

Full Length Research Paper

Adjunctive intralesional antifibrotics following transurethral incision of Bladder Neck Contractures

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Iatrogenic bladder neck contractures (BNC) represent a challenging problem for urologists and patients alike and may require several treatments to improve associated LUTS. Mitomycin C (MMC) injection as an adjunctive therapy to transurethral bladder neck incision (TUIBN) has shown promise in achieving durable bladder neck patency. We report outcomes from patients with BNC treated by TUIBN and subsequent injection of an adjunctive agent, either MMC and tacrolimus, an immunomodulator not previously tested but chosen for antifibrotic properties. This is a retrospective review of a single surgeon experience using MMC or tacrolimus injections after TUIBN for BNC. Thirteen patients with iatrogenic BNC were treated with TUIBN. Two were treated with laser incision alone. Two received post-incision injection with tacrolimus, and nine received post-incision injection with MMC after incision. Both patients treated with tacrolimus failed treatment and had obliterated bladder necks, while all MMC patients had patent bladder necks at follow up cystoscopy. MMC, but not tacrolimus, demonstrated safety and efficacy as an adjunctive therapy after TUIBN for refractory BN. Use of adjunctive injection of antifibrotic agents with TUIBN may be an effective method of maintaining bladder neck patency compared to simple incision.

Key words: Bladder neck contracture, mitomycin c, tacrolimus, transurethral incision of bladder neck.

INTRODUCTION

Bladder neck contractures, a well-documented complication after radical prostatectomy, are reported to occur anywhere from 1.3-27% of patients postoperatively (Wessells, 1998; Moul, 1998; Kao, 2000) and are often managed with simple dilation. Refractory cases pose a challenge and leave patients with poor quality of life stemming from urgency, frequency, and incontinence. (Mundy, 2012). If unresolved, patients may require salvage bladder neck reconstruction or diversion, thus methods to improve endoscopic management are desirable.

Recently, injection of the antifibrotic agent MMC at the time of transurethral incision of BNC has shown promise as a method of chemical stabilization. An initial report demonstrated promising results among a cohort of patients with refractory BNC with 75% patency after 1 treatment and 89% patency after 2 treatments at a median of 12 months follow-up. (Vanni, 2011). The initial excitement over these results has been somewhat

tempered more recently by the results of a larger cohort study of 66 patients reporting 58% resolution with 1 treatment at a median of 9.2 months and an overall success rate of 75% after multiple treatments. Seven percent of patients enrolled in the study experienced a serious adverse effect. (Redshaw 2014).

Tacrolimus, a calcineurin inhibitor with antifibrotic properties, has been commonly used as an immunomodulating agent in patients undergoing organ transplantation. It has shown some success in the treatment of other diverse conditions such as lichen sclerosis and atopic dermatitis. (Schachner 2005; Pandher 2003). While never tested, we postulated that tacrolimus, when injected into a bladder neck contracture after TUIBN, could have similar effects to mitomycin C in terms of scar stabilization.

In this study, we report our results with patients undergoing TUIBN of BNC with adjunctive injection of either MMC or tacrolimus compared to a group managed by simple incision of the bladder neck. We review our cohort of patients receiving one of these two adjunctive anti-fibrotic agents after bladder neck incision as well as those managed with simple holmium laser incision.

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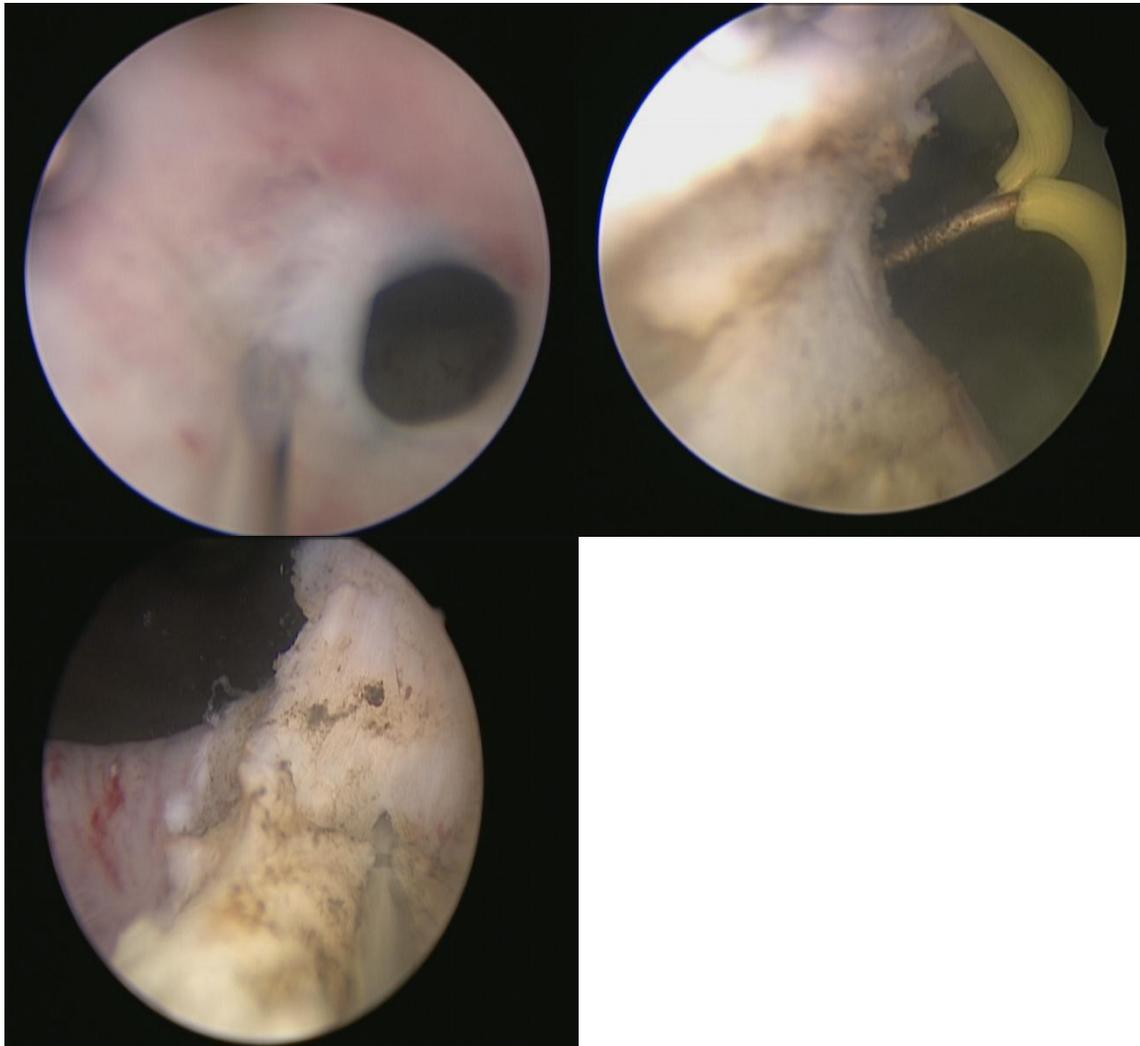


Figure 1. Injection (upper left panel), incision with Collin's knife (upper right panel), and re-injection (bottom) of bladder neck contracture with adjuvant anti-fibrosing agents.

MATERIALS AND METHODS

We retrospectively reviewed the charts of thirteen patients with BNC treated between February 2011 and October 2013 by a single surgeon with TUIBN. All patients were treated with either incision of the bladder neck contracture either with or without injection of adjunctive compounds, either tacrolimus or MMC. Data collected including demographics, findings at the time of follow-up office cystoscopy, and post-operative flow/PVR and symptom scoring at post-operative office visit, when available.

Surgical Technique

In patients undergoing adjunctive injection therapy, bladder neck contractures were initially incised at three points (4, 8, and 12 o'clock positions) to the level of the

perivesical fat with a Collings knife. The three incision sites were then injected with either 1cc of tacrolimus (0.5 mg/mL) or 1cc of MMC (0.5mg/mL) through a Deflux® needle (Figure 1). All patients went home with a urethral catheter for a period of 3-5 days.

In patients undergoing TUIBN without injection of adjuvant therapies, bladder neck contractures were incised radially in the 3, 9, and/or 12 o'clock positions to the level of the perivesical fat with a Holmium laser using settings of either 1 Joule at a frequency of 6Hz, or 0.8 Joules at a frequency of 8Hz until a 24F scope could be easily passed.

RESULTS

Baseline patient demographics: Mean patient age at time of treatment was 69 years (range 55 to 85). Regarding potentially relevant comorbidities, 84.6% (11/13) had

Table 1. All patients treated with MMC showed patency of bladder neck at interval follow up cystoscopy while those treated with tacrolimus were ultimately obliterated. PVP: photovaporization of prostate; RRP: radical retropubic prostatectomy; XRT: external beam radiation; TURP: transurethral resection of prostate.

Patient	Age	Etiology	Modulator	Prior intervention	Follow Up (Months)	Outcome
1	82	PVP	None	None	7	Obliterated, kept suprapubic catheter.
2	85	RRP	None	None	2	Patient reports improved FOS. Pleased.
3	65	RRP and XRT	Tac	Dilation x 2, TUIBN	2	Remained obliterated, kept suprapubic catheter.
4	66	XRT	Tac	Dilation x 1, TUIBN	24	Cystoscopy at 11 months showed patent bladder neck, but obliterated at 24 months.
5	55	Perineal Prostatectomy	MMC	None	41	Cystoscopy at 7 months showed patent bladder neck, had AUS placed at 9 months.
6	68	RRP	MMC	Dilation x 2	14	Followed at Veteran's Affairs Hospital, voiding well.
7	72	RRP	MMC	TUIBN x 1	32	Required balloon dilation at 9 months.
8	55	TURP	MMC	TUIBN x 2	29	Cystoscopy at 11 months showed patent bladder neck.
9	70	RRP	MMC	None	14	AUS placed at 4 months, cystoscopy showed patent bladder neck at that time.
10	72	Brachy	MMC	TUIBN x 1	9	Cysto at 9 months, BN re-stenosed. Followed up at referring urologist.
11	68	PVP and Brachy	MMC	TUIBN x 1	22	11 months AUS/cysto showed BN patent
12	85	Brachy, XRT, TURP x 3	MMC	Resected x 3	13	Dilated at 8 months, repeat incision and injection with MMC at 10 months. AUS at 13 months, patent.
13	59	RRP	MMC	Incised x 2 with kenalog	9	Cystoscopy at 4 months during AUS placement demonstrates stable bladder neck.

hypertension, 30% (4/13) had diabetes, 30% (4/13) had coronary artery disease, and 54% (7/13) had a smoking history. Mean BMI was 27.9 kg/m².

The etiology of the BNC was iatrogenic in all patients in our cohort (7 radical prostatectomy (RP), 1 transurethral resection of the prostate (TURP), 3 brachytherapy (BT), 1 external beam radiation (EBRT), 1 KTP laser vaporization of prostate). Nine patients in had undergone at least one prior procedure attempting to treat their BNC including prior dilations, TUIBN, and bladder neck resections.

Patients underwent TUIBN with MMC (9), TUIBN with tacrolimus (2), or laser incision without adjunctive agents (2) (Data summarized in Table 1). Tacrolimus was chosen for two patients due to the severe nature of their disease with significant scarring from treatment with both surgery and radiation. Median follow up for the entire cohort was 14 months.

Surgical Outcome Summary

Mitomycin C: All patients receiving MMC demonstrated patent outlets at interval follow-up cystoscopy. Only 1 patient (11%) required subsequent intervention (dilation at 10 months and repeat TUIBN with MMC injection at 13

months). Five (55%) of those who have remained patent ultimately went on to have an AUS placed.

Tacrolimus: Of the two patients receiving adjunctive tacrolimus, one underwent a concomitant urethroplasty for a bulbar urethral stricture. This patient had a patent bladder neck at 11 months, but had recurrence of BNC with near-obliteration by 24 months and ultimately left his suprapubic catheter to drainage. The second patient also had recurrence of a clinically significant contracture on follow-up cystoscopy and was lost to follow up.

Laser incision: Of the two receiving laser monotherapy, one remained obliterated and has since expired, while the other reported improved flow at his postop visit and has since been lost to follow up.

At last follow-up, no serious adverse events were noted in any patient treated with or with adjunctive therapy.

DISCUSSION

Iatrogenic bladder neck contractures are a relatively uncommon, but unfortunate result of urologic surgery. The reported incidence of BNC ranges from 0-17% for RP, 1.7% for EBRT, 1.8% for BT, and 2.5% for cryotherapy (Mundy, 2012; Breyer, 1020; Besarani, 2004;

Elliott, 2007) and seems to be diminishing in the era of robotic assisted radical prostatectomy. However, these data likely underestimate incidence of the problem as wide caliber BNC may either go undetected or untreated to avoid worsening incontinence. As open surgical reconstruction in these patients is often a challenging undertaking for both surgeon and patient alike, most initial attempts at management have focused on endoscopic procedures.

Many BNC respond to dilation or endoscopic incision, suggesting that such management is reasonable before moving on to more aggressive open reconstruction or urinary diversion (Mundy, 2012; Anger, 2005; Pansadoro, 1999; Elliott, 2006; Yurkanin, 2001). Following cold knife urethrotomy, one study reported a need for repeat procedure at 17% with an overall success rate greater than 80% (Yurkanin, 2001). While cold incision continues to be a commonly used procedure for endourologic treatment of BNC, new approaches intended to improve the success of endoscopic approaches are being utilized to address the underlying fibrotic pathology in contractures.

As contracture formation involves progressive fibrosis, augmentation of TUIBN with antifibrotic agents has been suggested to improve treatment response (Vanni, 2011; Ramirez, 2013). Eltahawy et al. injected steroids after holmium laser incisions, reporting an 83% success rate at 24 months in a cohort of 24 patients with recurrent BNC after radical prostatectomy. Vanni et al. injected 0.3 to 0.6 mg of MMC after cold knife incision with 75% success without need for further procedures at a mean follow up of 9.4 months and an overall success rate of 89% for patients undergoing a second procedure.

More recently Redshaw et al. reported somewhat more tempered results of TUIBN followed by MMC injections with a larger cohort of 68 patients. Their group reported a lower success rate with only 58% of patients demonstrating patency at 9.2 months using MMC. In patients who failed initial TUIBN with MMC injection, 60% were patent at 8.6 months after a second treatment, and 40% of those receiving a third treatment achieved patency. Attempts have been made to refute the value of MMC by asserting the success rate of simple TUIBN in a retrospective single surgeon study (Ramirez, 2013). That study was somewhat misleading as 22% of patients had no prior treatment for BNC and the authors stated that many cases were incidental findings (not clinically significant) following referral for UI. Despite what appears to be a more favorable population of patients, their failure rate was actually worse than that seen in the study by Vanni et al. Even when aggressive TUIBN was repeated, half of the patients failed again. Given the reported successes with MMC and the relative safety profile (no complications in Vanni et al. and 7% in Redshaw's study of 87 patients), MMC injections into an incised contraction appears to be a reasonable treatment to augment TUIBN.

In this report, our experiences with MMC generally support the enthusiasm generated by initial reports. Among our patients, the etiology of BNC was uniformly iatrogenic, but heterogenous in terms of the causative factor (type of surgical or radiation therapy). Patients demonstrated a variety of risk factors for poor wound healing including diabetes, hypertension and tobacco use (Breyer, 2010; Besarani, 2004; Elliott, 2007). Similar to the outcomes reported by Vanni et al. and MMC et al., patients receiving MMC were patent at interval follow-up cystoscopy and for us, there were no side effects of anti-fibrotic agent injections reported.

Our experience with tacrolimus, however, was unremarkable. The two patients injected with tacrolimus did not experience positive outcomes; however, conclusions are difficult to ascertain from such a small experience. Additionally, both cases were complex and the result of prior surgery radiation. Stenotic lesions secondary to radiation are notoriously difficult to treat, likely due to the resultant obliterative endarteritis (Mundy, 2012; Elliott, 2007; Elliott, 2006). One of the tacrolimus treated cases was further complicated by a concomitant bulbar urethroplasty. The patient lost to follow-up maintained a suprapubic catheter to drain post-procedure after the Foley was removed, raising the question of whether the absence of regularly voiding through the anatomic outlet could have been a factor in the recurrent stenosis. Ultimately, we lack enough data to make any firm conclusions regarding tacrolimus as an adjunctive therapy or toward the value of further research in the application of this agent.

CONCLUSIONS

Based on our early experience, MMC seems to represent a valuable adjunct to endoscopic management of refractory BNC. While our initial experience of using adjunctive tacrolimus in two patients has not proven successful, additional study may still be warranted. Future investigation should involve prospective investigation among multiple centers.

DISCLOSURES

No disclosures.

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