	3.1% (n = 8)	3.0% (n = 7)	4.5% (n = 1)	0.52
Heavy alcohol use (≥ 7 drinks/week)	11.8% (n = 30)	12.0% (n = 7)	9.1% (n = 2)	1
ASA class				0.83
1	3.1% (n = 8)	3.4% (n = 8)	0% (n = 0)	
2	60.8% (n = 155)	60.5% (n = 141)	63.6% (n = 14)	
3	35.7% (n = 91)	35.6% (n = 83)	36.4% (n = 8)	
4	0.4% (n = 1)	0.4% (n = 1)	0% (n = 0)	
Preoperative urinary retention	17.3% (n = 44)	17.2% (n = 40)	18.2% (n = 2)	1
Mean preoperative IPSS score	17.6 ± 7.8	17.73 ± 7.8	15.95 ± 7.3	0.29
Mean quality of life score	3.6 ± 1.6 (n = 170)	3.6 ± 1.5	3.4 ± 2.3	0.83
Median preoperative prostate volume	120 cc (IQR 100-150)	120 cc (IQR 102-150)	123 (IQR 99-165)	0.93
Median preoperative PSA (ng/dL)	6.1 (IQR 3.6-9.2)	6.1 (IQR 3.7-9.3)	5.4 (IQR 2.5-8.3)	0.40
Median preoperative PVR (cc)	118 cc (IQR 61-224.5); (n = 227)	125 (IQR 62-229)	83 (IQR 40-155)	0.12
Median Qmax (cc/sec)	8.3 cc/sec (IQR 6.2-11.8); (n = 192)	8.3 (IQR 6.3-11.7)	9.3 (IQR 5.7-14.6)	0.76

*p value refers to comparisons between patients with no postoperative antispasmodic use and patients requiring postoperative antispasmodics
OSA = obstructive sleep apnea; CPAP = continuous positive airway pressure; ASA = American Society of Anesthesiology; IPSS = International Prostate Symptom Score; PSA = prostate specific antigen; PVR = post-void residual; Qmax = maximal urinary flow rate

TABLE 2. **Complications following robotic simple prostatectomy**

Clavien grade							
1		2		3		4	
Complication	**n (%)**	**Complication**	**n (%)**	**Complication**	**n (%)**	**Complication**	**n (%)**
Total	13 (5.1%)	Total	12 (4.7%)	Total	23 (9%)	Total	1 (0.4%)
Wound seroma	1 (0.4%)	Acute blood loss	5 (2%)	Urethral stricture	16 (6.3%)	Septic shock	1 (0.4%)
Ileus	3 (1.2%)	UTI	3 (1.2%)	Clot retention	3 (1.2%)		
Clot retention	9 (3.6%)	Wound infection	2 (0.8%)	Incisional hernia	2 (0.8%)		
		Sepsis	2 (0.8%)	Urinary retention	1 (0.4%)		

dilation, which occurred early in this series and was thought to be secondary to use of a large bore 3-way foley catheter (24 Fr); following routine use of 20 Fr catheters, no further urethral strictures were noted.

Median postoperative follow up was 12.4 months (IQR 5.5-18.3). Only three patients (1.2%) developed stress urinary incontinence postoperatively. After RASP, 8.6% of patients (n = 22) initiated antispasmodics at a median time of 2.5 months (IQR 1.3-4.2); when restricted to de novo medication use after the first 3 months postoperatively, only 2.4% of RASP patients initiated antispasmodics during this time frame. The median duration of antispasmodic use was 6.5 months (IQR 1.7-14.7). Mirabegron was the most commonly used medication, comprising 31.8% of all prescriptions, Figure 1.

Differences in clinical and demographic characteristics between patients requiring postoperative anticholinergics or ß3-agonists and those who did not is illustrated in Table 1. The

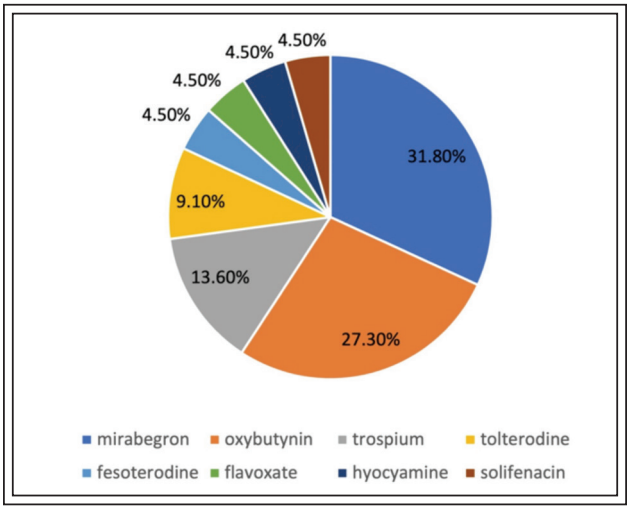

Figure 1. Initial prescribed antispasmodic medications for persistent irritative symptoms after robotic simple prostatectomy.

TABLE 3. **Multivariable logistic regression analysis of factors associated with postoperative spasmodic use**

Factor	OR	95% CI	p value
Age	1.03	0.97-1.10	0.33
BMI	1.02	0.93-1.12	0.66
Preoperative IPSS score	0.96	0.91-1.02	0.22
History of OSA (reference = no)	8.13	2.02-32.67	0.003
History of diabetes mellitus (reference = no)	0.34	0.08-1.44	0.14
Smoker (reference = no)	1.44	0.14-14.36	0.76
Alcohol use > 7 drinks/week (reference = no)	0.72	0.16-3.64	0.72

BMI = body mass index; IPSS = International Prostate Symptom Score; OSA = obstructive sleep apnea

incidence of OSA was over 4 times greater among patients requiring postoperative anticholinergics (p = 0.007). There was no significant difference in the proportion of patients who had a history of diabetes (p = 0.58), smoking (p = 0.52), or heavy alcohol use (p = 1) between antispasmodic and non-antispasmodic groups. Additionally, there was no difference in rates of preoperative retention (p = 1), median preoperative prostate size (p = 0.93), or mean preoperative IPSS score (p = 0.29) among patients. On multivariable logistic regression analysis, Table 3, OSA history was independently associated with postoperative antispasmodic use (OR 8.13, 95% CI 2.02-32.67, p = 0.003). Treated OSA did not appear to be significantly associated with antispasmodic use postoperatively (p = 0.61).

Discussion

Postoperative medication use following surgical de-obstructing procedures not only impacts patient satisfaction and quality of life, but also increases the cost of managing BPH patients. To our knowledge, this is the first study within the literature to describe rates of de novo use of anticholinergics, ß3-agonists, or other bladder relaxing agents for men with significantly enlarged prostates following RASP. Overall, 8.6% of patients have persistent LUTS after RASP necessitating additional medication, with nearly 75% of these men initiating medication within the first 3 months postoperatively. Additionally, we identify OSA as an independent risk factor for antispasmodic use after RASP, conferring an over 8-fold increased odds.

The proposed theory for persistent LUTS following de-obstructing bladder outlet procedures is based on bladder remodeling during a prolonged period of chronic obstruction before surgery. High bladder pressures and prolonged ischemia are thought to induce histologic changes within the bladder, including smooth muscle hypertrophy and collagen deposition.[1,2] This may be reflected by lower cystometric capacities and greater detrusor amplitude on preoperative urodynamics.[7] Notably, detrusor overactivity is noted in up to 52% of patients with bladder outlet obstruction at baseline.[8] Such morphologic and functional changes may be further exacerbated by systemic disease, as features of metabolic syndrome (obesity, elevated fasting glucose, hypertension, dyslipidemia, and hyperlipidemia) have been associated with lower degrees of symptomatic LUTS improvement following TURP or holmium laser enucleation of the prostate (HoLEP).[9,10]

Previously reported rates of de novo postoperative medication use after de-obstructing procedures for BPH are limited, and published studies have focused primarily on antispasmodic use following TURP. Campbell et al found a 15% rate of anticholinergic or ß3-agonist prescription after the first 90 days following TURP. Similarly, Sabharwal and colleagues describe de novo rates of anticholinergic and ß3-agonist use at 3-6 months after TURP to be 4.52% and 0.39% respectively; by 1 year of follow up, these numbers grew to 10.2% and 1.71%, respectively. For open simple prostatectomy, rates of anticholinergics and ß3-agonists were reported as 4.63% and 0% at 3-6 months postoperatively, respectively, and 4.63% and 0.76% at 1 year, respectively.[3] Though the 8.6% rate of de novo antispasmodic medication use in this study is higher than reported historical rates for open simple prostatectomy, the rate of antispasmodic use drops to 2.4% of post-RASP patients when restricted only to those who initiated use after 3 months postoperatively. Thus, this suggests that most antispasmodic use after RASP may be initiated to address immediate postoperative symptoms that are likely related to the cystotomy and cystorrhaphy at the time of RASP. Indeed, use of anticholinergic medication in the immediate postoperative period has been shown in randomized-controlled trials to alleviate bothersome storage symptoms and improve quality of life after surgical de-obstructing procedures, and this has proposed as an early treatment option for men with bothersome postoperative irritative LUTS.[11,12]

Though mirabegron was the most commonly prescribed initial medication among patients requiring antispasmodics after RASP (31.8% of prescriptions), oxybutynin still remained very frequently prescribed (27.3% of prescriptions) as the initial medication of choice. This practice pattern likely reflects an underlying effort by practitioners to avoid anticholinergic medication in this generally older population of patients, in accordance with national urologic society recommendations.[13] However, the decision to prescribe an anticholinergic as the initial medication of choice may be driven by other factors including cost, insurance coverage, prior patient experience, and anticipated duration of use. Such factors must be carefully considered in the context of a patient population that tends to be older and susceptible to polypharmacy.

Campbell et al have previously found postoperative use of anticholinergics and ß3-agonists after TURP to be positively associated with older age and diabetes mellitus, and negatively associated with a history of urinary retention.[4] In this study we did not find any

of these factors to be independently associated with de novo antispasmodic use after RASP, despite similar ages and comorbidity rates in our cohort. However, we did find that patients with a prior history of OSA had a greater than 8-fold increase in the odds of requiring antispasmodic medications postoperatively. This finding is consistent with known associations between OSA and symptoms of overactive bladder, urgency incontinence, and nocturia, which increase with worsening OSA severity.[14-17] These symptoms are thought to result, at least in part, from production of atrial natriuretic peptide triggered by distension of the atrial wall, as well as structural and functional changes of the detrusor muscle that result from hypoxic conditions and oxidative stress.[18,19]

Notably, in this study, treated OSA did not appear to be a significant factor for postoperative medication use. Prior studies have demonstrated improvements in nocturia and overall LUTS following treatment of OSA with CPAP.[20,21] However, it is unclear whether treatment of OSA was causally responsible for lower rates of de novo antispasmodic use after RASP in this study, due to the small number of patients with treated OSA. Moreover, the retrospective study design precluded our ability to quantify duration and compliance with CPAP treatment perioperatively, which are critical factors to evaluate the impact of OSA treatment on postoperative LUTS.

This study is not without several limitations. In addition to a retrospective study design, our study may have limited generalizability to the practicing urologist in the community, as all RASPS were performed at a tertiary care academic referral center. Though prescribed medications could be tracked, patient compliance with prescribed medications could not be definitively determined retrospectively through chart review. However, all documented communications between the patient and clinical care team were reviewed to determine if a medication was stopped earlier than planned. As it is not part of the practice pattern at our institution to routinely obtain urodynamic studies preoperatively, we were unable to determine the baseline rate of detrusor overactivity prior to and following RASP; thus we are unable to determine whether baseline rates of detrusor overactivity, or changes in detrusor overactivity postoperatively contribute to the rates of antispasmodic use in this study. Additionally, many patients with long term indwelling foley catheters preoperatively did not have preoperative IPSS scores and were therefore excluded from this study. Thus, the results of this study may not be generalizable to these patients. Lastly, the median follow up time of 12.4 months precludes any conclusions regarding long term use or delayed initiation of antispasmodic medications following RASP. However, as our data suggests that most patients requiring postoperative antispasmodics initiate these medications shortly after RASP and remain on them for a relatively short duration, our cohort likely captures the majority of patients with significant postoperative LUTS.

Conclusion

Postoperative LUTS after RASP are infrequent but may require initiation of anticholinergics, ß3-agonists, or other bladder relaxants to adequately manage symptoms in up to 8.6% of patients. Most of these are initiated within the first 3 months postoperatively and are used for relatively short durations of time. A history of OSA is associated with need for these medications following RASP, though the impact of OSA treatment in this population remains unclear. These patients may benefit from more tailored preoperative counseling to help guide postoperative expectations. □

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