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POST-PROSTATECTOMY AND ACQUIRED VOIDING DYSFUNCTION (V TSE, SECTION EDITOR)

Urethral Bulking and Salvage Techniques for Post-Prostatectomy Incontinence

Benjamin M. Dropkin[1] · Sophia D. Delpe[1] · Melissa R. Kaufman[1]

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Abstract

Purpose of Review Despite limited evidence and efficacy, urethral bulking remains a common treatment for post-prostatectomy stress urinary incontinence (PP-SUI). Herein we provide an overview of the existing evidence for synthetic bulking agents and emerging evidence for stem cell-based sphincter rejuvenation in this setting. We also touch upon salvage techniques for management of PP-SUI after failed anti-incontinence interventions.

Recent Findings Autologous stem cell (ASC) therapies are currently undergoing phase III trials for use in female SUI and are poised to enter the market within the next decade. Early data suggests that they may have a future role in PP-SUI management as well. The artificial urinary sphincter (AUS) has emerged as the standard of care for salvage PP-SUI treatment.

Summary Treatment paradigms for PP-SUI continue to evolve. Synthetic bulking remains common while autologous bulking looms as a potential future therapy. The AUS remains the last line of defense.

Keywords Post-prostatectomy stress urinary incontinence · Artificial urinary sphincter · Urethral bulking · Male sling · Autologous stem cell transplant · Pelvic floor physical therapy · Adipose-derived stem cells · Muscle-derived stem cells · Urethral sphincter regeneration · Salvage anti-incontinence therapy

Introduction

Radical prostatectomy (RP) is the most common source of male stress urinary incontinence. Reported rates of post-prostatectomy stress urinary incontinence (PP-SUI) vary widely in part due to differences in definition, data acquisition, and severity assessment [1, 2]. Nevertheless, PP-SUI has been reported at a range of 2.9–87% [3] with reports since the introduction of robotic surgery demonstrating lower rates ranging from 4 to 31% [4]. Despite improvements in surgical technique and technology, PP-SUI continues to negatively impact a substantial number of men. An estimated 140,000 radical prostatectomies are performed in the USA [5] and nearly 6% of men experience PP-SUI for which they pursue surgical intervention [6]. Herein we provide an overview of the existing management options for PP-SUI with a focus on urethral bulking agents and salvage treatment strategies.

PP-SUI can be a complex diagnosis and requires a detailed history and physical exam to rule out other sources of incontinence such as overactive bladder and/or overflow incontinence. A voiding diary and post void residual may prove informative [7]. In patients diagnosed with straightforward PP-SUI via history and physical exam, some surgeons will choose to forego preoperative urodynamics (UDS). UDS should be strongly considered for any patient with atypical symptoms. Cystourethroscopy should be performed to rule out urethral and vesicourethral anastomotic stricture [8–11].

Treatment options for PP-SUI vary widely in invasiveness and efficacy. Weak evidence supports the use of pelvic floor physical therapy (PFPT) in the preoperative and immediate post-operative settings [12, 13]. Late PFPT, 1–17 years after RP, may result in fewer incontinence episodes [14]. The addition of biofeedback and pelvic floor stimulation has not demonstrated benefit [15].

External passive urethral compression devices were first employed in the eighteenth century and currently remain an

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✉ Benjamin M. Dropkin
benjamin.m.dropkin@vanderbilt.edu

[1] Department of Urologic Surgery, A-1302 Medical Center North, Vanderbilt University Medical Center, Nashville, TN 37232-2765, USA

option for PP-SUI management [16]. The Cunningham clamp is the device most commonly utilized, though large-scale data are lacking. Moore et al. conducted a crossover study assessing efficacy and patient satisfaction with the Cunningham clamp and found that 10/12 (83.3%) patients were satisfied. Potential complications include penile edema, urethral erosion, pain, and urinary obstruction [17]. The authors suggest use of the Cunningham clamp can be considered in patients who are cognitively intact with healthy penile skin, adequate genital and bladder sensation, and appropriate manual dexterity.

Limited data are available regarding the use of oral agents for the treatment of PP-SUI and none are currently FDA approved for this indication. Duloxetine, a serotonin and norepinephrine inhibitor, has been investigated for use in PP-SUI but has not been tested in a randomized controlled trial [18]. Filocamo et al. randomized 102 patients to rehabilitation with or without duloxetine for a period of 16 weeks. While the authors found a significant increase in the number of patients that became dry by 16 weeks in the combination therapy group (39 vs. 27, $p = 0.007$), at 20 weeks the findings were reversed (23 vs. 38, $p = 0.008$). After 24 weeks, there were still more dry patients in the rehabilitation monotherapy group (31 vs. 41, $p = 0.08$). The authors concluded combination therapy might be a viable treatment option for patients with PP-SUI who seek non-invasive, immediate therapy [19].

Up to 10% of patients who attempt conservative measures for PP-SUI will progress to surgical management [20]. Surgical interventions are utilized selectively in the first year after RP as improvement in PP-SUI has been demonstrated up to 1–2 years post-operatively [21–22]. Contemporary surgical options for PP-SUI include artificial urinary sphincter (AUS), male sling, adjustable continence balloons, and urethral bulking.

The AUS can be used for varying severities of PP-SUI and has become the gold standard since its introduction in 1972 with patient satisfaction rates > 90% and total continence rates of 30–90% [23–26]. Post-operative risks include infection, cuff erosion, urethral atrophy, and mechanical failure—all of which require device removal or revision. Additionally, patients require good manual dexterity and cognitive function to utilize the device [27]. Brant et al. reported an explant rate of 8% among 386 patients (50% considered high risk) followed for an average of 2.3 years [28]. Linder et al. reviewed 1082 primary AUS implants and found that 26% of patients required surgical revision within 5 years [29].

Despite excellent outcomes for the majority of AUS patients, the desire for a less invasive, simpler therapy with decreased risks led to the re-development of the male urethral sling in the 1990s. Following release and subsequent market removal of bone-anchored devices, the AdVance polypropylene monofilament mesh sling was introduced to the USA in 2005 by American Medical Systems and remains one of the most widely used male slings. Two to 3 years after surgery, cure (0–1 pads per day) rates range from 43 to 60% and improvement ($\geq$ 50% reduction in daily pad use) rates range from 13 to 20% [30–32]. Patient satisfaction has remained high in the first few years after surgery [32, 33]. Major complications and intraoperative complications appear limited. Post-operative complications include urinary retention in 14–23% of patients and transient perineal pain in up to 50% of patients [34, 35]. Efficacy appears to gradually decrease with time [31, 32]. Treatment outcomes are worse in patients with prior radiation therapy, > 5 ppd use at baseline, an abdominal leak point pressure < 100 cm H_2O, and/or preoperative detrusor overactivity [36–38]. In light of these predictive variables, urodynamics should be strongly considered during an evaluation for male sling candidacy.

The Virtue quadratic male sling was introduced by Coloplast in 2009 and utilizes two prepubic and two transobturator polypropylene mesh arms to simultaneously promote urethral elevation and prepubic compression. A multinational, prospective clinical trial assessed efficacy at 12 months and found that objective (> 50% decrease in 24-h pad weight) and subjective (improvement quantified by patient global impression of improvement survey) rates were 41.9% [39]. The median pad weight reduction was 51.1% and varied based on baseline incontinence. The authors also assessed a fixation technique in which the transobturator arms of the sling were passed subcutaneously back towards midline and sutured together and each prepubic arm was sutured to the ipsilateral pubic periosteum at the junction of the pubis and pubic rami. Fixation was associated with improved outcomes, including an objective success rate of 70.9% and subjective success rate of 79.2%. There was a median pad weigh reduction of 88.3% regardless of baseline incontinence with the fixation technique.

The adjustable transobturator male sling (ATOMS) is an anchoring macroporous, monofilament, polypropylene mesh with an adjustable urethral cushion that can be manipulated through a subcutaneous port [40, 41]. It has been available in Europe since 2009. At 30 months follow-up, success rates (defined as improvement in daily pad use) ranged from 77 to 90% with dry rates (0–1 ppd) of 48–64%. Three port manipulations were done on average per patient. Complication rates ranged from 7 to 25% and were all Clavien Dindo class I–III with wound infection and device malfunction being the most common [42, 43].

The male Adjustable Continence Therapy (ProACT) is the most recent treatment introduced to the US market. Two silicone balloons are inserted at the location of the vesicourethral anastomosis and can be further filled or deflated post-operatively. Gregori et al. reported on 79 patients were followed for an average of 25 months after surgery. Rates of cure, improvement, and failure were 66, 26, and 8%, respectively. Success rates were inversely related to the degree of preoperative incontinence [44].

Urethral Bulking Agents

History

Urethral bulking with an injectable agent was first attempted over a century ago with the use of paraffin wax for female incontinence [45]. Subsequent agents studied include biologics such as cross-linked bovine collagen (Contigen) [46], porcine collagen (Permacol) [47], and autologous fat [48] as well as synthetic agents such as morrhuate sodium [49], polytetrafluoroethlene (Teflon) [50], ethylene vinyl alcohol (Tegress) [51], and hyaluronic acid dextranomer (Zuidex, Deflux) [52]. Three agents are currently FDA-approved for the treatment of female SUI—carbon coated zirconium oxide beads (Duraphere) [53], calcium hydroxyapatite (Coaptite) [54], and polydimethylsiloxane (Macroplastique) [55]. Additional agents approved in Europe include a polyacrylamide hydrogel (Bulkamid) [56] and a silicone gel that polymerizes in situ (Urolastic) [57]. Bulking agents are believed to function by adding central filler to the external urethral sphincter, which increases the length of the muscle fibers and raises the pressure required to open the sphincter [58]. Their use for female SUI has been tempered by moderate success rates, limited durations of improvement, and the need for multiple procedures.

Use in PP-SUI

Considerable attention has also been given to the use of bulking agents in the setting of PP-SUI. Despite the previously discussed limitations of bulking agents, urethral bulking stands as the only male incontinence procedure offered by half of urologists with case logs available for review in 2010 [59]. An analysis of 2000–2007 SEER data found that among the 6% of post-prostatectomy patients electing for PP-SUI treatment 18% received urethral bulking alone [60].

Injectable collagen is the best studied bulking agent for PP-SUI. Cummings et al. initially reported on 19 patients of whom 4 reported good results (defined as dry or occasional pad use) with 7 indicating improved results (defined as 75% subjective improvement) after a mean follow-up of 10.4 months [61]. Martins et al. reviewed 46 cases and found that severe incontinence, prior radiation, and detrusor overactivity were predictors of poor outcomes [62]. A Valsalva leak point pressure (VLPP) of $\geq$ 60 cm H_2O was identified as a predictor of treatment outcome among 31 patients, with 70% of such patients responding favorably while 81% of patients with VLPP < 60 cm H_2O responded unfavorably [63]. Smith et al. found that patients were significantly more likely to improve if the cause of their SUI was transurethral resection of the prostate (TURP) (62.5% improved) versus prostatectomy (35.2% improved) [64].

Collagen bulking has also been compared head-to-head with other treatments for PP-SUI. Kuznetsov compared collagen bulking with AUS and found that AUS provided significantly better social continence rates (75 vs. 20%) and improved quality of life scores after a mean follow-up of 19 months [65]. Importantly, prior collagen bulking may delay but does not seem to affect the efficacy of subsequent AUS insertion [66]. The InVance bone-anchored male sling also outperformed collagen bulking, with 70% of sling patients cured or significantly improved vs. 30% of bulking patients [67].

A variety of other agents have also been studied. Transurethral bulking for PP-SUI was first attempted with polytetrafluoroethlene (Teflon) [68], which showed promising results (50–80% cured or improved) but fell out of favor due to safety concerns about polymer migration [69]. Autologous fat improved continence in only one out of six men studied [48]. Similarly, carbon coated zirconium oxide beads (Duraphere) failed in all eight [70] and hyaluronic acid dextranomer (Deflux) in all four patients studied [52]. Ethylene vinyl alcohol (Tegress) was successful (defined as $\geq$ 50% subjective improvement) for 41% of the 18 patients studied; however, 41% experienced urethral erosion and 22% had severe pain; this product has since been removed from the market [51]. Rahman et al. are the only group to have reported on use of a wrapable bulking agent (porcine derived Surgisis) at the time of AUS replacement, with success in four of five patients after a mean follow-up of 11 months [71].

Polydimethylsiloxane (Macroplastique) remains an option for men with PP-SUI. Kylmala reviewed records from 50 men and found that 60% were cured and 24% improved with an average of 2.42 injections and 7.1 mL of product injected per patient [72]. Polydimethylsiloxane was compared with AUS in a randomized trial of 21 patients with minimal (group 1) and 24 patients with total (group 2) incontinence. Continence (dry) rates favored AUS in both groups (91 vs. 80% in group 1 and 73 vs. 23% in group 2) but the difference was not statistically significant for patients in group 1, leading the authors to recommend a bulking trial only in patients with minimal incontinence [73].

The efficacy of urethral bulking is intuitively dependent on appropriate placement in the continence zone. Unfortunately, there are significant limitations in defining this zone in men with a history of prostatectomy. Degradation of results over time is expected. Extensive counseling regarding the risk-benefit ratio of bulking agents is mandatory so that patients can make informed decisions and that results match expectations.

Stem Cell Therapy

History

Stem cell therapy is an exciting potential treatment modality for urethral sphincter repair. These cells possess unique

capabilities including multipotency (ability to develop into multiple cell types), homing (ability to migrates to sites of injury), and paracrine and autocrine functions that can enhance tissue repair [74]. While embryonic stem cell (ESC) therapies have been plagued by ethical concerns and issues of immunocompatibility and potential for malignant transformation, autologous stem cells (ASCs) have been investigated for use in stress urinary incontinence with promising results. Adipose-derived (ADSCs) and muscle-derived (MDSCs) stem cells have been the primary ASCs studied in this setting.

ASCs are typically obtained via muscle biopsy, isolated and expanded in culture, and subsequently injected into an existing, weakened urethral sphincter. Animal studies using MDSCs injected into female rats have shown that these cells remain in the urethral wall [75] and can lead to increased leak point pressures in animals with prior pudendal nerve damage [76]. Eberli et al. drew similar conclusions from their canine study [77]. Lecour et al. described an alternative method in which intact myofibers that contain satellite precursor cells (MDSCs) under the basal lamina are surgically transplanted into the area of destroyed external sphincters of adult female pigs, with the goal of generating a new urethral sphincter. Their early work has shown that these transplanted cells can lead to the development of an innervated sphincter [78].

The first study of stem cells used for treatment of SUI in humans took place in 2007 but was later retracted due to ethical concerns. Strasser et al. reported on 63 women with SUI randomized to ultrasound-guided transurethral injection of myoblasts and fibroblasts (42 women) or collagen (21 women). Women receiving the stem cells demonstrated significantly higher rates of continence (median baseline incontinence score 6/6, median end score 0/6 for stem cells and 6/6 for collagen), increased urethral sphincter thickness (mean baseline thickness 2.13 mm, mean end thickness 3.4 mm for stem cells vs. 2.3 mm for collagen), and greater urethral sphincter contractility (mean baseline contractility 0.58 mm, mean end contractility 1.56 mm for stem cells vs. 0.67 mm for collagen) 1 year after treatment [79].

Carr et al. first reported on the injection of MDSCs in eight women with SUI in 2008. Four women improved and one was cured after a median follow-up of 16.6 months [80]. They then performed a follow-up dose-ranging study with 38 women treated with low-dose (1–16 × 10(6)) or high-dose (32–128 × 10(6)) MDSCs derived from quadriceps femoris biopsy. Efficacy rates (> 50% improvement in symptoms) were high in both groups and favored the high-dose group for all reported outcomes. There were no serious adverse events [81]. These conclusions were affirmed by a combined analysis of 80 women reporting no serious adverse events and demonstrating a dose-response curve [82]. Three subsequent Phase III studies, as yet unpublished, were designed to evaluate the MDSC product known as autologous muscle-derived cells for urinary sphincter regeneration (AMDC-USR, Cook Medical) via double-blind, randomized, placebo-controlled trials. The first study has been presented in abstract form and indicated a response rate (defined as $\geq$ 50 improvement in incontinence episode frequency) of around 60% over 12 months of follow-up [83, 84]. The pivotal randomized, placebo-controlled Phase III study being conducted at 29 sites in the USA, Belgium, and Germany recently completed enrollment of 311 patients and is expected to be completed in 2020 [85]. The Adaptive Design Study of Autologous Muscle-Derived Cells Compared to Placebo for Female Urinary Sphincter Repair (CELLEBRATE), another multinational phase III trial, will be opening recruitment soon with a target enrollment of 320 patients and an expected completion date of 2023 [86].

Sebe et al. have also evaluated MDSCs for urethral sphincter repair. In this analysis, 12 women were injected and results were reported 12 months [87] and 6 years [88] later. The two women dry at 1 year remained so after 6 years but of five women improved but not dry at 1 year, all worsened over time. Gras et al. studied MDSCs for SUI in 20 uncomplicated and 15 complicated women with SUI and introduced a streamlined, cultureless preparation protocol of simply mincing the biopsy tissue prior to injection [89]. Cure (25 vs. 7%) and improvement (63 vs. 57%) rates favored the uncomplicated group.

Other types of stem cells have been tested in small series of women with SUI. Autologous adipose-derived stem cells were injected into five women, with two reporting continence at 12 months [90]. Human umbilical cord stem cells were injected in 39 women, 72% of whom reported > 50% improvement in symptoms at 1 year follow-up [91].

Use in PP-SUI

Studies of ASC injections for PP-SUI have followed those for female SUI. Mitterberger et al. were the first group to report on the use of MDSCs for PP-SUI. Sixty-three patients were followed for 1 year, with 41 (65%) dry and 17 (27%) improved at the end of follow-up [92]. Gerullis et al. also tested MDSCs in PP-SUI and observed a response in 120/222 patients (26 dry, 94 improved) with a mean time to response of 4.7 months after injection [93]. Gotoh et al. reported on 11 men (9 with PP-SUI and 2 with SUI after HoLEP) injected with ADSCs and followed for 1 year. Eight of these men improved, with an average 60% decrease in 24-h leakage. They also demonstrated increases in urethral closure pressure (35.5 cm H_2O pre and 44.7 cm H_2O post injection) and functional profile length (20.4 mm pre and 26.0 mm post injection) [94]. Another phase I trial of ADSC for PP-SUI demonstrated improvements in 24-h leakage and quality of life scores in all six men treated [95]. The Autologous Adipose-Derived Regenerative Cells for the Treatment of Male Stress Urinary Incontinence (ADRESU) study, a phase I trial of ADSCs for PP-SUI, is ongoing in Japan with 45 patients enrolled and a

planned end date in 2019. The primary outcome is a > 50% reduction in 24-h pad weight [96]. A Phase I and II study to assess the use of the aforementioned AMDC-USR in 30 men with PP-SUI recently closed and results have not yet been reported [97].

Salvage Anti-Incontinence Procedures

Male sling failure can be expected in up to 25–35% of patients [98] and may be managed with observation, insertion of an additional sling with or without removal of the failed sling, insertion of the adjustable suburethral balloon system (ProACT), or insertion of an AUS. The literature addressing the management of these cases is quite limited. Martinez et al. studied salvage sling insertion in 18 patients and found that those with late failure (> 6 months after initial sling insertion) were significantly more likely to be cured after salvage sling than those with early failure (63 vs. 20% at 18 month follow-up) [99]. AUS has proven a viable option after sling explant for erosion or infection [100]. Ajay et al. reviewed records of 61 patients presenting after sling failure, of whom 32 underwent AUS insertion and 29 underwent secondary sling placement. Despite worse incontinence preoperatively, patients in the AUS cohort were significantly less likely to fail their salvage intervention when compared to patients in the secondary sling cohort (6 vs. 55% failure) [101]. Soljanik reported on 29 patients followed for an average of 16.6 months after repeat transobturator male sling placement with fixation and found that 72.4% were using either zero or one dry pad per day [102]. For patients who have failed Virtue quadratic sling placement, the sling can be revised with the addition of imbricating prolene sutures and re-tensioned until the retrograde leak point pressure (RLPP) approximates 60 cm H_2O. The authors suggest this sling revision does not compromise further surgical intervention, such as AUS, if warranted [103]. When comparing repeat AUS vs. adjustable retropubic sling in the setting of failed AUS, Tuygun et al. found that cure and pad reductions were significantly more likely with AUS insertion (5 of 8 patients vs. 1 of 8 patients) [104].

Emerging Anti-Incontinence Techniques

Improving continence rates after radical prostatectomy remains an important goal. Several investigators have recently reported innovative anti-incontinence procedures performed at the time of prostatectomy.

Kojima et al. described a bladder neck suspension procedure in which absorbable suture is passed through the pubic bone periosteum and underneath the vesicourethral anastomosis [105]. Fifty-seven patients were randomized to bladder neck sling (27) or no sling (30). One-hour pad weights and IPSS scores at 4 weeks post-op were significantly lower in the sling group (4.5 vs. 15.5 g and 11 vs. 16, respectively) but did not differ significantly during subsequent follow-up. There were no episodes urinary retention after catheter removal or other post-operative complications in either group.

Cestari et al. have used an autologous vas deferens sling placed beneath the reconstructed rectourethralis prior to vesicourethral anastomosis formation [106]. The sling is tensioned via Cooper's ligament to bring the vesicourethral anastomosis to the pubic symphysis. Among 60 patients randomized to sling or no sling, sling patients had improved mean pad use at 30-days post-op (0.4 vs. 1.1 pads) and were more likely to be pad free through 12 months of follow-up (97 vs. 80% pad free). Operative times did not differ between groups. The vas deferens sling has subsequently been shown by functional studies with urodynamics to increase retrograde leak point pressure to a pre-prostatectomy level [107]. Nguyen and colleagues tested a similar vas deferens sling among 203 patients but did not find significant differences in rates of continence or near continence or in IPSS scores after 6 months of follow-up [108].

Conclusion

Post-prostatectomy incontinence remains a common problem that poses serious quality-of-life consequences for patients and technical challenges for urologic surgeons. Treatment paradigms continue to evolve. Despite modest success rates and limited durations of improvement, synthetic urethral bulking agents remain a frequently utilized treatment modality, especially among urologists not familiar with other anti-incontinence procedures. Stem cell therapies offer the potential for urethral sphincter regeneration and have shown some promising results but remain in the early investigative stage for use in PP-SUI. AUS insertion has been identified as the standard of care after failed male sling. Efforts to minimize incontinence have included surgical innovations at prostatectomy that attempt to raise urethral resistance. Providing novel and durable solutions for men suffering from incontinence after prostatectomy remains an active area of investigation.

Compliance with Ethical Standards

Conflict of Interest Dr. Kaufman serves as Global Principal Investigator for Cook Myosite.

Human and Animal Rights and Informed Consent This article does not contain any published studies with human or animal subjects performed by any of the authors. Dr. Kaufman is the Principle Investigator of the CELLEBRATE trial [86].

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