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Treatment of Severe Urinary Incontinence following Radical Prostatectomy: Experience with Bioceram as a Bulking Agent

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ABSTRACT

Background: To evaluate the efficacy of Bioceram injection in men with severe stress urinary incontinence following radical prostatectomy.

Methods: A total of 18 patients underwent retrograde injection of Bioceram for severe stress urinary incontinence following radical prostatectomy. Evaluation by pad test, international consultation on the Incontinence Questionnaire - Short Form (ICIQ-SF) and American Urology Association Symptom Score - Quality of Life (AUASS-QOL) was performed before and after injection therapy. Patients were considered cured if they were using no pads or only one safety pad per day.

Results: Of 18 patients, 14 had received postoperative external beam radiation therapy. Furthermore, 5 patients required transurethral incision due to simultaneous stricture of the urethrovesical anastomosis. The baseline daily pad count changed from a mean of 6.1± 0.8 to 5.3 ± 1.7 (p = 0.010). None of the patients were cured and only 3 patients showed signs of improvement following injection.

Conclusion: In patients with severe urinary incontinence, treatment with bulking agent injection is associated with modest efficacy.

Keywords: Bioceram, Bulking Agent, Radical Prostatectomy, Urinary Incontinence

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INTRODUCTION:

Urinary incontinence (UI) is a well-known complication of radical prostatectomy (RP) and is associated with a significant negative impact on patients' quality of life (QOL)[1].

Reports on the incidence of persistent post-RP incontinence after 1 year range from 2 to 33% [2-5]. This wide range is dependent on several factors such as patient selection, the experience of the surgeon, the definition of incontinence and method of patient questioning[6]. After this duration, little recovery of continence is expected.

Post-prostatectomy incontinence (PPI) is usually secondary to intrinsic sphincter deficiency (ISD)[7]. ISD occurs as a result of injury to the sphincter mechanism, predominantly during ligation and division of the dorsal vein complex.

About 6-10% of patients who experience PPI require surgical intervention following failure of conservative treatment[8,9]. Common procedures include artificial urinary sphincter implantation (AUS), injectable bulking agents, and male urethral slings. AUS is considered the gold-standard in patients with moderate to severe ISD[10], but the implantation of an artificial sphincter is costly and has significant complications in comparison with endoscopic procedures[11-13]. Injection therapy has been used for many years for the treatment of incontinence following urological surgeries. Various materials including collagen, macroplastique (polydimethylsiloxane), Durasphere (pyrolytic carbon particles) and Teflon (Polytetrafluoroethylene) have been used as bulking agents for the treatment of iatrogenic stress urinary incontinence (SUI) in males, with varying results[14-17].

Over the past decades, bioceramics use in medicine has evolved dramatically, with the production of materials possessing characteristics such as biocompatibility, non-toxicity, and stability in the physiological environment of the body. Recently, two novel bioceramic particles, silica-calcium phosphate, and cristobalite, have been used as bulking agents in animal models[18]. Prior studies have shown that bioceramics stimulate tissue attachment to the porous surface via serum protein adsorption, tissue formation, and cell attachment[19].

Bioceram (Tesla Pharma AG, Windisch, Switzerland) is a ceramic paste, composed of Tri-Calcium-Phosphate suspended in polyethylene glycol 600. It is non-degradable ceramic implant with good biocompatibility.

In the present study, we evaluate the efficacy and safety of Bioceram injection in the treatment of UI following radical prostatectomy.

METHODS:

From May 2015 to October 2016, 18 consecutive patients with a mean age of 60.9 ± 5.2 years (ranging from 53 to 69) were included in the study. All patients suffered from severe incontinence (using more than 4 pads per day) after RP for prostate cancer. The mean duration of incontinence after RP was 20.9 ± 7.3 months (ranging between 12-36 months). Fourteen patients had undergone postoperative radiation to the prostate bed. The interval between radiation therapy and Bioceram injection was at least 1 year.

Preoperative evaluation consisted of history, physical exam and common laboratory tests. Patients did not undergo a urodynamic study; however, those with known neurogenic bladder dysfunction and decreased capacity were excluded from the study.

Preoperative incontinence was assessed by using a pad test and international consultation on the Incontinence Questionnaire – Short Form (ICIQ-SF) as well as the American Urology Association Symptom Score- Quality of Life (AUASS-QOL). The Institutional review board approved the study and all patients provided written informed consent after a thorough discussion of the risks and benefits of the procedure. Early and late complications were recorded. Postoperative parameters (number of pads used daily, ICIQ-SF score and AUASS-QOL score) were compared with baseline

measurements using chi-square and T-test and paired T-test. The Wilcoxon test was used if the variables were not normally distributed. (Postoperative radiation therapy, Urethrovesical stricture, Time elapsed from radical prostatectomy, months) Data analyses were performed using SPSS version 18. P values lesser than 0.05 were considered statistically significant.

Surgical technique

Transurethral retrograde Bioceram injection was done under general anesthesia. All patients received prophylactic fluoroquinolone antibiotics prior to surgery. Antibiotics use was continued for 3 days postoperatively. After passing a 21F rigid cystoscope sheath with a 30-degree lens in the lithotomy position, Bioceram was forced through the needle until it appeared at the tip. The needle was then inserted into the cystoscope channel and the Bioceram particles were injected into the submucosa of the bladder neck, proximal to the striated sphincter at the 5 and 7 o'clock position until coaptation occured. The needle was left in place for at least 30 seconds to allow the material to settle. All patients were discharged on the same day. Patients were followed 1 month after the surgery. Patients were considered cured if they were using no pads or only one safety pad per day.

RESULTS:

Table 1 shows the demographic and baseline characteristics of the patients. All patients received just one retrograde injection. Five patients had urethrovesical stricture that required transurethral incision prior to injection.

The baseline daily pad count decreased significantly from a mean of 6.1 ± 0.8 to 5.3 ± 1.7 (p = 0.010). ICIQ-SF score and AUASS-QOL score changed from 8.6 ± 1.0 and 5.4 ± 0.8 at baseline to 7.9 ± 1.8 and 5.3 ± 1.0, 1 month following the intervention, respectively. However, these changes were not statistically significant. Among 18 patients, 3 showed modest satisfaction and daily pad use decreased from 5±1 to 2±1. We did not observe any improvement in the remaining 15 patients. **Table 2** summarizes changes in pad use, ICIQ-SF and AUASS-QOL scores 1-month after surgery, compared

Table 1. Baseline Characteristics in Study Population

Variables		
Age (mean ± SD)		60.9 ± 5.2
Postoperative radiation therapy		
	No	4 (22.2%)
	Yes	14 (77.8%)
Gleason Score		
	6	3 (16.7%)
	7	10 (55.5%)
	8-10	5 (27.8%)
Urethrovesical stricture		
	No	13 (72.2%)
	Yes	5 (27.8%)
Time elapsed from radical prostatectomy, months (mean ± SD)		20.9 ± 7.3

Table 2. Changes in pad use, ICIQ-SF and AUASS-QOL scores 1-month after surgery compared to baseline

	Baseline	1 month after Injection	P-value
Daily Pad Use	6.1 ± 0.8	5.3 ± 1.7	0.010
ICIQ-SF	8.6 ± 1.0	7.9 ± 1.8	0.070
AUASS-QOL	5.4 ± 0.8	5.3 ± 1.0	0.755

Note: ICIQ-SF, international consultation on Incontinence Questionnaire - Short Form; AUASS-QOL, American Urology Association Symptom Score - Quality of Life

to baseline.

There was no statistically significant association between improvement in continence with the history of radiation treatment, Gleason score, and age. The post-operative course was uneventful and minor complications occurred in 3 patients, including dysuria in 2 and acute urinary retention in one patient which required catheterization. The dysuria responded to conservative management.

DISCUSSION:

PPI represents a bothersome complication of RP. These patients suffer from social and health problems that are associated with a significant decrease in QOL 1.

Knowledge of the natural history of urinary function recovery after RP is important in deciding when and how to proceed with further specialized post-operative management. Silica Calcium Phosphate: Cross-sections of the injection site showed coaptation of the urethral mucosa, with particles located in the submucosa and urethral smooth muscle[18].

There is consensus to postpone evaluation and treatments for UI to at least a year after surgery[14,20]. Conservative management includes limiting fluid intake, avoidance of known bladder irritants and pelvic floor muscle exercises (PFME). Possible side effects of Bioceram injection include acute inflammation and irritative or obstructive urinary symptoms. Surgical treatments are usually not entertained for men with SUI unless conservative treatments fail to produce results. Compared to major surgical techniques, such as placement of an AUS, injection of bulking agents is minimally invasive. However, it is best used for women with mild incontinence[21,22]. Studies addressing the efficacy of transurethral injection of bulking agents are not homogeneous in terms of number of injections and definition of outcome measures; therefore, success rates vary significantly in different studies, from 17 to 38% [23-25].

Most investigators do not consider urethral bulking agents as a durable treatment for male SUI, particularly PPI. Kylmala and colleagues evaluated the effect of macroplastique injections on mild to moderate post-operative SUI in male patients. Of 50 patients only 6 were completely dry after the first injection. A further 40 and 23 patients required a second and third injection, respectively, and a fourth injection was given to 8 patients. They concluded that repeated injections are necessary in order to achieve satisfactory results[26].

The severity of UI also affects the outcome of injection treatment. Smith and colleagues investigated the efficacy of transurethral collagen injection therapy in 62 men with PPI. They found that patients who used 3 or fewer pads had a 50% cure rate at 29 months, whereas those who used more than 3 pads per day had a 28% cure rate[24].

In another study, Cespedes et al. assessed collagen injection therapy for UI in patients who needed 6 pads or

more per day. Cure rate was found to be as low as 29% in this cohort[14].

Likewise, Aboseif et al. evaluated the efficacy of collagen injection in 88 men with ISD. Among 27 patients with severe incontinence, 13 patients showed decline in pad use from more than 4 pads per day (range: 4-10) to less than 5 (3 to 5)[27].

It has been shown that postoperative radiation therapy and interventions such as anastomotic incision worsen the efficacy of bulking agent injection and decrease the likelihood of an effective cure. Stephenson et al. investigated 100 consecutive patients who underwent RP after RT for PCa and found that the rate of urinary continence was 39% at 5 years follow-up[28].

Similarly, Smith et al. showed that of 14 patients who underwent transurethral incision of bladder neck contracture, only 3 responded well to this treatment[24].

In the present study, we noted poor outcomes associated with Bioceram injections. A significant proportion of our patients (77.8%) had received radiation therapy and/or incision of vesicourethral stricture that could explain the compromised success rate. Although we noted a statistically significant decline in pad use from 6.1 ± 0.8 to 5.3 ± 1.7, this change does not seem to be clinically significant.

Radiation therapy results in extensive scarring. Alterations in tissue characteristics impede proper injection of the bulking agent. We also noted significant decrease in compliance of the mucosal tissue, an issue that interfered with agent injection. However, these patients could not be considered suitable candidates for AUS. Insertion of a prosthesis following radiation therapy may result in tissue hypovascularity, atrophy and subsequent severe complications[29,30]. Therefore, we decided to evaluate the efficacy of bulking agents before proceeding to a more invasive approach.

Several limitations exist in this study. First, we did not perform UDS in our patients. UDS can help in distinguishing between detrusor and sphincteric causes of incontinence. However, all male patients in our study had adequate bladder capacity upon cystoscopic examination, and clinical findings were not in favor of neurogenic bladder dysfunction. Second, all patients underwent a single injection in this study. As mentioned earlier, repeated injections might improve the success rate. Due to unsatisfactory results after the initial injection, we did not recommend further injections in our cohort. Other limitations included the single-arm design and relatively small sample size. Comparison between radiated and non-radiated PPI patients with larger sample groups may better show the effect of RT on success rate. Non-degradable agents are hypothetically associated with durable responses; however, in the present study, we were not able to show satisfactory outcomes using a non-degradable material. Furthermore, the high viscosity of Bioceram impeded proper injection in some patients. Future research should focus on finding an ideal injectable biomaterial that is safe, with a durable response and easy to inject.

CONCLUSIONS:

Our findings revealed that injection of bulking agents has limited value in patients with severe UI following RP. Previous radiation therapy and/or incision of vesicourethral stricture may aggravate the severity of UI and increase the rigidity of the injection site; therefore, such patients have poorer outcomes following injection therapy.

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