Treatment of stress urinary incontinence using polyacrylamide hydrogel in women after radiotherapy: 1-year follow-up

Jan Krhut1 · Alois Martan2 · Michaela Jurakova3 · David Nemeč1 · Jaromír Masata5 · Peter Zvara4

Received: 27 May 2015 / Accepted: 18 August 2015 / Published online: 5 September 2015 © The International Urogynecological Association 2015

Abstract
Introduction and hypothesis Information on urethral bulking therapy in women after previous pelvic radiotherapy is lacking. This study compared the safety and efficacy of polyacrylamide intraurethral injections in patients with and without previous radiotherapy.
Methods A total of 46 patients with severe stress urinary incontinence (SUI) were enrolled in this multicenter prospective trial. Group A consisted of 24 patients with previous radiotherapy to the pelvis for the treatment of a gynaecological malignancy. Group B consisted of 22 patients without previous radiotherapy. All patients were treated with a transurethral injection of a bulking solution (Bulkamid). The average follow-up was 12.4 months. The paired Wilcoxon test was used to compare the results before and after the procedure within the groups, and the two-sample Wilcoxon test was used for comparisons between groups.
Results Complete continence was achieved in 25 % of patients in group A and in 36.4 % of patients in group B. Significantly reduced urine leakage was observed in both groups (p=0.0164 in group A and p=0.0002 in group B).

Keywords Pelvic radiotherapy · Polycrylamide hydrogel · Stress urinary incontinence · Urethral bulking

Introduction
Radiotherapy, alone or in combination with radical surgery, for pelvic malignancies often aggravates existing lower urinary tract dysfunction, or leads to de-novo dysfunction, which is frequently associated with stress urinary incontinence (SUI). This condition is a significant therapeutic challenge. Behavioral therapy (including fluid intake regulation, weight loss, reducing caffeine intake) and pelvic floor muscle exercises are first-line treatments. For those who do not respond to conservative therapy, more invasive interventions are available.

The midurethral sling is considered the gold standard for treatment of SUI in women and the efficacy and safety of this method has been well documented [1]. However, information on implantation of a midurethral sling after radiotherapy in women is lacking. Studies evaluating sling therapy in preirradiated men with incontinence after prostatectomy have
been published. They show clear evidence that previous radiotherapy decreases the efficacy of the procedure and increases the complication rate [2]. Based on these observations, it is likely that there is an increased risk of severe sling-related complications (e.g., vaginal or urethral sling protrusion) in women who have previously received radiotherapy.

Submucosal injection of bulking agents is another treatment option for SUI. It is much less invasive than the sling; however, reports on the safety and efficacy of urethral bulking in women after pelvic radiotherapy is lacking. Bulkamid® (Contura International A/S, Soeborg, Denmark) is a biocompatible homogeneous polymer gel consisting of 2.5 % crosslinked polyacrylamide in water. After injection, the gel is invaded by macrophages and giant cells, followed by fibroblasts, ultimately forming a fibrous network. Tissue integration is completed approximately 12 months after injection [3].

The aim of this study was to evaluate the efficacy and safety of Bulkamid in patients who had previously undergone radiotherapy and to compare the outcomes with the outcomes in patients with SUI who did not have previous radiotherapy. This study was designed to test the hypothesis that urethral bulking might be used effectively in patients who have previously undergone radiotherapy of the small pelvis for the treatment of cervical or uterine cancer.

Materials and methods

Patients

A total of 46 women (average age 67.4 years, range 44 – 87 years) with severe SUI were enrolled in this study. Patients with the following conditions were excluded: symptomatic urinary tract infection, mixed urinary incontinence in which urgency incontinence was the predominant factor, clean intermittent catheterization, indwelling catheter, postvoid residual volume more than 200 mL, clinically significant pelvic organ prolapse, diabetic neuropathy, and neurogenic bladder. All patients were informed about the risks associated with the study and each patient provided informed consent. The study protocol was approved by the Ethics Committee of University Hospital, Ostrava. The study was designed in accordance with the principles of the Declaration of Helsinki of the World Medical Association.

Group A consisted of 24 patients who had previously undergone external beam radiotherapy or brachytherapy to their pelvic region. The average interval between the radiotherapy and Bulkamid injection was 92.9 months (range 16 – 384 months). Group B consisted of 22 women with severe SUI after at least one failed anti-incontinence procedure. The average interval between the last anti-incontinence procedure and Bulkamid injection in group B was 68.6 months (range 6 – 264 months).

Study design

The study was designed as a prospective, multicentre study. Subjective, semiojective and objective parameters were evaluated immediately before and 3, 12 and 24 months after treatment. The average follow-up was 12.4 months. Subjective self-assessment was performed using the International Consultation on Incontinence Questionnaire – short form (ICIQ-UI) and the Patient Perception of Bladder Condition questionnaire (PPBC) [4, 5].

Frequency of micturition and functional bladder capacity were evaluated based on a 3-day bladder diary. A 24-h pad weight test was used to assess the total amount of urine loss. The patients were advised to follow their normal daily activities and change their pad every 4 – 6 h during the day. The soiled pads were stored in an airtight bag to avoid evaporation. Pads were weighed in the clinic by a healthcare professional the following day. The weight gain in grams represented the urine leakage in millilitres. A urine culture and local pelvic examination were performed during every study visit to screen for possible complications. The cough test was performed with the bladder filled to 200 mL with the patient in the supine position. It is recommended that the bladder be filled to 300 mL immediately before performing the cough test [6]. However, since the study population consisted of patients with restricted bladder capacity due to previous interventions, we reduced bladder filling to 200 mL. The test was considered positive if any urine leakage during three strong consecutive coughs occurred. Postvoid residual urine was measured using transabdominal ultrasonography. Uroflowmetry, filling cystometry and profilometry of the urethra were used to obtain objective data. The invasive urodynamic evaluation (MMS, The Netherlands) was performed using a 6Ch bladder catheter while the patient was in a supine position, with filling rate determined as one-tenth of the average functional bladder capacity reported in the voiding diary (e.g. 300 mL capacity = 30 mL/min filling rate). A catheter was inserted into the rectum to measure intraabdominal pressure. Both catheters were zeroed against atmospheric pressure at the level of the symphysis according to Good Urodynamic Practice [7].

Procedure

Prior to the procedure, each patient received a single intravenous dose of sulbactam 0.5 g plus ampicillin 1 g (Unasyn 1.5 g) as prophylactic antibiotic treatment. All patients were treated with a transurethral injection of Bulkamid under local anaesthesia, with 4 mL of 2 % lidocaine dissolved in 6 mL of saline injected into the periurethral tissue at the 3 and 9 o'clock positions. Three transurethral injections of Bulkamid were administered submucosally approximately 1 cm distal to the bladder neck at the 2, 6 and 10 o’clock positions using a 23-G needle. The bulks were created under visual
urethroscopic control until complete coaptation of the proximal urethra was observed. The total masses of Bulkmakid injected per procedure was 1.113 mL (group A) and 1.384 mL (group B). Patients were discharged after a successful voiding trial on the first day after the procedure.

Statistical analysis

Data were processed and statistical analyses performed using the Number Cruncher Statistical System. Data are expressed as means ± standard errors of the mean (SEM). The paired Wilcoxon test was used to compare the parameters before and after the procedure within groups, and the two-sample Wilcoxon test was used to compare results between the two groups. A p value of < 0.05 was considered statistically significant.

Results

The patients’ baseline characteristics and baseline urodynamic values are presented in Table 1.

Full continence (defined as a negative cough test) was achieved in 6 of 24 patients (25 %) in group A, and in 8 of 22 patients (36.4 %) in group B. The 24-h pad weight test showed a significant reduction in urine leakage in both groups (−61.5 mL in group A, p = 0.0164, and −197.5 mL in group B, p = 0.0002). The difference between groups did not reach statistical significance (p = 0.0713). Self-assessment using the ICIQ showed a decrease in the total score of 5.2 in group A (p = 0.0000) and 6.36 in group B (p = 0.0001). The difference in this outcome did not reach statistical significance between groups (p = 0.5079). Subjective assessment using the PPBC scale showed a significant decrease in the total score of 1.54 in group A (p = 0.0001) and 2.59 in group B (p = 0.0000), and the difference in this outcome between groups was significant (p = 0.0224).

No significant changes in the urodynamic parameters before and after treatment were observed in either group, except for voided volume (−61.7 mL in group A, p = 0.0069, and −110.1 mL in group B, p = 0.0045), with a significant difference between groups (p = 0.3557) and normal desire to void (−6.1 mL in group A, p = 0.7861, and −32.1 mL in group B, p = 0.0261; not significant difference between groups, p = 0.0883). The urodynamic values are presented in Table 2.

No severe adverse events were noted after the procedure. In total, six adverse events were seen in group A (two patients with urinary tract infection, three patients with de novo urgency, and one patient with an episode of haematuria) and six adverse events were seen in group B (two patients with urinary tract infection, three patients with de novo urgency, and one patient with temporary incomplete bladder emptying).

Discussion

To our knowledge, this is the first study to prospectively assess the safety and efficacy of submucosal injection of a bulking agent for the treatment of SUI in women who have previously undergone irradiation of the pelvis for the treatment of a gynaecological malignancy. External beam radiotherapy of the pelvis is an integral part of the treatment of gynaecological cancers. In addition, brachytherapy is used in some patients with cervical cancer. Despite ongoing technical innovations, radiotherapy may still result in severe, long-term damage to the bladder, urethra and vaginal tissue. The latency time between radiotherapy and the manifestation of late radiotherapy-induced complications can be several decades [8]. Radiotherapy worsens the vascularization of tissues, resulting in hypotrophicity, damage to peripheral innervation, and fibrotic remodelling [9]. Subsequently, there is a loss of bladder capacity and urethral sphincter function. In some patients, a “frozen urethra” can develop after radiotherapy. Lower urinary tract symptoms in irradiated patients are very
common. The most common symptoms are urgency, frequency and urge incontinence due to loss of bladder tissue elasticity and damage to the sensory innervation. Damage to the sphincter often leads to stress incontinence. Mixed incontinence also frequently occurs. The prevalence of urinary incontinence in patients after radiotherapy has been reported to be as high as 53.7 – 80 % [10].

There are no guidelines for treatment of SUI in patients after irradiation of the small pelvis. Because internal sphincter deficiency has a high frequency of occurrence in these patients, the use of a bulking agent seems to be a logical choice for the treatment of SUI. Evidence reported in the literature on this topic is sparse. Radiotherapy is generally considered an exclusion criterion, and previously irradiated patients have not been enrolled in studies assessing the efficacy and safety of bulking agent injections [11]. The efficacy of urethral bulking therapy in patients with SUI, based on both intrinsic sphincter deficiency and urethral hypermobility, has been documented in several studies [12]. Sokol et al. found full continence 1 year after Bulkamid injection in 24 % of SUI patients who had not received radiotherapy [13]. Similar results (25 % continence rate at 1 year) have been reported published by Vecchioni-Scaldazza et al. in 20 patients aged over 80 years [14]. Our results showed that Bulkamid injection in previously irradiated women can provide comparable outcomes.

Some investigators consider the bulking agent therapy as a process and, rather than a single intervention, advocate repeated bulking agent administration to achieve continence [15]. This suggests that the therapeutic potential of this method in patients with complicated radiation-induced damage to the lower urinary tract could be further improved [16]. The main reason that urethral bulking has been avoided in irradiated patients is a concern about safety. In this study, we did not observe any serious adverse events. In addition, adverse events in group A were comparable to those in the control group, as well as those reported in the literature [17, 18].

Although our data suggest that patients who had previously undergone radiation therapy clearly benefited from the treatment with Bulkamid and that this therapy was safe and effective, the small sample size did not allow a definitive conclusion to be drawn from the comparison of its efficacy between the two groups of patients. A significantly greater improvement in the subjective parameters (PPBC) was noted in group B without previous radiotherapy. No statistically significant difference between the two study groups was noted in objective parameters (number of patients achieving full continence and a reduction of urine leakage based on the 24-h pad weight test). However, a trend towards better objective outcomes in group B without previous radiotherapy was noted. This suggests that in a larger study, this difference could reach statistical significance.

In summary, based on these outcomes, we propose that previous irradiation of the pelvis should not be considered a contraindication for the use of Bulkamid periurethral injections. We suggest that this form of therapy is a viable option for this challenging group of patients. A larger randomized multicentre study is, however, necessary to draw a definitive conclusion regarding the efficacy of this treatment in this specific group of patients.

### Conclusion

In our study, the efficacy of urethral bulking therapy using Bulkamid in women with severe SUI, with and without previous pelvic radiotherapy, was comparable with respect to several parameters. The low complication rates observed in both study groups included in this study suggests that pelvic radiotherapy should not be considered a contraindication to urethral bulking therapy. Based on these results, we conclude that urethral bulking therapy is a valuable treatment option for previously irradiated patients with severe SUI.

### Table 2  Urodynamic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>p value</th>
<th>Group B</th>
<th>p value</th>
<th>Difference between groups</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voided volume (mL)</td>
<td>−61.7±104.28</td>
<td>0.0069</td>
<td>−11.0±167.20</td>
<td>0.0045</td>
<td>0.3557</td>
<td></td>
</tr>
<tr>
<td>Maximal flow rate (mL/s)</td>
<td>−4.54±8.23</td>
<td>0.0268</td>
<td>−4.99±11.01</td>
<td>0.0852</td>
<td>0.9737</td>
<td></td>
</tr>
<tr>
<td>Residual volume (mL)</td>
<td>0.63±3.70</td>
<td>0.3397</td>
<td>1.82±5.88</td>
<td>0.1672</td>
<td>0.8954</td>
<td></td>
</tr>
<tr>
<td>First desire to void (mL)</td>
<td>12.32±57.01</td>
<td>0.3605</td>
<td>19.24±128.89</td>
<td>0.7825</td>
<td>0.7003</td>
<td></td>
</tr>
<tr>
<td>Normal desire to void (mL)</td>
<td>−6.11±49.97</td>
<td>0.7861</td>
<td>−32.14±71.33</td>
<td>0.0261</td>
<td>0.0883</td>
<td></td>
</tr>
<tr>
<td>Cystometric capacity (mL)</td>
<td>−8.98±59.18</td>
<td>0.1887</td>
<td>−27.88±62.02</td>
<td>0.0906</td>
<td>0.8950</td>
<td></td>
</tr>
<tr>
<td>Maximal urethral closure pressure (cm H2O)</td>
<td>−4.09±15.57</td>
<td>0.3531</td>
<td>−1.42±14.73</td>
<td>0.7332</td>
<td>0.7666</td>
<td></td>
</tr>
</tbody>
</table>
Acknowledgments Authors thank Josef Tvrdík for the statistical analysis. This study was supported by the Grant Agency of the Ministry of Health, Czech Republic, NT/13509-4.

Conflicts of interest J. Khrut: none
A. Martan: preceptor for Bard, Meditrade; consultant for Astellas
M. Juráková: none
D. Nemec: none
J. Masata: none
P. Zvára: none

References

Springer