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Urinary Incontinence: An Update

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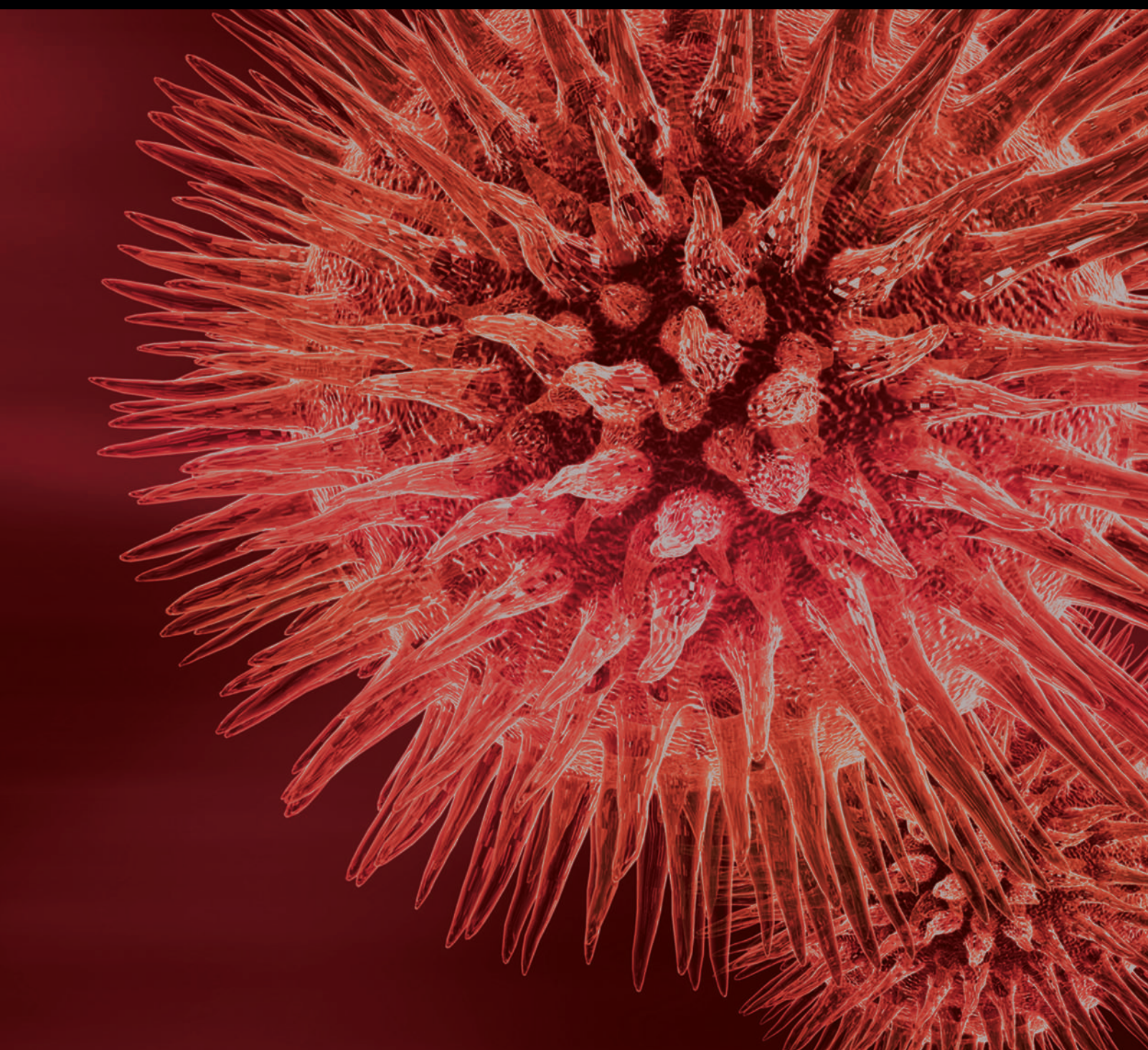

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Editorial

Urinary Incontinence: An Update

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Urinary incontinence is a medical condition characterized by involuntary loss of urine that occurs during the day, or during the night. It is a global health issue which affects 400 million citizens worldwide. There are several forms of urinary incontinence: stress incontinence, urge incontinence, mixed incontinence, and nocturia. Regardless of the form and severity of the condition, it affects patient's daily life, and it can have repercussions on their physical, financial, social, and emotional well-being. Not an irrelevant issue is a negative influence on their sexual health.

It is not a simple condition with straightforward treatment protocols. This condition is also treated by a number of different medical and nonmedical professionals, alone, or as members of a multidisciplinary team. Deciding on a treatment regimen is a multifactorial decision process dictated in part by urinary incontinence subtype and symptom severity.

Our aim as the editors was to cover the problem of urinary incontinence from the gynecological, urological, pediatric, and physiotherapeutic perspective. After careful evaluation of the submitted articles, 9 were selected for publication. All of the articles were either gynecologic (6) or urologic (3) topics.

In a paper by T. Rechberger et al., the authors found that treatment with solifenacin or mirabegron may significantly reduce the incidence of undesired lower urinary tract infections after midurethral sling operation. Therefore, the prevalence of urgency and frequency episodes one week after sling placement were significantly reduced.

In the prospective study by E. Malanowska et al., the authors wanted to figure out if surgical repair with laparoscopic uterine lateral suspension could improve the symptoms of overactive bladder (OAB). In their study the OAB resolution after the procedure was found in 76% of women, while de novo OAB was present in 2.6%.

On the other hand, S. Ciećwież et al. showed in their prospective observational study that "de novo" onset of OAB is more frequent in patients after Burch suspension than in patients after the sling operations, due to the postoperative bladder volume reduction after Burch suspension.

Similar topic was covered by J. H. No et al. They studied the modalities of prediction of OAB in patients following midurethral sling operations (REEMAX). They found out that reduced peak urinary flow rate after the procedure could be a promising and noninvasive metric procedure which could predict the onset of OAB.

The randomized trial performed by M. Ptak et al. showed that the combined training of the pelvic floor muscles (PFM) and the synergistic transversus abdominis muscle improves the quality of life of women with stress urinary incontinence (SUI). The exercises for the PFM and the synergistic muscles give better results in women who have given birth fewer than three times than isolated PFM exercises.

The review article by D. Franic and I. Fistonic made an overview of up-to-date data of laser treatment possibility in women with SUI and genitourinary syndrome of menopause (GSM). They chronologically stressed the evidence based medicine data concerning laser treatment in women with SUI and GSM and precisely showed which women could be the candidate for laser treatment and how important is to

select the women where laser treatment could be a therapy of choice for treating SUI or GSM. Moreover, very important was to introduce the laser as a potential therapy of choice for treating GSM in breast cancer survivors. Nevertheless, they also conclude how important is to follow up the patients after the procedure and emphasized the importance of long-term well-designed prospective studies to disclose the effectiveness of laser in SUI and GSM treatment.

P. Miotla et al. evaluated the effectiveness of a phytotherapic drug (Canephron N) in preventing urinary tract infection in high-risk women undergoing urodynamic studies (UDS). They have showed that prophylaxis of UTI with a phytodrug (Canephron N) may be considered as a good alternative to antibiotic prophylaxis use after UDS in high-risk female patients.

A paper by S. H. Kim et al. describes an alternative option for measuring the total prostate volume (TPV) in patients with colorectal cancer where standard transrectal ultrasonography (TRUS) is not an option. The authors estimated the correlations of the TPV measurements made using computed tomography (CT), magnetic resonance imaging (MRI), and TRUS in 122 patients. They found that, when stratified by a prostate size of 30 mL, TRUS and CT or MRI did not correlate well with the prostate size < 30 mL; however, CT and MRI had a better correlating power for prostate size ≥ 30 mL. The authors concluded that preoperative MRI is the best alternative modality for TPV measurement for the patients who cannot undergo a TRUS assessment.

T. Y. Shin and Y. S. Lee presented a prospective study of 95 patients who underwent robot-assisted radical prostatectomy (RARP) and analysed whether their postoperative continence rates depend on surgical technique of detrusor repair. Standard RARP was performed in forty five patients, and their detrusor was closed by standard approximation of resected detrusor muscle. RARP using novel detrusorrhaphy technique was performed in fifty patients. The point of the detrusorrhaphy technique is "zig–zag" suturing which aims to reconstruct, thicken, and strengthen intraoperatively damaged detrusor in a physiologically and anatomically ideal way. The authors concluded that detrusorrhaphy technique is simple, safe, and feasible, with significantly better outcomes than those achieved with the standard RARP technique in terms of urinary incontinence.

J. van Uhm et al. presented minimally invasive treatment of postprostatectomy incontinence using Opsis, injectable bulking agent. The authors analyzed 10 patients with minimal urine loss (<30gr/24h). Nine patients had unsuccessful treatment, and only one patient improved his incontinence. Moreover, four patients reported complications as urinary frequency and hematuria. This pilot study revealed that treatment of urinary incontinence with Opsis bulking agents is not an effective option and it can lead to the worsening of incontinence symptoms.

We believe that the articles in this special issue give a valuable perspective on different aspects of urinary incontinence.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

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Vladimir Kojovic
Damir Franic

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Review Article

Laser Therapy in the Treatment of Female Urinary Incontinence and Genitourinary Syndrome of Menopause: An Update

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Vaginal birth trauma is the leading cause of stress urinary incontinence (SUI) in women. Also, the process of ageing and hormonal deprivation in postmenopause alters the metabolism of connective tissues and decreases collagen production leading to pelvic floor dysfunction. Noninvasive treatment is recommended as first-line management of urinary incontinence (UI) in women. Surgical procedures are more likely to be implemented to cure UI but are associated with more adverse events. Sex hormone deficiency affects changes also in the lower urinary tract where estrogens are the main regulators of physiological functions of the vagina. In the last decade, laser treatment of SUI and of the genitourinary syndrome of menopause (GSM) has been shown a promising treatment method in peer-reviewed literature. This review's aim is to present the evidence-based medical data and laser treatment of SUI and GSM in an outpatient setting to be a good treatment option, regarding short-term as well as long-term follow-ups. Long-term follow-up studies are needed to confirm that laser treatment is a good, painless outpatient procedure with no side effects in postmenopausal women.

1. Introduction

In the female population, conventional treatments of SUI include noninvasive (pelvic floor muscle training), minimally invasive (bulking methods), less invasive (tape and mesh), and invasive surgical procedures. Less invasive operative techniques are related to >15% of complications (bleeding, erosions, urethral injury, infection, chronic pain, and urinary retention) [1], whereas the conventional surgery relates to anesthesia risks and high recurrence rates (25%) [2].

The association between SUI and collagen is well established. The expression levels of Type I and Type III collagen are significantly lower in patients with SUI when compared to the control group ($p<0.01$) [3], as well as pubocervical fascia of incontinent women [4]. Lack of hormonal support in menopause additionally depletes collagen reserve. That is a possible explanation for the failure of many surgical procedures in urogynecology with a frequent recurrence of symptoms [5].

Scientific and technological progress has led to better clinical outcomes with less invasive procedures with shorter recovery times and lower implicated costs. In this sense, recent evidence supports laser treatment as an alternative and effective intervention for SUI [6].

Almost 50% of menopausal women experienced symptoms of the genitourinary syndrome of menopause (GSM) during their lifetime. [7]. More than one-third of postmenopausal women on systemic hormone therapy (HT) express the symptoms of GSM thus needing additional local estrogen therapy. Therefore, laser treatment might improve the symptoms of GSM especially in women where local estrogen therapy is contraindicated (i.e., breast cancer survivors) [7].

2. Laser Mode of Action

Pulsed laser photothermal energy can improve collagen structure and initiate neocollagenesis in the skin [8] and pelvic floor with nearby tissue [9]. Elevation in temperature up to 63°C increases the contraction of collagen fibers in vaginal epithelium and provokes neocollagenesis, elastogenesis, neoangiogenesis, and increased fibroblast pool, as well [10]. In addition, morphometry showed an increase in the volume density of blood capillaries and the thickness of the epithelial layer [10].

The Er:YAG laser SMOOTH® (Fotona, Slovenia) is a noninvasive nonablative laser procedure for the functional strengthening of connective tissue inside the vaginal wall, improving the pelvic floor support and diminishing symptoms of pelvic floor dysfunction. Er:YAG laser energy is strongly absorbed in water. Therefore, laser pulses achieve controlled heating of the collagen in the deeper mucosa layers (lamina propria), with no ablation or overheating of the mucosa surface, reducing the risk of perforation or accidental lesions of the urethra, bladder, or rectum. The recommended parameters are as follows: laser spot size of 7 mm, the frequency of 1.6 Hz, and fluence (laser energy emitted per unit area) of 6.0 J/cm^2. Mechanical pull of the deeper tissue layers following shrinkage of the upper, photothermally processed tissue layers further contributes to the tightening effect [11]. No general anesthesia is needed. The lower vaginal third and introitus can be covered with a thin layer of anesthetic cream. Treatment regime consists of three sessions 3 to 4 weeks apart. When the process of neocollagenesis is well on its way and assuming the patient Collagen Remodeling Capacity (CRC) is not fully reached during the first session, some previously not affected collagen fibers are additionally captured with the second and third session. Minor side effects include a sensation of warmth, increased vaginal discharge, and only rarely transient urge urinary incontinence [12].

CO_2 laser system MonaLisa Touch® (DEKA, Florence, Italy) is a fractional ablative intravaginal therapy that is delivered once a month for 3 consecutive months. No matter that laser settings could be adjusted according to the age and indication for the procedure, the recommended settings [13, 14] of the microablative fractional CO_2 laser (MFCO2-Laser) are the following: D-Pulse mode, dot power 40 W; dwell time 1,000 μs; and dot spacing 1,000 μm for the treatment of the vaginal canal and the dot power 24 W; dwell time, 400 μs; and dot spacing 1,000 μm for the treatment of the vaginal introitus. The procedure is usually performed in an outpatient setting and does not require any specific preparation or anesthesia. It is recommended to avoid vaginal sexual intercourse for at least 3 days after the laser application in order to prevent an inflammatory reaction which might last up to 48 h.

3. Laser Treatments for Stress Urinary Incontinence

The first pilot study regarding Er:YAG laser in the treatment of female SUI started on September 20th, 2009 [15]. The degree of incontinence and its impact on the quality of life (QoL) were assessed with the self-reported International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form (ICIQ-UI SF) [16], where a maximum score of 21 represented permanent incontinence.

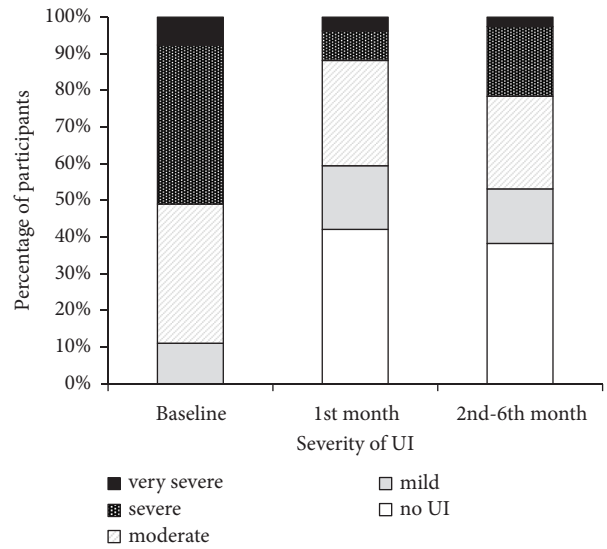

Figure 1: Kloving's categories of ICIQ-UI SF score severity at the baseline and follow-up visits. ICIQ-UI, Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form; UI, urinary incontinence. Reproduced with permission (Taylor & Francis [15]).

At the first follow-up measurement (1 month after the intervention) the number of completely continent patients increased from zero to 17/52 (42.3% continent). At the second follow-up measurement, 2–6 months after the intervention, 18/47 (38.3% continent) had an ICIQ-UI score = 0 (Figure 1). From baseline to the second follow-up, 34/47 (72.3%) participants experienced improvement, whereas 11/47 (23.4%) experienced no change in the ICIQ-UI score, and two (4.3%) experienced worsening of symptoms. No major adverse events were noticed or reported throughout the course of laser treatment and the follow-up period. The rare mild reported symptoms such as slight edema, vaginal discharge, and transient urgency vanished spontaneously after 8 days.

Ogrinc BU et al. published a study on 175 women with newly diagnosed SUI (66%) and mixed urinary incontinence (MUI, 34%) [17], treated according to the uniform Er:YAG laser protocol. Follow-ups were performed at 2, 6, and 12 months after the procedure. The results were based on the Incontinence Severity Index (ISI) and the reduction in ICIQ-UI SF scores. One year after laser treatment, 77% of the SUI patients and only 34% of the MUI remained continent. No difference in the efficacy was noted between pre- and postmenopausal patients.

In another study [18] using the same Er:YAG protocol for SUI, urodynamic studies, pad testing, lower urinary tract symptoms (LUTS), and sexual function were assessed before and after treatment. The authors concluded that the

procedure for mild SUI was effective at 6-month follow-up, but not in the patients with an initial pad weight >10 g. Moreover, it improved LUTS, QoL, and sexual function. Urodynamic values did not differ across the timeline. The authors speculate that this paradox originates from tighter and more elastic collagen that acts as a "hammock," preventing urine leakage and reducing pad weights. Although the follow-up was only up to the sixth month, the authors summarized that IncontiLase™ should not replace mid-urethral sling (MUS) surgery as the standard therapy for SUI patients who fail to improve following first-line therapy. In addition, the authors stressed that the injection of bulking agents has been reported to have a cure rate of 53–73.2%, which is better than the cure rate of 39.3% they achieved at 6 months with IncontiLase™. In conclusion, the authors admitted that, based on its minimally invasive nature and the lack of significant adverse effects, the IncontiLase™ procedure may be used as an alternative therapy for mild SUI cases.

In a long term, a 24-month follow-up study [19] on 114 postmenopausal women suffering from SUI, the vaginal erbium laser (VEL) treatment induced a significant decrease in baseline ICIQ-SF scores of 12.2 ± 2.5. The ICIQ-UI SF scores remained significantly ($p<0.01$) lower than the basal values after 1 (4.8 ± 1.8), 3 (6.2 ± 1.9), 6 (7.0 ± 2.3), and 12 (8.0 ± 1.8) months after the last VEL application. However, the scores after 18 (9.3 ± 2.7) and 24 (9.9 ± 2.8) months from the last VEL application were not significantly different from the baseline values.

Several other observational studies in which Er:YAG was used for mild to moderate SUI also showed improvement in SUI symptoms [20–22]. To date, there is only one patient-blinded randomized controlled trial for SUI [23] consisting of 114 women receiving a single session of nonablative thermal-only Er:YAG laser treatment. This study reports improvement of SUI symptoms, QoL (ICIQ-UI SF), and sexual function (PISQ12 and FSFI) in premenopausal parous women. A 21.4% (12/56) of the laser group patients were continent 3 months after treatment according to ICIQ-UI SF (score = 0) in comparison to only 3.6% (2/56) continence in the sham control group. The covariates age, BMI, and parity had no significant effect on the outcome. All pelvic floor muscle variables, derived from perineometry studies (duration and maximum pressure), showed a significant improvement in the laser group but not in the sham control group.

Carbon (CO_2) laser has been used for GSM treatment, particularly focusing on the vulvovaginal atrophy segment [9]. To date, very few studies regarding CO_2 laser treatment of SUI have been published.

Isaza et al. [24] used the SmartXide2 V2LR fractional microablative CO_2 laser system (MonaLisaTouch™; DEKA, Florence, Italy) in a prospective study on 161 postmenopausal women suffering from mild SUI. The patients received four sessions 30–45 days apart. SUI was evaluated using the 1-h pad test and the ICIQ-UI SF at baseline and at 12, 24, and 36 months. The basal ICIQ-UI SF score (14.34 ± 2.65) significantly decreased at 12 (7.09 ± 1.1, $p < 0.001$), 24 (7.49 ± 0.94, $p < 0.001$), and 36 months (6.76 ± 0.82, $p < 0.001$) of follow-up. The 1-hour pad test reduced from 9.89 ± 0.57 g at baseline to 3.52 ± 1.89 g, 3.55 ± 1.88 g, and 3.72 ± 2.05 g at 12, 24, and 36 months, respectively (all $p < 0.001$). Histology analysis which was done before and 6 weeks after the first treatment showed essentially thicker epithelium with a higher population of intermediate and superficial cell shedding. CO2 laser ablative vaginal treatments could increase the possibility of vaginal scarring and infection. Using the nonablative laser treatment, possible side effects could be reduced [23].

The significant improvement in dyspareunia, dryness, burning, itching, dysuria, urgency, and SUI scores was evaluated in the prospective observational study including postmenopausal women with moderate to severe clinical signs of GSM [25]. The women received intravaginal therapy with CO_2 laser system (MonaLisa Touch®, DEKA, Florence, Italy), once a month for 3 consecutive months. As a secondary outcome, the authors noted that urinary symptoms improved, as the scores of the urinary and QoL questionnaires decreased significantly. ICIQ-UI SF at the baseline was 8.1±5.6 vs. 3.4±4.3 at the 3-month follow-up. All participants showed a > 5-point improvement in the King's Health Questionnaire (KHQ) score, which includes psychometric aspects of UI. The authors concluded that the factors predictive of ideal CO_2 laser therapy candidates were not identified. Considering predictive, preventive, and personalized medicine (PPPM) the current goal is to predict not only the risk of an adverse clinical event but also the benefits [26]. A recent study [27] identified predictors for the segment of patients achieving optimal Er:YAG laser treatment short-term outcomes. The best results after Er:YAG laser treatment of SUI should be expected in younger women (< 47.5 years) with a body mass index of < 23.3, average newborn birth weight of > 3.6 kg, ICIQ-UI at a baseline of < 10, and a perineometer squeeze duration at a baseline of > 3.51 seconds.

However, despite the rigorous selection of patients, laser treatment will not succeed in a certain group. Namely, SUI is induced by urethral hypermobility not only as a result of weakening or disruption of the pelvic floor musculature and/or pubourethral ligament but also due to the weakening of the urethral sphincter, resulting in more severe intrinsic sphincter deficiency (ISD) [28]. The urethral sphincter function depends on the muscular component, the rhabdosphincter, extending along 60–70% of the urethral length, and the mucosal or intrinsic component, extending across the urethra and contributing to urethral closure [29].

Women whose urodynamic studies showed a maximal urethral closure pressure (UCP) of less than 40 cm H_2O received three fractional CO_2 laser treatments four weeks apart in the study of Patel [30]. Post-hoc urodynamic reevaluation, three months after the treatment, showed an increase in maximal UCP of 19-33 cm H_2O to 45-73 cm H_2O.

4. Overactive Bladder

Perino et al. [31] analyzed the effect of CO_2 laser treatment in postmenopausal women with overactive bladder (OAB) symptoms (≥ 8 times micturition/24h) and ≥1 symptoms of GSM (itching, burning, reduced lubrication, and superficial and/or severe dyspareunia) in the previous 3 months. OAB symptoms were assessed using the validated Overactive

Bladder Questionnaire Short Form (OAB-Q SF). The results at a 1-month follow-up after the 3rd laser session indicated a significant reduction of the number of micturitions and the number of urge episodes ($p < 0.0001$). Since atrophy of muscles and reduction of collagen content may be important factors in the increased prevalence of UI, the authors stress that fractional CO_2 laser system can irradiate deeper layers of the vaginal wall, ultimately enhancing tissue tropism and reactivating the extracellular matrix and collagen synthesis, with beneficial effects in the 3 layers of the vaginal wall, in contrast to estrogens or other local therapies that treat the epithelium only.

Besides improvement in SUI episodes using Er:YAG protocol, Tien and coauthors [18] also found a positive effect over OAB, as evidenced by the improvements in Urgency Severity Scale Questionnaire (USS), Overactive Bladder Symptoms Score Questionnaire (OABSS), nocturia episodes, and daytime frequency episodes. Since the majority of women with stress predominant MUI experience significant improvement in OAB symptoms following incontinence surgery [32], the authors speculate that their findings may be at least partly related to SUI improvements following laser treatment.

In patients with SUI, urine leakage into the proximal urethra may stimulate urethral afferents and facilitate the voiding reflex [33]. Lin et al. [34] hypothesized that laser therapy may slightly increase the entire urethral pressure, including proximal urethral pressure, and in turn alleviate OAB symptoms due to a reduction of the bladder reflex response observed in SUI patients. The treatment with Erbium:YAG laser included two sessions. The second session was 4 weeks after the first one. The results concerning OABSS scores were significantly improved after the 3-month follow-up ($p < 0.027$), with particular impact on urinary frequency ($p < 0.001$). Unfortunately, OABSS scores were not equal at the 12-month follow-up. By most patients' report, the optimal therapeutic effect was maintained for the duration of three to six months, similar to the results observed by Fistonic et al. [15] (2-6 months). Neocollagenesis induced by Er:YAG SMOOTH® mode can change the composition of the pelvic floor structures and thus increase the pressure over the entire length of the urethra. In SUI patients, the increased proximal urethral pressure may alleviate OAB symptoms by reducing the bladder reflex response.

5. Nonablative Photothermal Er:YAG Laser and Microablative Fractional CO_2 Laser in SUI Treatment: Differences

Lasers used in SUI treatment emit thermal energy at different wavelengths (Er:YAG 2,940 nm; CO_2 10,600 nm), but they both induce similar changes related to increased tissue trophysm such as retraction of collagen, neocollagenesis, elastogenesis, the enhanced density of connective particles, and neovascularization. CO_2 laser thermal action spreads to the depth of 50-125 μm in the vaginal tissue, causing superficial vaporization. Under the same conditions, Er:YAG laser reaches only 5-20 μm in depth with no ablation at all [9].

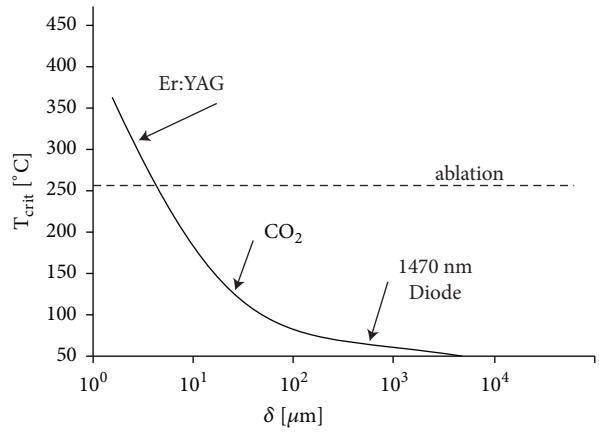

Figure 2: Critical temperature depends on penetration depth. Reproduced with permission (Laser and Health Academy [38]).

Er:YAG laser has 10 to 15 times the affinity for water absorption compared with the CO_2 laser. Mucous membranes have a very high percentage of water, which is a good target for the Er:YAG laser beam. Because of the extremely high absorption in water, the incident photon energy is almost totally attenuated in the first few micrometers of the tissue, producing, at appropriate parameters, a very controlled column of ablation with an extremely narrow band of secondary coagulation. This process has been known as residual thermal damage (RTD) [35]. This translates into shorter downtime with quicker healing and has been the cornerstone for the use of the Er:YAG in full-face ablative laser resurfacing when compared to the CO_2 laser, which has a much larger RTD zone [36]. This was the rationale for Lee to use Er:YAG in the treatment of vaginal relaxation syndrome [37]. The author emphasizes that the depth control associated with the Er:YAG wavelength offers major benefits as ablative damage depth is minimized. Multiple micropulses create a shallow, few μm-thick epidermal windows in the vaginal epithelium with minimal RTD, and subsequent micropulses create a pulse-stacking effect without further ablation, but with thermal build-up down into the lamina propria, increasing the RTD zone. Only Er:YAG laser is characterized by the critical temperature above the ablation temperature, making this laser the safest medical laser for Dual Tissue Regeneration mechanism (DRM) nonablative resurfacing (Figure 2) [38].

Atanasiou et al. [14] stressed, based on the studies by Hutchinson-Colas et al. [39], that Er:YAG laser has a thermal effect only, whereas the $MFCO_2$-Laser has both ablative and thermal effects, thus stimulating heat shock proteins and other factors (e.g., TGF-β), promoting neocollagenesis.

6. Vaginal Microbiota

An effect of laser on vaginal microbiota has been reported by Athanasiou et al. [14]. They assessed the effect of microablative fractional CO_2 laser ($MFCO_2$-Laser) therapy on the vaginal microenvironment of postmenopausal women. The findings suggest that, in their sample of 53 postmenopausal

women with moderate to severe GSM symptoms, the completion of three laser therapies (at monthly intervals) significantly increased Lactobacillus ($p < 0.001$) and normal flora ($p < 0.001$). Those changes consequently decreased vaginal pH from 5.5 ± 0.8 (baseline) to 4.7 ± 0.5 (3^{rd} month, $p < 0.001$). Therefore, the prevalence of Lactobacillus changed from the baseline value of 30% to 79% at three months. Nevertheless, signs and symptoms of bacterial vaginosis or candidiasis did not appear in the participants included in the study. Although significant decreases were observed only in E. coli and Mobiluncus, there was a trend of lower growth of all Lactobacillus antagonists.

The authors suggest that the observed increase in the normal vaginal epithelial cells confirms the results of the histological study of Zerbinati et al. [40] where it was demonstrated that one of the effects of the $MFCO_2$-Laser therapy on the vaginal mucosa was a high degree of epithelial exfoliation, with superficial cells filled with glycogen shedding at the epithelial surface. In conclusion, the authors believed that $MFCO_2$-Laser therapy is a promising treatment for the improvement in postmenopausal vaginal health, aiding the repopulation of the vagina with normally existing Lactobacillus species, and reconstituting the normal flora as that observed in the premenopausal status.

7. Laser Devices in GSM Therapy

Sex hormone deficiency influences many organ systems including the lower urinary tract. The genital tract is particularly sensitive to a decline in estrogen levels and approximately half of postmenopausal women experience the symptoms of vaginal atrophy that affect sexual function and QoL. The clinical manifestations of vaginal atrophy generally occur 4-5 years after menopause and 25-50% of postmenopausal women present with objective changes as well as with individual symptoms. The most common symptoms of vaginal atrophy include dryness (75%), dyspareunia (38%), burning sensation, discharge, and pain (15%) [41]. Discussing the possibility of CO2 laser to restore the vaginal mucosa for GSM in postmenopausal women, Salvatore et al. [42] investigated microscopic, ultrastructural, and biochemical modifications of the postmenopausal atrophic vaginal mucosa. They made mucosal biopsies (before the treatment and 1 hour after it) to find the real impact of CO2 laser on the vaginal mucosa: the epithelium before the treatment did not present any superficial desquamation, and its basal surface appeared relatively smooth. The connective tissue was stained. One hour after the treatment the epithelium was thicker, and the connective tissue penetrated into the epithelial layer constituting newly formed papillae. Also, many penetrating small vessels were observed inside them. This proved the immediate influence of CO2 laser therapy on vaginal mucosa. The newly formed collagen was also increased in the treatment group from 2.18 to 10.52 nm with a slight decrease in thick fibers (old collagen).

Siliquini GP et al. [7] assessed 87 postmenopausal women before and after the treatment using VAS for vaginal dryness and dyspareunia and DIVA (Day-by-Day Impact of Vaginal Ageing) for subjective measures. Objective measures included VHI and VVHI (Vulvo-Vaginal Health Index). The follow-up was done at 4 and 8 weeks and at 3, 6, 9, 12, and 15 months. Multivariate analysis showed that the follow-up time was correlated with better VHI and VVHI ($p<0.001$). DIVA was also improved over time ($p<0.001$). All this implies that CO2 laser treatment of vulvovaginal atrophy significantly improves the symptoms in the long-lasting manner.

Similar results were obtained earlier by Salvatore S et al. [13], using CO2 laser treatment for 12 weeks in 50 women. This was a pilot study using the subjective VAS scale and objective Vaginal Health Index Score (VHIS) scale only. The results showed a statistically significant improvement in vaginal dryness, vaginal burning, vaginal itching, dyspareunia, and dysuria ($p<0.001$) at the 12-week follow-up. A recent study by Athanasiou S et al. [43] assessed the efficacy of microablative CO2 laser therapy in treating GSM in a follow-up period of 12 months using retrospective analysis at baseline and at 1, 3, 6, and 12 months after the last laser therapy. Of the 94 women included in the study, 35 were treated with 3 therapies, 35 with 4, and 24 with 5 laser therapies. All GSM statistical symptoms improved significantly. The results showed that 4-5 laser treatment might be superior in lowering the GSM symptoms than 3 therapies in short- as well as in long-term follow-up.

Gambacciani M et al. [44] introduced the Vaginal Erbium Laser Academy Study (VELAS) in 1500 postmenopausal women including eleven centers in Italy using the same protocol and the same Er:YAG laser technology. All centers used Female Sexual Function Index (FSFI), VAS, and VHI questionnaires for the evaluation of VEL on GSM symptoms. The first results of VELAS study [19] showed that VEL treatment significantly improves GSM at 12 months after the last laser application, whereas the effects decrease afterward. The study confirms that VEL is effective in the treatment of GSM with clinical effects similar to those exerted by the established local therapies.

Gaspar A et al. [45, 46] hypothesized that, by targeting the mucosal component of the urethral sphincter, urethral coaptation could be increased. In a pilot study, they assessed the possibility of a 4-mm intraurethral Er:YAG laser cannula in treating GSM in postmenopausal women (2 lasers sessions 3 weeks apart). The idea was to assess the new technology of using a laser to target the urinary mucosa for the relief of GSM symptoms. The thickness of the urethral mucosa and the vascularization of the submucosa are responsible for its sealing and therefore confer in the continence ability. By using the intraurethral procedure, the continence could be improved by enhancing the urethral tropism. After 3 months, dysuria improved in all the patients, frequency in 97% of patients, and urgency in 93% of patients. The VAS values for dysuria, urgency, and frequency decreased from baseline values 66, 58, and 49 to 8, 13, and 11 after 3 months and 20, 28, and 21 at a 6-month follow-up ($p<0.0005$). ICIQ-UI was also decreased from 13 at the baseline to 5.2 at a 3-month and to 8.1 at a 6-month follow-up ($p<0.0005$). As assessed by a questionnaire addressing QoL (ICIQ-UI SF) and the 1-hour pad test, therapeutic efficacy was measured at 3 and 6

Table 1: Clinical studies using different laser devices for the treatment of UI/GSM.

Author(s)	Laser type	Primary goal	Study type	N	Outcome	Follow-up (months)
Fistonic I, et al. [52] 2012	Er:YAG SMOOTH®	SUI	Obs	39	3.3[1]	6
Fistonic N, et al. [15] 2015	Er:YAG SMOOTH®	SUI	Obs	73	5[1], 38.3[2]	6
Fistonic I, et al. [11] 2015	Er:YAG SMOOTH®	SUI	Obs	31	5.1[1], 32.5[2]	6
Ogrinc BU, et al. [17] 2015	Er:YAG SMOOTH®	SUI/MUI	Obs	175	4.7[4], 62[2]	12
Gambacciani M, et al. [19] 2015	Er:YAG SMOOTH®	SUI/VVA	Obs	19	6.4[1], 11[3],	6
Leshunov E, et al. [21] 2015	Er:YAG	SUI	Obs	37	5[3]	1
Khalafalla MM, et al. [53] 2015	Er:YAG SMOOTH®	SUI	Obs	50		6
Pardo J, et al. [20] 2016	Er:YAG SMOOTH®	SUI	Obs	42	8[1], 38.1[2]	6
Tien YW, et al. [18] 2016	Er:YAG SMOOTH®	SUI/OAB	Obs	35	12[5], 50[2]	6
Pitsouni E, et al. [25] 2016	CO2	GSM/SUI	Obs	35	4.7[1]	4
Perino A, et al.[31] 2016	CO2	OAB	Obs	30		1
Isaza GP, et al. [24] 2017	CO2	SUI	Obs	161	7.5[1]	36
Gaspar A, et al. [45] 2017	Er:YAG SMOOTH®	SUI	Obs	22	10[1], 46[2]	6
Lin YH, et al. [34] 2017	Er:YAG SMOOTH®	SUI/OAB	Obs	30	4.5[1]	3
Lapii GA, et al. [10] 2017	Er:YAG SMOOTH®	SUI	Obs	98	Histology	2
Neimark AI, et al. [22] 2018	Er:YAG SMOOTH®	SUI	Obs	98	73[2]	2
Blaganje M, et al. [23] 2018	Er:YAG SMOOTH®	SUI	RCT	114	4[1], 21[2]	3
Gaspar A, et al. [46] 2018	Er:YAG SMOOTH®	SUI	Obs	29	4.9[1], 14[3], 45[2]	6
Fistonic I, et al. [27] 2018	Er:YAG SMOOTH®	SUI	Obs	85	19[3]	6
Gambacciani M, et al. [19] 2018	Er:YAG SMOOTH®	SUI/GSM	Obs	114	4.2[1]	12
Okui N [51] 2018	Er:YAG SMOOTH®	SUI	Pro	50	11[1], 31[3]	12
Pardo Shanz J, et al. [54] 2018	Er:YAG diode	SUI	Pro	19	8[1], 26.3[2]	3
Samuels JB, et al. [55] 2019	CO2	GSM/SUI	Obs	25	65[2]	12
Lin YH, et al. [56] 2019	Er:YAG SMOOTH®	SUI	Obs	41	3.5[1], 7.1[3], 36.6[2]	6

SUI, Stress Urinary Incontinence; MUI, Mixed Urinary Incontinence; OAB, Overactive Bladder; VVA, Vulvo-Vaginal Atrophy; GSM, Genito-urinary Syndrome of Menopause.
ICIQ-UI, International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; ISI, Incontinence Severity Index; KHQ, King's Health Questionnaire; PIFQ-7, Pelvic Floor Impact Questionnaire; OAB-Q SF, Overactive Bladder Questionnaire Short Form; Obs, Observational; RCT, randomized controlled trial; Pro, Prospective Outcomes.
1: Mean ICIQ score reduction; 2: percentage of the continent after follow-up; 3: mean pad test weight reduction (g); 4: mean ISI score reduction; 5: Mean KHQ (King's Health Questionnaire) score reduction.

months after the procedure. The results evaluated by ICIQ-SF questionnaire showed an improvement by 64% in average, at 3 months, and by 40%, at 6 months. A reduction of the quantity of leaked urine by 59% at 3 months and by 42% at 6 months was evaluated with the 1-hour pad test.

Bearing all these findings in mind we may conclude that intraurethral Er:YAG procedure could be the procedure of choice for the women with incontinence-dominated GSM. However, further randomized face-to-face Er:YAg procedures comparing a vaginal laser with intraurethral laser should be performed to confirm this basic idea.

8. Discussion

This is a nonsystematic review of the literature derived from PubMed database up to March 2019 (Table 1). Keywords "laser" and "urinary incontinence" yield 370 articles. After exclusion for incontinence in male, laser use in surgery, non-laser techniques, and review articles, 24 papers met criteria regarding laser use in women with urinary incontinence. Laser effect in SUI patients was the primary goal in 21 studies, OAB in 1, GSM in 1, and histology in 1 study. A total of 1,452 patients were enrolled at the 1-36-month follow-up (mean 7.04 months). In average 1.9 laser sessions per patient, an average reduction in ICIQ-UI SF scores was 5.9, and an average 1-hour pad test reduction was 16 grams with an average continence rate after laser treatment of 44.5%.

Food and Drug Administration (FDA) position statement on fractional CO2 laser treatment claims that "although there are a number of indications enumerated for this technology, the specific indication for the treatment of vulvovaginal atrophy is not listed" [47] and recent 2018 FDA warns against the use of energy-based devices (EBDs), including laser and radiofrequency devices, to perform "vaginal rejuvenation" or vaginal cosmetic procedures [48]. International Urogynecology Association (IUGA) committee opinion [49] and International Continence Society (ICS) ICS/ISSVD best practice consensus document [50] states that "therapeutic advantages of nonsurgical laser-based devices in urogynecology can only be recommended after robust clinical trials have demonstrated their long-term complication profile, safety, and efficacy" and "at this point, laser is not recommended for routine treatment of the aforementioned conditions

unless part of well-designed clinical trials or with special arrangements for clinical governance, consent, and audit," respectively.

It is obvious that additional studies are needed to explore the long-term safety and efficacy of various laser therapies for genitourinary symptoms. However, a number of prospective observational studies show the effectiveness and safety of vaginal Er:YAG SMOOTH®, confirmed by randomized sham-controlled data [23]. Long-term studies demonstrate that the effects of Er:YAG SMOOTH® treatment are comparable to local hormone treatment [19]. Head to head study by Okui N. [51] showed that Er:YAG SMOOTH® therapy in women improved urinary incontinence as effectively as the tension-free vaginal tape (TVT) and transobturator tape (TOT) procedures. For patients with mixed urinary incontinence (MUI), some in the TVT and TOT groups showed exacerbation; however, all patients in the laser therapy group tended to improve.

9. Conclusion

"Laser" in medicine stands for a number of diverse devices. They radiate different energy at different wavelengths and produce different effects in different tissues.

At the moment there is no available published head to head study with different laser devices for SUI and GSM treatment.

However, long-term well designed prospective studies are still needed to disclose the effectiveness of laser and other EBDs in SUI and GSM treatment.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Assessment of Overactive Bladder after Laparoscopic Lateral Suspension for Pelvic Organ Prolapse

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Background. Pelvic organ prolapses (POP) and overactive bladder (OAB) may coexist and both negatively impact quality of life in women. The correlation between POP and OAB remains unclear, but these patients may have the OAB resolution after the surgical treatment of POP. Aim of our study was to assess the anatomical results and the effect on OAB symptoms in women who underwent laparoscopic lateral suspension for POP. *Materials and Methods*. This prospective study included all women with apical POP who underwent surgical repair with laparoscopic uterine lateral suspension from January 2016 to December 2017. The baseline and the 1-year follow-up included post-void residual measurement, urinalysis, vaginal examination, OAB symptoms evaluation, and administration of questionnaires (PFDI-20, UDI 6). *Results*. 64 women underwent laparoscopic lateral suspension for uterine prolapse and 78.1% had concomitant anterior vaginal wall defect. At 1-year follow-up the anatomic success rates were 84.4% for the apical and 76.2% for the anterior compartment. The comparison between OAB symptoms before and after the surgical procedure showed the resolution of OAB in 76% of the women, while de novo OAB was present in 2.6%. With the questionnaires 95.3% (61/64) of our patients were satisfied after the POP repair. We documented a trend in ameliorating of OAB regardless of the POP-Q stage. However, the Pearson test showed this correlation as statistically significant only in women with anterior vaginal wall defect stage III and apical stage II. No patient had vaginal exposure of the polypropylene mesh. *Conclusion*. Our data show how laparoscopic lateral suspension is an effective procedure for apical and anterior vaginal wall defects. This study provides further evidence for the concept that OAB in women with POP >II stage improves after a successful POP surgery. These women may benefit from a resolution of OAB and POP symptoms with the improvement of patient's quality of life.

1. Introduction

Pelvic organ prolapses (POP) are one of the most common indications to surgery due to their detrimental effect on the quality of life [1, 2]. Overactive bladder (OAB) is also a disturbing common condition defined as the urinary urgency, usually accompanied by increased urinary frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [3].

POP and OAB symptoms are frequently encountered in the same patient [4]. The correlation between POP and OAB remains unclear. A potential cause of OAB may result from mechanical bladder outlet obstruction (BOO) [5]. In Urology it is well-known how in males the benign prostatic hyperplasia may create a chronic bladder obstruction resulting in OAB symptoms [6]. With a similar mechanism a POP may have an obstructive action on the female urethra creating the base to develop OAB symptoms. Indeed, patients may present a spectrum of voiding complaints and symptoms of both OAB and BOO. POP repair usually resolves the mechanical BOO but the effect on OAB symptoms may be unpredictable [7]. However, despite these hypotheses, the relationship between POP and OAB is not clear. If there is a causal relationship it

could be anticipated that OAB symptoms would improve after successful treatment of POP [5]. Therefore, POP surgery may cure or improve OAB, or it can result in de novo OAB [8–10].

Focusing on the upper vaginal compartment prolapses, the vaginal vault prolapse, or the uterine prolapse, several authors reported the effect of the different surgical techniques on OAB. In one RCT, Halaska et al. reported new OAB symptoms after vaginal vault repair with sacrospinous fixation or transvaginal mesh ranging from 9% to 21% [11]. Maher et al. reported de novo OAB after sacrospinous fixation and sacrocolpopexy, respectively, at 20.6% and 33.3% [12]. The first aim of this study was to assess the anatomical results and the effect on OAB symptoms in a cohort of women who underwent laparoscopic lateral suspension for POP.

2. Material and Methods

The study was approved by the Ethics Committee on Clinical Studies of Pomeranian Medical University. This prospective study included all women consecutively referred to our Department from January 2016 to December 2017, with symptomatic apical prolapse who underwent primary surgical repair with laparoscopic uterine lateral suspension.

Objective evaluations were performed with the International Pelvic Organ Prolapse Staging System (POP-Q), and the prolapse was assessed by maximum Valsalva effort in the seated semi-lithotomy position. Subjective assessment was achieved by the Pelvic Floor Distress Inventory Questionnaire (PFDI-20) and Urogenital Distress Inventory 6 (UDI 6).

We offered all patients comprehensive preoperative patient-centered counselling providing them with information and allowing them to participate in the decision-making process as reported in the recent literature [13]. Exclusion criteria were post-void residual volume, posterior vaginal wall defects, previous prolapse or incontinence surgeries, previous hysterectomy, neurological conditions, uncontrolled diabetes, and bladder pain syndrome. Stress urinary incontinence was not an exclusion criterion, but patients were informed that only surgical repair of POP would be done.

All surgical procedures were performed by a senior skilled surgeon (WB). Prophylactic antibiotics were routinely administered intravenously before surgery with 1 g cefazolin i.v. All patients were given low-molecular-weight heparin prophylaxis.

Follow-up was scheduled 12 months after the surgery and performed by a skilled urogynecologist (EM). Objective cure was defined in case of POP-Q sites Ba, C, and Bp as less than -1 cm stage at any point in time of follow-up. Pelvic floor disorders, lower urinary tract symptoms, and digestive symptoms were detailedly recorded. Tract urinary infection was excluded by urinalysis, and trans-vaginal ultrasonography was performed to assess the post-void residual urine evaluation.

OAB was assessed by response to (i) UDI 6 item number 1, (ii) UDI6 item number 2, and (iii) the interview at the follow-up. De novo SUI was assessed by UDI 6 item 3, and stress test.

The use of drugs affecting OAB was investigated and recorded.

Data were entered into the database by one author (EM) and double-checked by another author (AS). Complications were reported according to Clavien-Dindo classification (reference).

2.1. Surgical Technique. All women underwent laparoscopic supracervical hysterectomy. A T-shaped polypropylene mesh was used for the lateral suspension. The body of mesh was fixed to the uterine cervix and to the upper part of the anterior vaginal wall. The arms were introduced retroperitoneally towards lateral abdominal walls, alongside round ligaments. After the prolapse reduction using a posterior blade of speculum placed in the anterior vaginal fornix the mesh was tension-free suspended.

2.2. Statistical Evaluation. Data analysis was performed using the Student t-test, Pearson's correlation, and Gretl Software ver. 2017a. P value less than 0.001 was considered statistically significant.

3. Results

Sixty-four women who had uterine prolapse were consecutively included in the study, 78.1% of these (50/64) had a concomitant anterior vaginal wall defect, and no patient was lost at the follow-up. Demographic characteristics of the population are reported in Table 1.

A mild SUI was present in 21.8% of the population. These women reported the use of no more than one small pad/day.

All surgical procedures were done under general anesthesia. In 2/64 women (3.1%) there was a bladder injury that was resolved intraoperatively by suturing and leaving the urinary catheter for 7 days, rated grade 1 on the Clavien-Dindo classification. Operating time varied between 90 and 260 minutes depending on the number of surgical steps. No associated surgical procedure was done, and no blood transfusion was required. Patients were discharged from the hospital after 4-5 days. No woman had post-void residual requiring clean intermittent catheterization, or indwelling catheter at the discharge from the hospital. Postsurgical pain control was obtained with paracetamol, and no patient required more than 2 days of therapy.

At one-year follow-up the anatomic success rates were 84.4% (54/64) for the apical compartment, and 76.2% (32/42) for the anterior compartment. De novo posterior vaginal wall defect was present in 4.7% (3/64) of the population: one patient developed an enterocele in (1.6%), and two a rectocele (3.1%) (Table 5). The comparison between objective evaluation before and after the surgical procedure is reported in Table 2, whereas symptoms before and after surgery are listed in Table 3.

With the questionnaires 95.3% (61/64) of our patients were satisfied after the POP repair also in case of POP recurrence due to its lower stage at the POP-Q, and 4.7% (3/64) were dissatisfied with the procedure due to a POP recurrence stage like it was before the surgical treatment.

Subjective evaluation showed how 76% of the patients with preoperative OAB had the resolution of symptoms,

Table 1: Patients' characteristics.

Demographics	$n = 64$	
Age (years), mean (±SD)	59.4	(±9.3)
Menopausal status, n (%)	60.0	(93.7)
Systemic HRT at the time of surgery, n (%)	10.0	(15.6)
Body mass index, mean (±SD)	26.8	(±3.5)
Number of vaginal deliveries, mean (±SD)	2.17	(±1.1)
Birth weight of largest baby (g), mean (±SD)	3.74	(±421)
Age at the menopause (years), (±SD)	49.9	(±4.2)
Only uterine prolapse (%)	14	(21.9)
Uterine and anterior vaginal wall prolapse (%)	50	(78.1)

HRT: hormone replacement therapy; *SD*:standard deviation.

Table 2: Objective assessment: preoperative and the follow-up.

POP-Q parameters	Preoperative *Mean* (SD)	Follow-up at 12 months *Mean* (SD)	*P*
Aa	0.80 (±0.95)	-1.69 (±0,89)	<0,001
Ba	1.67 (±1,13)	-1.63 (±1,11)	<0,001
C	-0.06(1.63)	-5.55(±2,53)	<0,001
GH	4.00 (±0.59)	2.77 (±0.75)	<0.001
PB	2.33 (±0.84)	2.66 (±0.62)	<0.006
TVL	10 (±0)	10 (±0)	-
Ap	-0.44 (±1.08)	-1.54(±1,04)	<0,001
Bp	-0.47 (±1,01)	-2.19 (±2,29)	<0,001

POP-Q, Pelvic Organ Prolapse Quantification System.

Table 3: Symptoms before surgery, and at the 12-month follow-up.

	Preoperative *n* (%)	Follow-up *n* (%)	Valuable positive change, *n* (%)	Valuable negative change, *n* (%)	*P*
Bulging	62/64 (96.9)	10/64 (15.6)	52/62 (83.9)	0/2 (0.0)	<0,001
UUI	26/64 (40.6)	10/64 (15.6)	18/26 (69.2)	2/38 (5.3)	<0,001
SUI	14/64 (21.9)	7/64 (10.9)	9/14 (64.3)	2/50 (4.0)	<0,042
Urinary frequency∗	39/64 (60.9)	13/64 (20.3)	27/39 (69.2)	1/25 (4.0)	<0,001
Nocturia (≥ 1)	28/64 (43.7)	1/64 (1.6)	27/28 (96.4)	-	<0,001
Overactive Bladder	25/64 (39.1)	7/64 (10.9)	19/25 (76.0)	1/39 (2.6)	<0,001
Constipation	39/64 (60.9)	22/64 (34.4)	18/39 (46.1)	1/25 (4.0)	<0,001
Sexual activity	37/64 (57.8)	38/64 (59.4)	3/27 (11.1)	2/37 (5.4)	<0,658

UUI, urgency urinary incontinence; *SUI*, stress urinary incontinence, ∗ > 8 times/day.

while de novo OAB was present in 2.6% (Table 4). No patient was under therapy for OAB. To make a correlation between the different stages of POP and OAB, we divided the population into three groups: (i) Group 1 was composed of 11 women with anterior vaginal wall and cervix defect, both stage II; (ii) Group 2 was composed of 31 women with anterior vaginal wall defect stage III and cervix defect stage II; (iii) Group 3 was composed of 22 women with anterior vaginal wall and cervix defect, both stage III. This subanalysis documented a trend in ameliorating of OAB regardless of the POP-Q stage. However, the Pearson correlation showed this correlation as statistically significant only in women of Group II due to the low sample size of Groups I and III (Figure 1). No patient had vaginal exposure of the polypropylene mesh, or complained of urinary tract infections.

Table 5 reports the recurrence and reoperation rates. In this table the two women with postoperatively recurrent cystoceles had a predominant anterior vaginal wall prolapsed (Ba>C) as compared to those with uterine prolapse only (C>Ba).

The analysis of validated questionnaires showed the improvement of symptoms and quality of life as reported in Table 6 and represented in Figure 2.

4. Discussion

In our study data show how laparoscopic lateral suspension with mesh is a feasible and safe technique with good anatomic results at one-year follow-up. Moreover, we documented a strong coexistence of OAB among patients with anterior

Table 4: Overactive bladder symptoms, and stress urinary incontinence at the 12-month follow-up.

	n	%
Overactive bladder symptoms		
Resolution	19/25	76.0
Persistence	6/25	24.0
De novo	1/39	2.6
Stress urinary incontinence		
Resolution	9/14	64.3
Persistence	5/14	35.7
De novo	2/50	4.0

Table 5: Recurrences and reoperation rates.

	n	%
Total recurrences	8	12.5
Anterior vaginal wall recurrences	2	3.1
Apical recurrences	3	4.7
Enterocele recurrence	1	1.6
Posterior vaginal wall recurrences	2	3,1
Need for reoperation	7	10.9

Table 6: Subjective changes measured by validated questionnaires before and after the surgical treatment.

Questionnaires	Preoperative		Postoperative		*P*
	mean	*SD*	*mean*	*SD*	
PFDI20	99.2	± 33.4	16.5	±21.6	<0,001
POPDI6	51.0	± 18.3	4.2	±10.7	<0,001
CRADI8	9.1	± 9.8	4.8	±7.6	<0,001
UDI6	39.1	± 22.3	7.4	±13.3	<0,001

PFDI20, *Pelvic Floor Distress Inventory*; POPDI6, *Pelvic Organ Prolapse Distress Inventory*; CRADI6, *Colorectal-anal distress inventory*; UDI6, *Urinary Distress Inventory*.

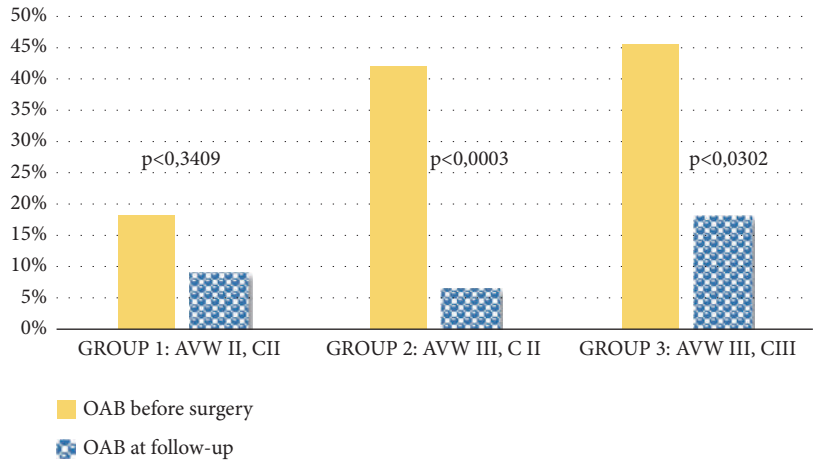

Figure 1: Subdivision of the cohort in three groups according to POP stage and correlation between stages and overactive bladder symptoms before surgery and at the 1-year follow-up. AVW, *anterior vaginal wall*; C, *cervix*; II, *II° stage* POP-Q; III, *III° stage* POP-Q.

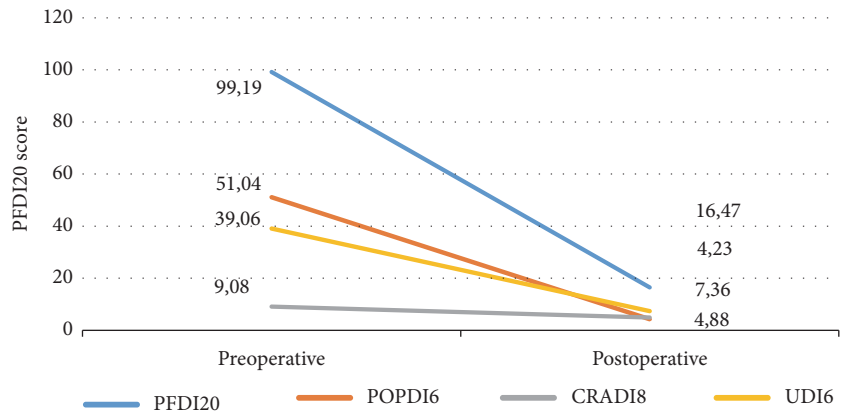

Figure 2: Representation of change before and after surgical treatment at the questionnaires. PFDI20, *Pelvic Floor Distress Inventory*, POPDI6, *Pelvic Organ Prolapse Distress Inventory*, CRADI6, *Colorectal-anal distress inventory*, UDI6, *Urinary Distress Inventory*.

vaginal wall defect and/or apical >2 stage II POP-Q. Before the surgical POP repair 39.1% of the women had OAB with 60.9% reporting urinary frequency ≥8/day, and 43.7% of nocturia. In the current literature the higher incidence of OAB in women with POP is well-known varying between 37 and 50% [14–16]. This provides some epidemiological evidence for the concept that anatomic defect may entail OAB symptoms [17]. Interestingly the prevalence of OAB was greater in women with higher stage POP-Q, but its cure was statistically significant only in anterior vaginal wall stage III and cervix stage II POP. Liedl et al. identified the higher prevalence of OAB in stage 2 POP than those in stages III-IV [18]. Our data showed similar results with a trend of improvement in all the stages of POP but achieving a significant improvement after POP treatment only in anterior vaginal wall stage III and cervix II. These findings confirm also what was reported by Petros who recognized OAB symptoms in Half Way System classification low grade POP and the cure of OAB after POP surgical treatment [19].

Our results support the conclusions of previous studies, which determined that OAB may improve, and even resolve, after successful POP surgery [14, 20–22]. OAB and symptomatic POP negatively impact the quality of life of women. However, these patients with the surgical treatment of POP seem also to have the resolution of OAB. The finding of our investigation is that adequate pelvic floor surgery can resolve OAB.

Considering stress urinary incontinence we documented a 64.3% of resolution probably due to the pre-op mild SUI requiring no more than one small pad/day in the patients who used it. The data of persistent SUI in 1/3 of the patients suggest that a concomitant SUI procedure should be proposed after appropriate counselling. Surprisingly an accurate physical examination did not eliminate the appearance of occult stress urinary incontinence (de novo SUI). The use of an accurate counselling was extremely useful and probably helped to improve the approval of the surgical procedure.

A first limitation of our study was dividing the population into 3 groups to correlate the different POP stages with OAB; we did not gain a sample size, in Groups 1 and 3, able to establish the statistically significant improvement. However, the trends are all in the ameliorating direction and bigger numbers would confirm this data.

A second potential limitation is the 1-year follow-up that would have been better if it had been longer. Nevertheless, it should be considered that 12 months is more than enough time to evaluate the evolution of OAB in patients surgically treated for POP, and it is a sufficient time to evaluate anatomical POP results. Moreover, with a follow-up of 1-year we were able not to lose patients.

Women with POP complain of a vaginal bulge or pressure, but they often report other coexisting pelvic symptoms that affect urinary function. The absence of a bulge during a postoperative pelvic examination does not accurately reflect postoperative patient satisfaction, and the presence of an asymptomatic POP recurrence without bladder symptoms does not necessarily correlate to an unsatisfied patient. For these reasons symptoms affecting bladder function, like OAB, should be investigated before and after the surgical POP repair.

Our study suggests that the surgical treatment of apical descensus and cystocele by laparoscopic lateral suspension resulted in the significant improvement in prolapse, OAB symptoms, and patients' quality of life.

5. Conclusion

Our data show how laparoscopic lateral suspension is an effective procedure for apical and anterior vaginal wall defects. This study provides further evidence for the concept that OAB in women with POP >II stage significantly improves after a successful POP surgery. These women may benefit from a resolution of OAB and POP symptoms with the improvement of patient's quality of life.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Correlation Analyses of Computed Tomography and Magnetic Resonance Imaging for Calculation of Prostate Volume in Colorectal Cancer Patients with Voiding Problems Who Cannot Have Transrectal Ultrasonography

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Objective. To evaluate the value of computed tomography (CT) and magnetic resonance imaging (MRI) in determining total prostate volume (TPV) for patients with colorectal cancer, as an alternative to transrectal ultrasonography (TRUS) of the prostate when TRUS is not an option. *Methods*. We retrospectively evaluated the medical records of 122 male cancer patients who were referred to our urology department between 2014 and 2016 for voiding problems. They underwent colorectal surgery within 3 months; we estimated the correlations of the TPV measurements made using CT, MRI, and TRUS. A total of 122 TRUS, 88 MRI, and 34 CT images were reviewed repeatedly, twice by 2 independent urologists within 1 month after the initial evaluation. The correlations were statistically evaluated using a Bland-Altman plot and Spearman and Pearson correlation analyses. *Results*. Overall median age was 70.5 years and the median TPV, as measured using TRUS, CT, and MRI, was 33.2, 43.4, and 30.1 mL, respectively. There was a good correlation in TPV measured with CT (coefficient >0.7) and MRI (>0.8). There was not a good correlation between TRUS and preoperative and postoperative CT/MRI; preoperative CT/MRI had a higher correlation (>0.7) than postoperative CT/MRI (>0.8). When stratified by prostate volume, preoperative CT (>0.58-0.59) correlated better for <30 mL and preoperative MRI (0.70-0.75) correlated better for ≥30 mL. *Conclusions*. The study showed that preoperative MRI had the best correlation with TRUS, especially in prostates ≥30 mL despite overestimations in CT and MRI measurements compared with TRUS.

1. Introduction

The increasing lifespan and high-calorie intake of the westernized lifestyle have contributed to a rapid increase in the incidence of patients with colorectal cancer (CRC) in Asia [1]. CRC has been reported as the third most common cancer, two times more predominant in men in 2012, and with a 30-40% higher rate of overall survival and mortality than in women [2, 3]. An increasing number of elderly patients with CRC undergo curative surgery to achieve oncologic control as the lifespan expectancy has been prolonged [2–4].

As for male patients with CRC >65 years old, diverse postoperative complications and impaired quality of life have been frequently encountered, such as voiding dysfunction [1]. Bladder dysfunction following colorectal surgery is most commonly related to extirpative procedures in the region of the autonomic pelvic plexus with an incidence rate of 15-50% after surgery [5, 6]. Although the most frequent cause of bladder dysfunction after colorectal surgery is the disruption of the autonomic nerve plexus, up to 40% of elderly male patients with an intact autonomic nerve plexus have predisposing lower urinary tract outlet abnormalities, such as benign prostatic hyperplasia (BPH) [1].

To differentiate patients with bladder dysfunctional due to lower urinary tract obstruction from those with intraoperative autonomic nerve plexus injury, measurement of total prostate volume (TPV) and its degree of obstruction in the lower urinary tract is important. It is typically measured using transrectal ultrasonography of prostate (TRUS) via the anus as well as cystoscopic evaluation [6–8]. Patients who underwent colorectal surgery can only have cystoscopy, as they cannot undergo TRUS until 3 months after surgery [8]. An alternative imaging modality other than TRUS would be needed to evaluate the TPV after colorectal surgery. The therapeutic effectiveness of the bladder dysfunction treatment will be improved if the TPV is correctly estimated and lower urinary tract obstruction can be ruled out using TRUS and other evaluating tools.

Under the circumstances in which TRUS cannot be used, computed tomography (CT) and magnetic resonance imaging (MRI) are other possible measuring tools for imaging of the prostatic anatomy because they are widely used imaging modalities for CRC, preoperatively and postoperatively. Therefore, this study investigated the correlation and reliability of prostate volume measurements by CT or MRI compared with TRUS in patients with CRC who underwent colorectal surgery.

2. Materials and Methods

2.1. Ethical Statement. All study protocols were conducted according to the ethical guidelines of the "World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects." This study was approved by the Institutional Review Board of the Research Institute and Hospital National Cancer Center (IRB No. NCC2016-0277). The requirement for informed consent from all of the patients was waived by the IRB.

2.2. Subjects and Clinical Parameters. From January 2014 to December 2016, 122 patients underwent colorectal surgery and had preoperative TRUS and either CT or MRI or both preoperatively and postoperatively under the discretion of the respective surgeon and according to the type of colorectal cancers. A total of 37 patients had enhanced CT images and 88 had contrast-enhanced MRI images within a 3-month interval after colorectal surgery. Patients were excluded for the following: urethral catheters, diagnosed as having prostate cancer, undergoing previous prostatectomy, neoadjuvant/adjuvant history of chemotherapy, or not having a TRUS-measured prostate volume. Age, height, weight, underlying diseases such as BPH, diabetes mellitus, hypertension, cerebrovascular disease, and others, and radiologic imaging were collected retrospectively.

2.3. Total Prostate Volume (TPV) Measurement. All TRUS procedures and urologic imaging interpretations were performed by a uroradiologist with 15 years of experience. TRUS-measured TPV was calculated by applying the ellipsoid formula: $\pi/6 \times$ [width (cm)] $\times$ [length (cm)] $\times$ [height (cm)]. We considered the TRUS-measured prostate as the true volume of the prostate.

The prostate volume measurement was independently measured by two blinded urologists with 7 years of experience after reviewing CT/MR images (JK Kim and YS Suh). To ensure standardization of measurements, an orientation was conducted by the investigator before the images were reviewed. All the participants were blinded to the TRUS-measured prostate volume results. The length and width of the prostate were measured in axial views, and the height was measured in sagittal views. Prostate volumes measured by CT and MRI were calculated by using the ellipsoid formula: $0.52 \times$ [width (cm)] $\times$ [length (cm)] $\times$ [height (cm)].

2.4. Comparison of CT/MRI and TRUS for TPV Measurement. TPVs were calculated to evaluate the correlation between those measured by CT/MRI and those measured by TRUS. Bland-Altman plots with multiple measurements per subject were performed to compare the two methods. To investigate the effect of prostatic size on the accuracy of the measurements, prostate volumes according to TRUS were classified into 2 categories: ≤30 mL and >30 mL.

2.5. The Reliability of CT Measurement: Inter- and Intrapersonal Variation Test-Retest. To determine inter- and intraobserver reliability tests, the results of the 2 independent interpreters were compared for both the test and retest using an intraclass correlation coefficient (ICC) (Supplementary Table 1). To evaluate the test-retest reliability, the same images were reviewed after 1 month, with the participants blinded to the results of the previous measurements.

2.6. Statistical Analyses. The baseline characteristics were summarized as median (range; minimum-maximum) for continuous variables and frequency (percentage) for categorical variables. Pearson's correlation coefficients were calculated to investigate how TRUS measurements correlated with CT and MRI measurements of TPV. Bland-Altman plots were also used to examine agreement between the CT and MRI measurements and the TRUS value. The closer the mean difference to zero, the better the agreement between the measures. TRUS-measured TPV tends to be overestimated (i.e., the mean difference is greater than zero) or underestimated (i.e., the mean difference is less than zero) compared with TPV measured by CT or MRI. The statistical limits (lower and upper) of agreement using the mean and standard deviation of the differences were presented with the mean difference. The MRI and CT images were reviewed twice by two urologists, as described above. The ICC was used to assess how consistent the estimated prostate volumes are with each other. For all analyses, a p-value less than 0.05 was considered statistically significant and statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA), and R software, version 3.3.3 (R Project for Statistical Computing).

Table 1: Baseline demographics.

Parameter	N(%) or median (range)
Age (years)	70.5 (40.0-90.0)
Benign prostatic hyperplasia, n (%)	20 (16.4)
Hypertension, n (%)	48 (39.3)
Diabetes, n (%)	28 (23.0)
Cerebrovascular disease, n(%)	10 (8.2)
Cardiovascular disease, n(%)	4 (3.3)
Others, n (%)+	21 (12.2)
Preoperative IPSS score, total/QoL^{++}	13.5 (0-35)/ 1 (1-6)
ASA score, 1/2/3	2/101/3 (1.9/95.3/2.8)
Preoperative voiding problem	8 (6.6)
Type of colorectal surgery	
Low anterior resection	68(55.7)
Hatmann (Proctosigmoidectomy)	2(1.6)
Miles operation (Abdominoperineal resection)	5(4.1)
Anterior resection of rectum	15(12.3)
Transanal total mesorectal excision	3 (2.5)
Subtotal- or hemi-colectomy	15 (12.3)
Others	14 (11.5)
Postoperative IPSS$*$	
Symptom Score	19 (10-35)
Quality of Life score	7 (3-7)
Postoperative uroflowmetry	
Maximal flow rate (ml/hr)	49 (9.1-49.1)
Residual urine (cc)	158.5 (0-600)
Time interval between CT/MRI and TRUS (days)	25.0 (12-30)
TRUS-TPV (cc)	25.0 (7.0-191.0)
Pre-CT volume, 1st / 2nd person	43.4 (10.2-131.5) / 42.4 (11.0-123.1)
Post CT volume, 1st / 2nd person	40.6 (30.3-55.0) / 37.3 (31.4-53.6)
Pre-MRI volume, 1st / 2nd person	29.7 (15.1-108.7) / 33.6 (15.8-101.9)
Post MRI volume, 1st / 2nd person	33.0 (11.7-67.1) / 33.1 (15.2-75.1)

+, Others included hepatitis, hyperlipidemia, chronic pulmonary obstructive disease, and asthma;++, only 8 patients completed preoperative IPSS questionnaires; $*$, only 72 and 77 patients completed postoperative IPSS questionnaires and uroflowmetry, respectively; PSA, prostate specific antigen; IPSS, International Prostatic Symptom Score questionnaire; ASA, American Society of Anesthesiologists score; TRUS, transrectal ultrasonography of prostate; CT, computed tomography; MRI, magnetic resonance imaging

3. Results

The median age of the patients was 70.5 years (range, 40.0-90.0 years). The concomitant diseases were as follows: benign prostatic hyperplasia (20 patients, 16.4%), hypertension (48 patients, 39.3%), diabetes (28 patients, 23.0%), and cerebrovascular disease (10 patients, 8.2%). Baseline characteristics, including the type of surgery, preoperative voiding information, and postoperative voiding information are described in Table 1. Only 8 (6.6%) patients had a preoperative history of voiding problems assessed via the voiding symptom questionnaire.

The median TRUS-TPV for all 122 patients was 25.0 mL (range, 7.0-191.0 mL). The median (range) of the preoperative CT volumes measured by the first and second urologists was 43.4 mL (10.2-131.5 mL) and 42.4 mL (11.0-123.1 mL), respectively. The median (range) of the postoperative CT volumes as measured by the first and second urologists was 40.6 mL (30.3-55.0 mL) and 37.3 mL (31.4-53.6 mL), respectively. The median (range) of the preoperative MRI volumes measured by the first and second urologists was 29.7 mL (15.1-108.7 mL) and 33.6 mL (15.8-101.9 mL), respectively. The median (range) of the postoperative MRI volumes measured by the first and second urologists was 33.0 mL (11.7-67.1 mL) and 33.1 mL (15.2-75.1 mL), respectively (Table 1).

The ICCs between the two urologists were all above 0.9. Therefore, based on the ICCs and Bland-Altman plots, the agreement between the two urologists for the pre- and postoperative Ct and MRI measurements was excellent (Supplementary Table 1, Supplementary Figure 1).

Pearson's correlation coefficients were assessed to evaluate whether CT and MRI could replace TRUS when TRUS is not an option. Pre- and postoperative CT and MRI images were reviewed, but for many patients the postoperative images were not measured. Pearson's correlation coefficients for the preoperative measurements were 0.7604 and 0.7787

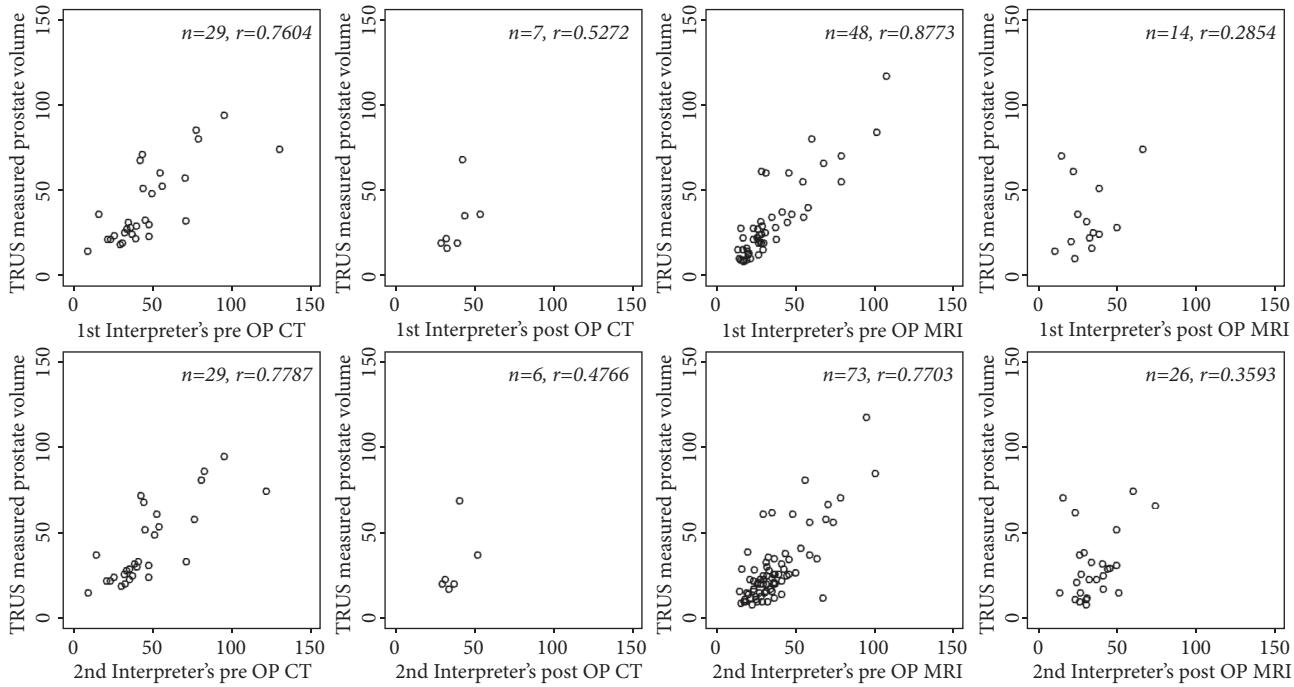

Figure 1: Scatter plot between TRUS total prostate volume and pre- and post-CT/MRI volume.

Table 2: Pearson correlation between TRUS total prostate volume and pre- and post-CT/MRI volume.

		N	Pearson Correlation
TRUS total prostate volume	1st person Pre-CT volume	29	0.7604
TRUS total prostate volume	1st person Post CT volume	7	0.5272
TRUS total prostate volume	1st person Pre-MRI volume	48	0.8773
TRUS total prostate volume	1st person Post MRI volume	14	0.2854
TRUS total prostate volume	2nd person Pre-CT volume	29	0.7787
TRUS total prostate volume	2nd person Post CT volume	6	0.4766
TRUS total prostate volume	2nd person Pre-MRI volume	73	0.7703
TRUS total prostate volume	2nd person Post MRI volume	26	0.3593

(for the first and second urologists, respectively) between the volumes measured by TRUS and CT, and 0.8773 and 0.7703 (for the first and second urologists, respectively) between the TRUS and MRI volumes. The postoperative Pearson's correlation coefficients between TRUS and CT volume were 0.5272 and 0.4766 (for the first and second urologists, respectively), and 0.2854 and 0.3593 (for the first and second urologists, respectively) between TRUS and MRI volume. The preoperative correlations between TRUS and CT and MRI were higher than those for the postoperative measurements (Table 2, Figure 1).

The agreements between CT, MRI, and TRUS were also confirmed using Bland-Altman plots (Figure 2). For the first urologist, the mean (lower, upper limit) differences in the preoperative CT and MRI measurements were -7.17 (-40.33, 25.99) and -5.21(-27.31, 16.9) and for postoperative measurements were -9.73 (-40.29, 20.82) and 1.74 (-41.07, 44.54), respectively. For the second urologist, the mean differences for the preoperative CT and MRI measurements were -7.29 (-38.78, 24.2) and -10.71 (-36.75, 15.33) and for postoperative measurements were -9.23 (-43.7, 25.23) and -7.79 (-45.97, 30.39), respectively. Overall, the TPV measured by CT and MRI tended to be overestimated compared with TRUS.

Subgroup analyses were performed by dividing the TPV measured by TRUS into two groups: <30 mL and ≥30 mL. Although the sample size was reduced when divided into two groups, the correlation between the CT, MRI, and TRUS measurements was still higher preoperatively. In the TPV <30 mL subgroup, TPV measured by CT correlated better with TRUS than TPV measured by MRI. However, TPV measured by MRI had a higher correlation with TRUS than TPV measured by CT when the TPV size was ≥30 mL (Table 3).

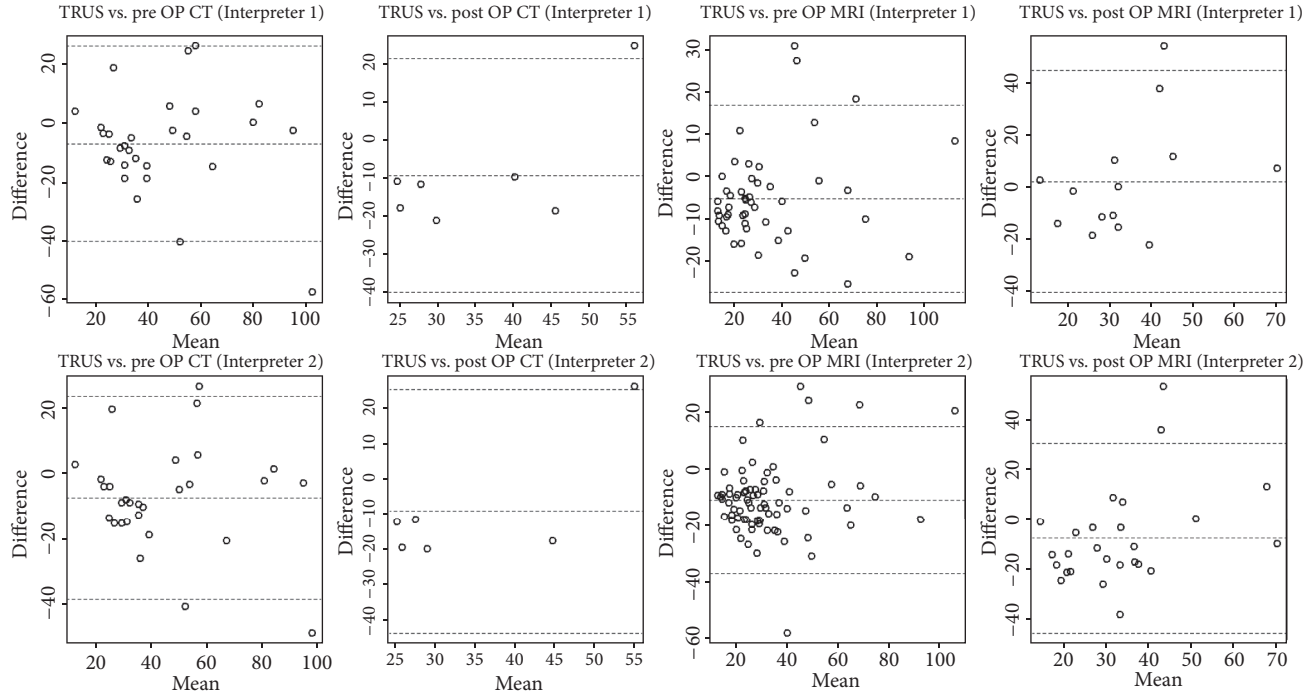

Figure 2: Bland-Altman plot to compare prostate volume according to CT and TRUS.

Table 3: Pearson correlation between TRUS total prostate volume and pre- and post-CT/MRI volume according to the size of prostate volume with a cut-off of 30 gm.

		<30 gm		≥30 gm	
		N	Pearson Correlation	N	Pearson Correlation
TRUS total prostate volume	1st person Pre-CT volume	13	0.6645	16	0.6142
TRUS total prostate volume	1st person Post CT volume	4	-0.0275	3	-0.5782
TRUS total prostate volume	1st person Pre-MRI volume	31	0.5550	17	0.7382
TRUS total prostate volume	1st person Post MRI volume	8	0.7599	6	0.2966
TRUS total prostate volume	2nd person Pre-CT volume	13	0.6532	16	0.6389
TRUS total prostate volume	2nd person Post CT volume	4	-0.2757	2	-1.0000
TRUS total prostate volume	2nd person Pre-MRI volume	52	0.3192	21	0.6925
TRUS total prostate volume	2nd person Post MRI volume	16	0.4399	10	0.1941

4. Discussion

The type of voiding dysfunction after CRC depends on the surgical procedure. The highest incidence of voiding dysfunction (approximately 50%) was reported for abdominoperineal resection and an incidence of 15-20% is reported for low anterior resection [9]. The main cause of postoperative voiding dysfunction is autonomic nerve plexus disruption that requires postoperative interventional management, such as intermittent catheterization, indwelling urethral catheterization, or suprapubic cystostomy.

In addition to the autonomic nerve disruption causes, obstructive lower urinary tract-related voiding symptoms are usually associated with enlargement of the prostate in elderly male patients (60-year-old with 60%, 70s with 70%, and 80s with 80%). These patients do not need any postoperative interventional management but benefit from medical therapies for BPH such as alpha-blockers and surgery to reduce a large TPV [10–13]. Accurate prostate volume determination is useful and critical for those patients with BPH.

Although TPV is not correlated with symptom severity [14], patients with a prostate volume of >40 mL have significant relief of voiding symptoms with a combination therapy of alpha-blockers and 5-alpha-reductase inhibitors; a single alpha-blocker is effective for patients with prostate volume <40 gm [15]. Those patients with a very large prostate volume (> 80 gm) are indicated for surgical prostatectomy, such as Holmium laser enucleation of the prostate or transurethral prostatectomy, rather than medical therapy [16].

TRUS is the standard modality for prostate volume measurement and is a versatile modality with an easy accessibility.

However, TRUS cannot be used under certain conditions, such as when anal strictures are present, or for 2 – 3 months after CRC surgery [1]. In such cases, CT or MRI might be an alternative imaging option to determine prostate volume. However, this study found that neither CT nor MRI have successfully demonstrated a high correlation with the TPV as measured by TRUS in pre- or postoperative settings. This is likely because of the small number of cases and the retrospective design. However, some important clinical findings were observed that suggest that preoperative MRI had the highest correlation with the TPV measurement by TRUS, especially for TPV >30 mL. A large-scale, prospective study would be needed to evaluate the feasibility of preoperative MRI as an alternative modality to TRUS in patients who have undergone CRC surgery.

Many researchers have already tried to define the best alternative modality to TRUS for prostate measurement by analyzing the correlation between CT or MRI and TRUS [17–19]. In a cohort of patients with prostate cancer, Hoffelt et al. showed that CT overestimated the prostate volume as compared with TRUS by up to 50%. Park et al. also compared prostate volume measured by prebrachytherapy CT or MRI with prostate volume by TRUS in patients with prostate cancer, including patients receiving neoadjuvant hormone therapy [20]. They showed that the prostate volume was roughly overestimated by 1.36 times with CT and by 1.33 times with MRI, with a mean difference of 9.05 mL in CT and 6.84 mL in MRI. Therefore, MRI was more closely correlated with the TRUS, similar to the finding in this study. Kang et al. overestimated the prostate volume by 8.4% compared with TRUS in patients with lower urinary tract symptoms [21].

Few studies have reported the correlation of prostate volume in patients without prostate cancer, and no reports have been made for patients with CRC. It has been suggested in previous studies that CT and MRI are inaccurate for prostate imaging, similar to this study in which we identified a weak correlation coefficient of less than 0.8, except for preoperative MRI (correlation coefficient, >0.8) (Table 2) [22, 23].

However, TRUS is a subjective and operator-dependent modality influenced by the size of the prostate gland. The actual gland size can be over- or underestimated, according to the size of the pathological specimen [24]. Bienz et al. have shown that TRUS underestimates the prostate volume when the prostate is smaller in size, and overestimates the volume when the prostate is larger; however, the measurements were more accurate for larger prostates, similar to the findings in this study (Table 3) [24]. We found that, when stratified by a prostate size of 30 mL, TRUS and CT or MRI did not correlate well (correlation coefficient 0.3-05 for prostate size < 30 mL, Table 2). The CT and MRI had a better correlating power (0.5-0.7) for prostate size ≥30 mL (Table 2).

This overestimated TPV as measured by CT or MRI is explained by an inherent error rate of the CT ellipsoid formula and the low soft tissue resolution around the prostate and the intraprostatic anatomy [25]. To enhance the exact volume calculation, step-section planimetry is regarded to be a more accurate method for the measurement of prostate volume [26–29]. However, it is more time consuming than the easily usable ellipsoid formula and requires the use of special equipment that it is not useful in a clinical setting. Eri et al. have shown that the simple ellipsoid formula was only marginally inferior to step-section planimetry [30]. Another accurate modality suggested by Jeong et al. was planimetry using the 3-dimensional reconstruction method in MRI [26]. However, it is more expensive, and MRI is usually not indicated for purposes such as routine check-ups. In this study, the prostate volume on axial and coronal views was used with the ellipsoid formula of width x height x length x $\pi/6$, because the axial and coronal views, or only the axial view, may be the only CT/MRI images available for calculation in real clinical settings.

The postoperative prostate measurement was smaller than the preoperative TPV measurement and a wider range of different volume measurements was detected using CT in this study (Table 1). One of the possible explanations is that removal of the mass by CRC surgery might affect the shape of the prostate anatomically, such that the prostate had been compressed and deformed by the colorectal mass. Another explanation might be that the inflammation and edema in the periprostatic tissue and the prostate resulted in preoperative overestimation of the TPV. After removal of the cancer and postoperative antibiotic management, the inflammatory and edematous prostate decreased to its normal size and repositioned to its normal anatomic shape to result in a decreased prostate volume measurement. Lastly, removal of periprostatic tissue by intraoperative adhesiolysis during CRC surgery causes prostatic atrophy or disappearance of periprostatic overenhancement. Adhesiolysis of the perimesorectal to periprostatic tissue and the prostatic capsule are needed to achieve free movability of the colon for the anastomosis to the anus in transanal total mesorectal resection where the periprostatic tissue was removed and appeared postoperatively.

This study has a few limitations, such as a retrospective design with a small number of cases and different types of colorectal procedures, as well as use of the ellipsoid equation to calculate volume. The different types of colorectal surgery might have an influence on the different rates and types of voiding problems, postoperatively. However, this study gave important clinical clues for the treatment of bladder dysfunction in elderly male patients with CRC after surgery. The necessity and importance of preoperative assessment of voiding suggests that clinicians need to plan the postoperative management of patients with voiding dysfunction by differentiating obstructive lower urinary tract disease from other etiologies. A simple voiding questionnaire, uroflowmetry, and serum prostatic specific antigen test are enough to predict patients with a high risk of voiding problems at outpatient clinics and TRUS can then be performed preoperatively. However, further prospective-designed studies with large numbers of patients according to the type of colorectal surgery will be needed for the evaluation of the appropriate imaging modalities for TPV measurement and to determine the efficacy of preoperative voiding assessments for postoperative obstructive lower urinary tract disease.

5. Conclusions

As patients undergoing CRC are predominantly elderly men, preoperative MRI is the best alternative modality for TPV measurement, even though it overestimates it when the TPV is > 30 mL, for these patients who cannot undergo a TRUS assessment.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author (Kang Hyun Lee, uroonco@ncc.re.kr; 5@ncc.re.kr) on reasonable request. The IRB and ethical committee of the National Cancer Center (in Korea) will review the requests because of the patients' information. After the approval of the committee with confirmation of the reasonable requests, the dataset will be freely available. The other contact e-mail besides the corresponding author's e-mail is irb@ncc.re.kr.

Conflicts of Interest

The authors have declared that no competing interests exist.

Supplementary Materials

Supplementary 1. Supplementary Table 1: (A)interpersonal variation test (intraclass correlation coefficient between 1st person and 2nd person).

Supplementary 2. Supplementary Figure 1: Interpreter 1 vs. 2.

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Research Article

Does Pharmacological Treatment Reduce the Incidence of Lower Urinary Tract Symptoms (LUTS) after Transobturator Sling?

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Aim. Lower urinary tract symptoms (LUTS) frequently affect patients immediately after midurethral sling (MUS) placement. The objective of the study was to assess if solifenacin or mirabegron decreases incidence of LUTS in women who underwent transobturator MUS. *Methods*. A prospective randomized trial was conducted on patients undergoing ambulatory transobturator midurethral sling due to stress urinary incontinence (SUI). All participants were questioned before and after surgery for occurrence of bothersome LUTS. A total of 328 patients who underwent transobturator MUS were randomly assigned to one of three groups: prophylaxis with 10 mg of solifenacin, prophylaxis with 50 mg of mirabegron, or without any additional treatment. LUTS evolution and efficacy of solifenacin and mirabegron were analyzed based on results of assessments made during follow-up visits at 1 and 6 weeks after surgery. Comparison of the prevalence of LUTS was done using chi^2 test. *Results*. Prevalence of urgency and frequency episodes increased notably 1 week after sling placement and then came down to baseline levels. Solifenacin and mirabegron significantly reduced the incidence of urgency after 1 week, but after 6 weeks the beneficial effect was observed only in case of solifenacin. Treatment with mirabegron reduced the percentage of patients suffering from frequency after 6 weeks. Although prevalence of nocturia did not raise after sling placement, both treatments significantly reduced the incidence of this complaint after 6 weeks. Pharmacological treatment did not modulate the course of hesitancy and terminal dribbling. *Conclusions*. Treatment with solifenacin or mirabegron may significantly reduce the incidence of undesired LUTS after MUS.

1. Introduction

Lower urinary tracts symptoms (LUTS) encompass a broad group of symptoms affecting proper storage of urine and effective self-controlled urination. These bothersome symptoms are categorized as storage, voiding, or postvoiding [1]. The steadily increased number of midurethral sling procedures performed to treat female stress urinary incontinence with or without concomitant prolapse surgery has resulted in a definite rise in the number of iatrogenic LUTS caused by anatomical obstructions of the urethra [2]. Moreover, even without obvious bladder outlet obstruction, a majority of women after sling procedures are transiently suffering from undesired LUTS [3]. In fact, reported rates of various voiding dysfunction vary between the different sling placement techniques, which include retropubic and transobturator sling passage and the different sling materials used, as well as patient and surgeon factors [4]. Even if, after sling surgery, the long-term retention rate (defined as catheter dependency for >28 days after surgery) varies between 1 to 10%, other voiding or storage dysfunctions are generally underreported—probably due to the fact that happy-to-be-dry patients might not be compelled to report minor voiding dysfunctions [5].

Keeping this in mind, there is no doubt that a considerable percentage of the LUTS in women encountered after sling procedures are, in fact, iatrogenic in nature [6]. The temporal relationship between surgery and the onset of new LUTS is the most important diagnostic issue [4]. These new undesired symptoms can vary tremendously and can be as

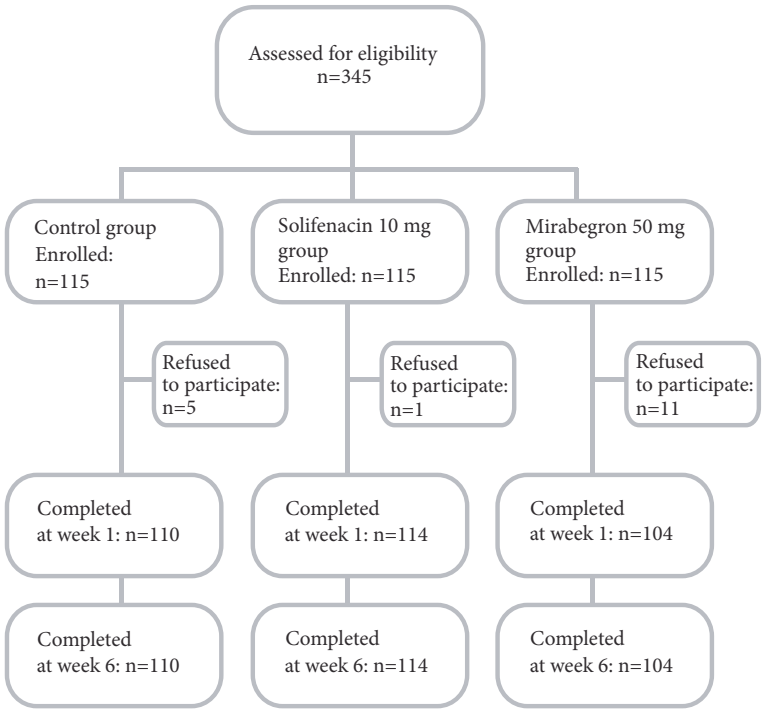

Figure 1: Flowchart of the participants in the study.

nonspecific as urgency and frequency, spraying and splitting, or findings of low-flow voiding on noninvasive uroflowmetry with increase of PVR in sonographic investigation. Even if surgeons and patients should anticipate a period of transient voiding dysfunction during postoperative recovery, every effort should be undertaken in order to decrease the percentage of undesired LUTS after incontinence surgery and, subsequently, to increase patient satisfaction.

Since the LUTS after MUS procedures are very bothersome for the patients and negatively affect their quality of life, we tested the hypothesis whether short-term prophylaxis with solifenacin or mirabegron introduced in the very early postoperative period may alter the incidence of postoperative LUTS.

2. Materials and Methods

The study protocol was approved by our local institutional ethical committee and all patients gave written informed consent before inclusion. Out of 630 patients with stress urinary incontinence treated in our department from October 2014 to January 2018, 345 agreed to participate in this study. Women were eligible for the study if they had symptoms of SUI as assessed via a positive cough test either in the supine or standing positions at bladder volume of approximately 250-300 ml and had a voiding frequency of 7 times or less per day, a bladder capacity ≥250 ml, postvoid residual (PVR) ≤ 50 ml without clinically relevant pelvic organ prolapse (POP-Q ≤1) [7]. Study exclusion criteria were the evidence of obstructed voiding in the absence of prolapse and previous pelvic surgery. Patients were questioned before and after surgery for occurrence of storage symptoms (urgency, increased day time frequency, nocturia) as previously described [3]. In patients who reported urgency at baseline, urodynamic testing was performed to exclude detrusor overactivity, and only those without detrusor overactivity during filling cystometry were included in this study. We consider the presence of undesired urgency if occurred at least 3 times daily or more before micturition but without uncontrolled urinary leakage. Nocturia was defined as 2 or more voiding episodes during nighttime.

Based on these criteria, the study was conducted on a group of 328 women who underwent an ambulatory transobturator midurethral sling (MUS) procedure with additional tape fixation as previously described [8]. Patients received a day preceding surgery single dose (3 gram) of fosfomycin trometamol orally as a standardized antibiotic protocol.

Before discharge, the patients were assessed via ultrasonography (postvoid residual and tape position) and uroflowmetry to exclude the possibility of bladder outlet obstruction. Simple randomization was used from pseudorandom numbers generated by a computer to allocate patients into the study groups in a ratio of 1:1:1. Investigators A.Z. and E.R. were not involved in the surgical procedures, but they were responsible for the randomization process. After randomization, but before surgery, 17 patients resigned from participation in this study: 5 from control group, 1 from the solifenacin group, and 11 from the mirabegron group (Figure 1). The remaining patients were then allocated into 3 study groups:

(1) without any additional treatment (control group, n=110),

Table 1: Demographic characteristics of patients groups.

Variable	Control group (n=110)	Treatment group 1 (10 mg of solifenacin) (n=114)	Treatment group 2 (50 mg of mirabegron) (n=104)
Age (years)	55.5 (±11.3)	54.6 (±13.1)	53.6 (±12.2)
BMI (kg/m^2)	27.3 (±3.3)	27.0 (±3.7)	26.8 (±4.2)
Postmenopausal n, (%)	73 (66.4)	69 (60.5)	61 (58.7)
Parity	1.9 (±1.0)	1.9 (±1.0)	1.7 (±1.2)

There was no statistically significant difference between all investigated groups.

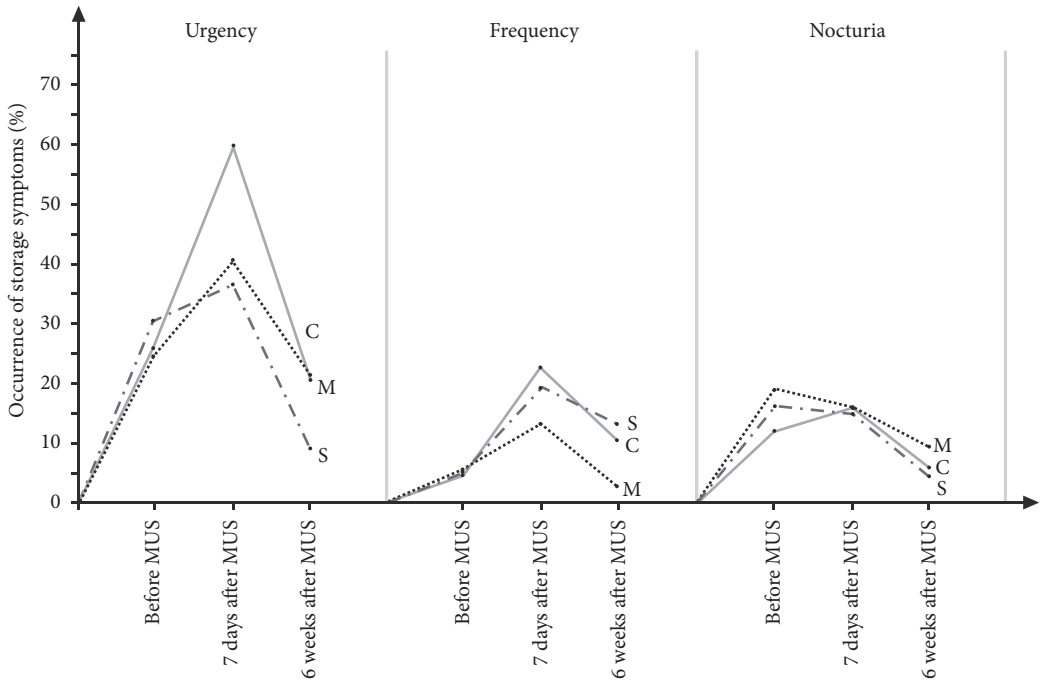

Figure 2: The evolution of storage symptoms after midurethral sling surgery in control (C), treatment with mirabegron 50 mg (M), and treatment with solifenacin 10 mg (S).

(2) prophylaxis with 10 mg of solifenacin taken orally once daily for 4 weeks (n=114),

(3) prophylaxis with 50 mg of mirabegron taken orally once daily for 4 weeks (n=104).

Follow-up visits were conducted by phone-call at one week, while an office-based examination occurred at 6 weeks after surgical intervention.

The sample size calculation was based on a previous study showing 52% incidence of urgency 1 week after sling placement [3]. To detect the decrease of urgency incidence by half, the sample size required for an alpha 0.05 and a power of 90% was 70 participants.

Statistical analyses were performed with Statistica package version 12.0 (StatSoft Inc., Tulsa, OK, USA). A p value <0.05 was considered statistically significant. The Chi-squared test was used as statistical test applied to sets of categorical data to evaluate how likely it is that any observed difference between the sets arose by chance. Interim analysis of data obtained from 65 patients in the control group and 56 in the treatment group showed that, for urgency occurrence, 50 participants in each group would be enough to reach more than the 95% power of chi^2 at a 2-sided significance level of 0.05 for each group. For comparison of continuous variables (age, BMI, parity) ANOVA with post hoc tests and the Student's t test were applied. Continuous variables are presented as the mean ± SD.

3. Results

Demographic and clinical data did not differ between investigated groups (Table 1).

At baseline, the incidence of LUTS did not differ significantly between the investigated groups. The evolution of storage symptoms in all studied groups is presented in Figure 2.

In all groups, the occurrence of urgency rose significantly 1 week after sling placement and then came down to baseline

Table 2: The evolution of urgency in the course of the study.

Variable	Baseline n (%) [B]	Week 1 n (%) [W1]	Week 6 n (%) [W6]	Statistical analyses inside each group
Control group (n=110) [C]	29 (26.4)	66 (60.0)	23 (20.9)	B *vs.* W1, p <0.001 B vs. W6, NS W1 *vs.* W6, p <0.001
Treatment group 1 (10 mg of solifenacin) (n=114) [S]	35 (30.7)	43 (37.7)	11 (9.7)	B *vs.* W1, NS B vs. W6, p < 0.001 W1 *vs.* W6, p < 0.001
Treatment group 2 (50 mg of mirabegron) (n=104) [M]	26 (25)	43 (41.3)	23 (22.1)	B *vs.* W1, p<0.05 B vs. W6, NS W1 *vs.* W6, p<0.005

Baseline: C vs. S (NS); C vs. M (NS); S vs. M (NS).
Week 1: C vs. S (p <0.001); C vs. M (p <0.001); S vs. M (NS).
Week 6: C vs. S (p<0.05); C vs. M (NS); S vs. M (p<0.05).

Table 3: The evolution of frequency in the course of the study.

Variable	Baseline n (%) [B]	Week 1 n (%) [W1]	Week 6 n (%) [W6]	Statistical analyses inside each group
Control group (n=110) [C]	5 (4.5)	25 (22.7)	12 (10.9)	B *vs.*W1, p <0.001 B vs. W6, NS W1 *vs.* W6, p <0.05
Treatment group 1 (10 mg of solifenacin) (n=114) [S]	6 (5.3)	22 (19.3)	12 (10.5)	B *vs.*W1, p <0.005 B vs. W6, NS W1 *vs.* W6, NS
Treatment group 2 (50 mg of mirabegron) (n=104) [M]	6 (5.8)	15 (13.6)	3 (2.9)	B *vs.*W1, p <0.05 B vs. W6, NS W1 *vs.* W6, p <0.005

Baseline: C vs. S (NS); C vs. M (NS); S vs. M (NS).
Week 1: C vs. S (NS); C vs. M (NS); S vs. M (NS).
Week 6: C vs. S (NS); C vs. M (p<0.05); S vs. M (p <0.05).

levels, or, as in the solifenacin group at the end of the study, was lower, in comparison with baseline evaluation. Both treatment regimens significantly reduced the incidence of urgency after 1 week, but after 6 weeks, this beneficial effect was observed only in case of solifenacin (Table 2).

Similarly to urgency, in all groups, the incidence of frequency rose noticeably after 1 week. At week 6, the percentage of patients suffering from this complaint was significantly higher in the control group and lower in the mirabegron group when compared to baseline (Table 3).

We did not observe any increase in the incidence of nocturia after sling placement. In fact, in all groups a notable drop in the prevalence of this symptom was found at final assessment. At week 6 in both treatment groups, the incidence of nocturia was significantly lower in comparison with the baseline. Indeed, comparisons between study groups did not show any significant differences (Table 4). In contrast, incidence of voiding symptoms (hesitancy, terminal dribbling) rose noticeably after MUS and remained more frequent at week 6, when compared to baseline evaluation. Pharmacological treatment, either with solifenacin or mirabegron, did not modulate the course of these symptoms (Table 5).

4. Discussion

Over the last decade, a dramatic rise in the use of midurethral synthetic slings has been reported due to its high clinical efficacy accompanied by technical simplicity, and minimal patient morbidity. However, the increase in midurethral procedures that has been observed around the world is accompanied by a varied proportion of de novo postoperative voiding dysfunctions manifested by increased voiding times, decreased maximum flow rates (Qmax), increased mean detrusor pressure (Pdet), increased detrusor pressure at maximal flow, increased mean urethral resistance, and elevated postvoid residual volumes [9–12].

Moreover, many women, even with urodynamic stress incontinence, often demonstrate other lower urinary tract symptoms (LUTS) including frequency, nocturia, and urgency [13]. The estimated prevalence of these symptoms among women suffering from urinary incontinence varies from 29 to 69% [14]. Nevertheless, most studies on SUI solely focus on the cure of incontinence after midurethral sling placement rather than the effect of these procedures on coexistent or de novo arising LUTS. To the best of our

Table 4: The evolution of nocturia in the course of the study.

Variable	Baseline n (%) [B]	Week 1 n (%) [W1]	Week 6 n (%) [W6]	Statistical analyses inside each group
Control group (n=110) [C]	16 (14.5)	18 (16.4)	8 (7.3)	B *vs.* W1, NS B vs. W6, NS W1 *vs.* W6, p <0.05
Treatment group 1 (10 mg of solifenacin) (n=114) [S]	19 (16.7)	17 (14.9)	5 (4.4)	B *vs.* W1, NS B vs. W6, p <0.005 W1 *vs.* W6, p <0.01
Treatment group 2 (50 mg of mirabegron) (n=104) [M]	20 (19.2)	17 (16.3)	10 (9.6)	B *vs.* W1, NS B vs. W6, p <0.05 W1 *vs.* W6, NS

Baseline: C vs. S (NS); C vs. M (NS); S vs. M (NS).
Week 1: C vs. S (NS); C vs. M (NS); S vs. M (NS).
Week 6: C vs. S (NS); C vs. M (NS); S vs. M (NS).

Table 5: The evolution of hesitancy and terminal dribbling.

Variable	Hesitancy				Terminal dribbling			
	Baseline n (%) [B]	Week 1 n (%) [W1]	Week 6 n (%) [W6]	Statistical analyses inside each group	Baseline n (%) [B]	Week 1 n (%) [W1]	Week 6 n (%) [W6]	Statistical analyses inside each group
Control group (n=110) [C]	11 (10)	45 (40.9)	29 (26.4)	B vs W1 chi^2=27.7 p<0.001 B vs W6 chi^2= 9.9 p=0.017 W1 vs W6 chi^2 = 5.2 p =0.022	2 (1.8)	43 (39.1)	23 (20.9)	B vs W1 chi^2=47 p<0.001 B vs W6 chi^2= 19.9 p<0.0001 W1 vs W6 chi^2 = 8.7, p =0.0033
Treatment group 1 (10 mg of solifenacin) (n=114) [S]	11 (10.6)	48 (46.2)	32 (30.8)	B vs W1 chi^2=15.8 p<0.001 B vs W6 chi^2=5.2 p=0.022 W1 vs W6 NS	2 (1.9)	48 (46.2)	32 (30.8)	B vs W1 chi^2=31.1 p<0.001 B vs W1 chi^2=23.5 p<0.0001 P1 vs P2 NS
Treatment group 2 (50 mg of mirabegron) (n=104) [M]	13 (11.4)	38 (33.3)	26 (22.8)	B vs W1 chi^2 =32.4 p<0.001 B vs W6 chi^2= 12.9 p=<0.0001 W1 vs W6 chi^2=5.2 p=0.023	2 (1.8)	32 (28.1)	26 (22.8)	B vs W1 chi^2 =57.1 p<0.001 B vs W6 chi^2= 31.6 p<0.0001 W1 vs W6 chi^2=5.2 p=0.023

Baseline: C vs. S (NS); C vs. M (NS); S vs. M (NS).
Week 1: C vs. S (NS); C vs. M (NS); S vs. M (NS).
Week 6: C vs. S (NS); C vs. M (NS); S vs. M (NS).
Pharmacological treatment did not modulate the course of these symptoms.

knowledge, this is the first randomized trial focused on active pharmacological prevention of undesired LUTS after transobturator sling placement among SUI sufferers.

The ideal timing of an intervention for undesired voiding dysfunctions after incontinence surgery has not been clearly established since transient voiding dysfunction, including urinary retention, may be seen during postoperative recovery. In our preliminary recently published study, we clearly show that in the first 6 weeks after MUS, more than 60% of all women will experience some undesired LUTS which negatively influence their quality of life [3]. As these LUTS are probably inherently connected with this type of surgical

intervention, all patients should be informed that such undesired symptoms could occur in the first few weeks after intervention, but will probably undergo natural resolution within few months after surgery [15]. In the past, several attempts have been undertaken in order to predict the probability of voiding dysfunction occurrence after sling placement based on preoperative and intraoperative variables. Even if, as in the SISTEr trial, sole focus was upon patients with dysfunctional emptying after sling procedure, the authors of such studies did not identify any preoperative predictors of voiding dysfunction, whereas other studies have suggested that altered preoperative detrusor contractility can predict postoperative sling obstruction with concomitant unwanted LUTS [16–19].

In the TOMUS trial, iatrogenic obstruction leading to LUTS following sling surgery was more likely to occur after retropubic slings placement rather than the transobturator route, although, overall, this was an uncommon event [19]. High-grade pelvic organ prolapse might also have a role in post-op voiding dysfunction by contributing to voiding obstruction, but this was not the case in our study since we only included patients without concomitant POP [20].

The prevalence of iatrogenic LUTS after MUS surgery is very common regardless of type of surgery, yet, symptoms severity, including urinary retention, urgency, urgency incontinence, hesitancy, straining to void, weak stream, nocturia, frequency, and UTI, could be different depending on the study population. The method of treatment can vary according to physician or patient preference and can include temporary intermittent catheterization, indwelling catheterization, pharmacological management, biofeedback therapy, urethral dilation, and office-based sling loosening [4].

Based on the literature data, it seems that in a majority of patients, some transient undesired LUTS after MUS procedures are simply unavoidable; however, simple, short-term pharmacological intervention can decrease the percentage nearly by half. There is no doubt that the best solution would be to identify patients with increased risks of developing undesired LUTS after MUS before the operation and, only in these, introduce prophylaxis with either anticholinergics or mirabegron. Still, as clearly shown before, the patient's preoperative history is only minimally useful in the identification of women at increased risk for the development of urgency, with the exception of the complaint of increased daytime frequency, which is a very common symptom among SUI patients [21].

It was also shown that the finding of increased detrusor pressure during the filling phase of cystometry on preoperative conventional urodynamics in particular may help identify (but, not at 100%) women at increased risk for postoperative de novo urge incontinence following a minimally invasive midurethral sling procedure. Nevertheless, proper identification of patients at increased risk of developing undesired LUTS after surgery would help to individualize preoperative counseling regarding expected outcomes and patient's satisfaction with their surgical procedure [22].

We understand that our study also has several limitations. First of all the single setting of this randomized trial and the exclusion of patients who had underwent any other types of midurethral slings (retropubic or single incision). The obvious limitation is also the fact that patients were aware of types of pharmacological intervention since we used pharmaceuticals already available on the market and that we tested only one antimuscarinic medication. The reasons for our choice of solifenacin were that this drug is reimbursed in Poland and it has relatively good clinical efficacy in reducing urgency, with relatively low side effects when compared to other antimuscarinics [23]. On the other hand, the strengths of our study were the prospective nature of this trial and the relatively large number of women in the study (exceeding by almost twice the calculated number in order to reach statistical power of the study). Of note, all participants had undergone standardized preoperative evaluation using standard ICS recommendations, met standard high-quality operative procedures performed by a high volume experienced surgeon (T.R.), and experienced continuous follow-up almost without drop-out.

5. Conclusions

Based on the results of this study, we can conclude that short-term pharmacological treatment (4 weeks) either with anticholinergic (solifenacin) or β-3-adrenergic receptor agonist (mirabegron) could significantly decrease the percentage of undesired LUTS (namely, urgency and frequency) after transobturator midurethral sling surgery.

Data Availability

The data used to support the findings of this study are included within the article.

Disclosure

An abstract (#213) with preliminary results of this study was presented at Scientific Podium Short Oral Session at the 48th Annual Meeting of the International Continence Society, Philadelphia (USA), 28-31 August 2018.

Conflicts of Interest

Tomasz Rechberger, Andrzej Wrobel, and Pawel Miotla serve as speakers for Angelini, Astellas, and Bionorica. Alicja Zietek, Ewa Rechberger, Beata Kulik-Rechberger, and Michal Bogusiewicz have no conflicts of interest. The authors did not receive any support from the listed companies to conduct the study.

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Research Article

Detrusorrhaphy during Robot-Assisted Radical Prostatectomy: Early Recovery of Urinary Continence and Surgical Technique

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Robot-assisted radical prostatectomy (RARP) has largely replaced open radical prostatectomy as the standard surgical treatment for prostate cancer. However, postoperative urinary incontinence still persists and has a significant impact on quality of life. We report the superior results of the detrusorrhaphy technique during RARP that helps achieve early continence. Our prospective study involved 95 consecutive patients who underwent RARP between March 2015 and May 2017; fifty patients underwent RARP using the new detrusorrhaphy technique (group 1) and 45 underwent standard RARP (group 2). The postoperative oncological and functional outcomes were compared between the two groups. The postoperative continence was assessed at 0 day, 1 week, 4 weeks, 8–12 weeks, and 6 months after catheter removal. Continence was defined as the use of no pad over a 24 h period. Mean operative time in groups 1 and 2 were 250 and 220 min, respectively. Intraoperative complications were not encountered in any patient. The continence rates after catheter removal in groups 1 and 2 were 68% and 0% at 0 day, 78% and 17.8% at 1 week, 86% and 64.4% at 4 weeks, 92% and 73.3% at 8–12 weeks, and 100% and 91.1% at 6 months, respectively. In the multivariate analysis, the nerve sparing technique, D'Amico risk groups, and prostate volume were involved in the early recovery of urinary continence. The detrusorrhaphy technique is simple, safe, and feasible, which helped achieve earlier continence. It showed significantly better outcomes than those achieved with the standard RARP technique in terms of urinary incontinence. Nevertheless, our findings need to be validated in further studies.

1. Introduction

Over the last decade, robot-assisted radical prostatectomy (RARP) has been increasingly adopted as a surgical treatment option for patients with localized prostate cancer [1, 2]. RARP achieves excellent oncological outcomes and is associated with a low risk of complications [3, 4]. Posttreatment quality of life (QoL) of patients with prostate cancer with respect to the recovery of urinary and sexual function has been an important area of study over the last decade. In particular, incontinence, temporary or permanent, is the most troublesome adverse complication of prostatectomy [5]. The incidence of incontinence at 12 months after surgery is estimated to range from 69% to 96% and can markedly impair the QoL of patients, particularly of those who are younger and more active [6]. However, this long recovery period is troublesome and psychologically distressful for patients. Moreover, it also has financial implications because of the need for medications and additional surgical procedures, such as the placement of a sling, urethral bulking agents, or an artificial urinary sphincter [7].

Many surgical adaptations that hasten continence recovery have been published. Various techniques have been used as long as oncological outcomes are not compromised [8–11].

We identified and implemented key operative techniques during RARP that are essential to achieve early continence in a step-wise manner. First, we preserved the periprostatic structures, such as the endopelvic fascia, deep dorsal vein, and puboprostatic ligament. Second, we performed dissection of the vas deferens, seminal vesicles, and pedicles using athermal means and with no or minimal clipping. Third, we secured maximum length of the urethra and performed the detrusorrhaphy technique, which is a zigzag flap of detrusor muscles. Herein, we present the detrusorrhaphy technique to achieve earlier recovery of urinary continence and assess the postoperative outcomes.

2. Materials and Methods

2.1. Study Design. This is a prospective study involving 95 consecutive patients who underwent RARP between March 2015 and May 2017; fifty patients underwent RARP using the new detrusorrhaphy technique (group 1) and 45 underwent standard RARP (group 2). Our prospective study was planned by dividing the groups with and without the detrusorrhaphy technique (50:50) among 100 consecutive patients, and the order numbers are summarized based on the previously prepared random number table. The random number table was applied sequentially to the patients who permitted the consent form. In group 2, there were 5 missing values. Due to their personal issues, two patients withdrew their consents after the operation, and three of the patients from the other country could not follow up and manage after our surgical treatment. The enrolled patients were divided into two subgroups in group 1 (enrolled numbers 1–25, 26–50) and group 2 (enrolled numbers 1–23, 24–45) according to a time criterion to compare the learning curve. The data were collected in a customized database and analyzed. The study protocol was approved by the University Hospital Ethics Committee. Indications for RARP are identical to those for open prostatectomy. RARP can be performed in patients with prostate cancer who have clinical stage ≤ T3b (seminal vesicles invasion) disease with no clinical or radiographic evidence of metastasis. Exclusion criteria were patients who received prior radiation therapy and those with a previous history of urethral stricture and urinary incontinence. One surgeon (YS LEE) with an experience of > 500 RARPs performed these surgeries.

2.2. Surgical Technique. Ninety-three patients underwent transperitoneal RARP, and two patients who had a prior history of abdominal operation underwent extraperitoneal RARP. Patient position and port placement were standard and are previously described [11]. We described the main surgical steps of RARP.

2.2.1. Preservation of the Endopelvic Fascia. After exploration of abdominal cavity, we first dissect the intestines adhered to the abdominal wall. This is to ensure visibility during the operation by keeping the intestines away from the pelvic cavity. After clearance of the retropubic space, the outline of the prostate is identified and the periprostatic fatty tissues are removed as much as possible. The endopelvic fascia is preserved for those with clinical stage ≤ T2c disease. However, in patients with clinical stage T3 disease and suspected periprostatic invasion, the endopelvic fascia is incised.

2.2.2. No Ligation of the Deep Dorsal Vein. The deep dorsal vein complex (DVC) is not sutured. Instead, it is incised with cold scissors prior to the dissection at the prostatic apex and urethra. Incision of the DVC leads to moderate bleeding; however, the bleeding typically stops after removal of the prostate.

2.2.3. Athermal Dissection of the Vas Deferens and Seminal Vesicles. The vas deferens and seminal vesicles are dissected athermally using clips. The posterior layer of the Denonvilliers' fascia is incised in an inverse U shape in the proximity of the prostate gland to the prostatic apex area.

2.2.4. Complete Intrafascial Nerve Saving Technique. The main purpose of approach to prostatic dissection is cancer control and functional recovery. Therefore, the dissection plane in patients with clinical stage ≤ T2c disease is intrafascial nerve saving technique, if indicated. We develop this plane athermally by sharp and blunt dissection without the use of Hem–o–lok clips. However, 4 mm hemoclips are used if there are perforating small arteries entering the prostate capsule.

2.2.5. Prostatic Apex and Urethral Dissection. The main purpose of the prostatic apex and urethral dissection is to retain the maximum length of the urethra and to preserve the puboprostatic ligament, provided the margins are not pathologic positive. The dissection is started once the prostate is adequately mobilized. After lifting the mobilized prostate upward, the DVC is incised directly with cold scissors, which exposes the urethra. We identified the distinct plane between the prostate apex and the urethra by sweeping the apex away from the urethra (Figure 1).

2.2.6. Pelvic Lymph Node Dissection. After prostate whole dissection (Figure 2), we performed bilateral standard pelvic lymph node dissection, if indicated: prostate-specific antigen (PSA) ≥ 10 ng/mL or Gleason score ≥ 7 or clinical stage ≥ T3. Hem-o-lok clips are used during lymph node dissection instead of cauterization to prevent lymphocele formation.

2.2.7. Bladder Reconstruction and Detrusorrhaphy Technique. The anterior dissected bladder is held and pulled back by the fourth robotic arm to identify the bladder opening and posterior part of the dissected bladder. We designed the detrusorrhaphy technique based on the hypothesis that detrusor muscles would be functionally reinforced by anatomically correct reconstructions. First, the widened posterior part of the bladder opening is closed with a tennis racquet stitch using a 3–0 V–Loc suture enough to accommodate an 18Fr Foley catheter in the opposite direction after checking the trigone area inside the widened bladder opening and the ureteral orifices below it [12]. Second, the posterior gap behind the newly constructed bladder neck is widely covered by detrusorrhaphy using a flap of detrusor muscles from the posterior bladder neck to the bilateral dissected pedicles and approximated in the midline by a 3–0 V–Loc suture (Figure 3), which completes the detrusorrhaphy technique with support to the bladder neck [13]. The point of the detrusorrhaphy technique is "zigzag" suturing, which thickens and strengthens the deteriorated muscles of detrusor during posterior dissection of the bladder (Figure 4). It aims to reconstruct a physiologically and anatomically ideal shape of detrusor muscles. In the standard narrowing techniques, which simply suture both wings of the dissected bladder, this posterior reinforcement is based on the principles of Parsons and colleagues [14].

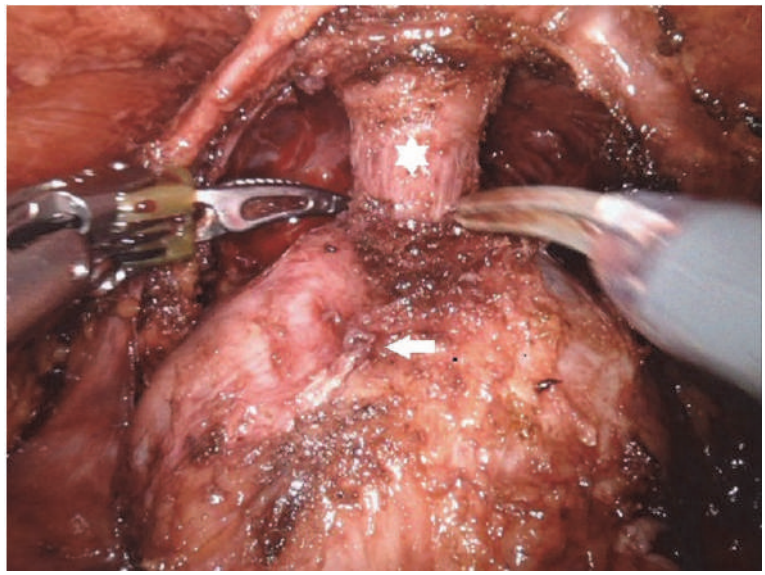

Figure 1: Prostatic apex and urethral dissection (urethra: white star, prostate: white arrow).

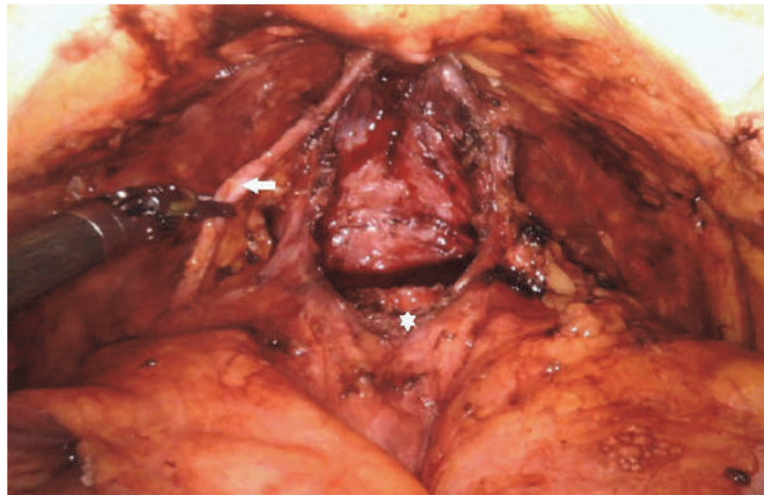

Figure 2: After prostate whole dissection (accessory artery: white arrow, bladder neck opening: white star).

2.3. Data Collection. Demographic data and preoperative and postoperative functional and oncological results were compared between the two groups. Complications were recorded and evaluated using the Clavien-Dindo classification [15]. Recurrent cancer was defined according to the American Urological Association guidelines as two consecutive PSA values > 0.2 ng/mL and rising [16].

The preoperative functional parameters were assessed by the International Prostate Symptom Score (IPSS) score with Urinary Incontinence Quality of Life Scale questionnaires.

The postoperative continence was evaluated using the Expanded Prostate Cancer Index Composite survey question [17]. A patient was defined as continent if he answered "0 pad" per day. In all patients, catheter was removed at postoperative 7 days. Urinary outcomes were assessed by measuring the number of pads for 24 h and the weight of pads in patients with urinary incontinence at 0 day, 1 week, 4 weeks, 8–12 weeks, and 6 months after catheter removal. We also evaluated the IPSS score and performed uroflowmetry. Finally, the relationships between the surgeon's learning curve and the recovery of continence were analyzed by comparing the subgroups in group 1 (enrolled numbers 1–25, 26–50) and group 2 (enrolled numbers 1–23, 24–45) according to a time criterion.

The characteristics of patients were analyzed using Student's t-test or the Mann-Whitney rank sum test. Proportions were compared using chi-square test. Continuous variables were reported as the median values and interquartile range (IQR). The frequencies and proportions of categorical variables were reported as percentages. A p value of < 0.05 was considered indicative of statistically significant differences. SPSS 22.0 for windows (IBM® SPSS® version 22.0, IBM, Armonk, NY, USA) was used for all statistical analyses.

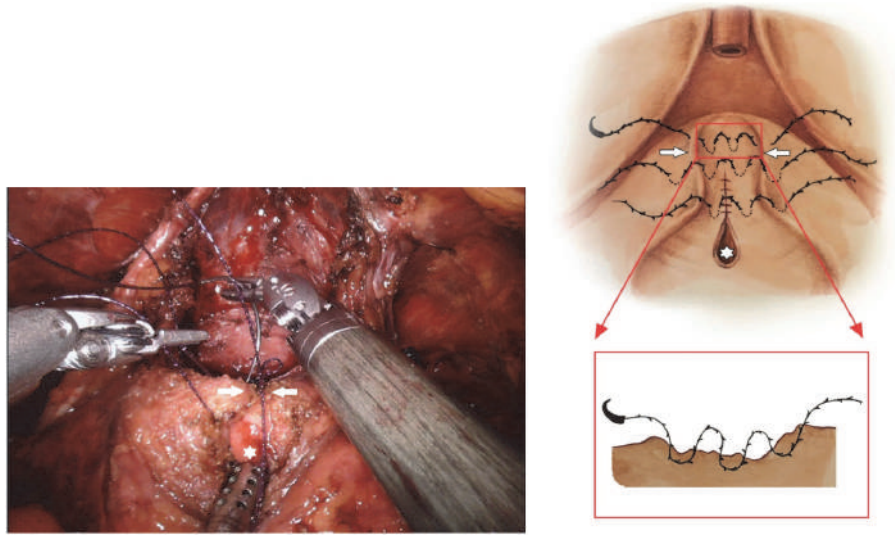

Figure 3: Operative and schematic view of the detrusorrhaphy technique by a flap of dynamic detrusor cuff muscles (detrusor muscles: white arrow, bladder neck opening: white star).

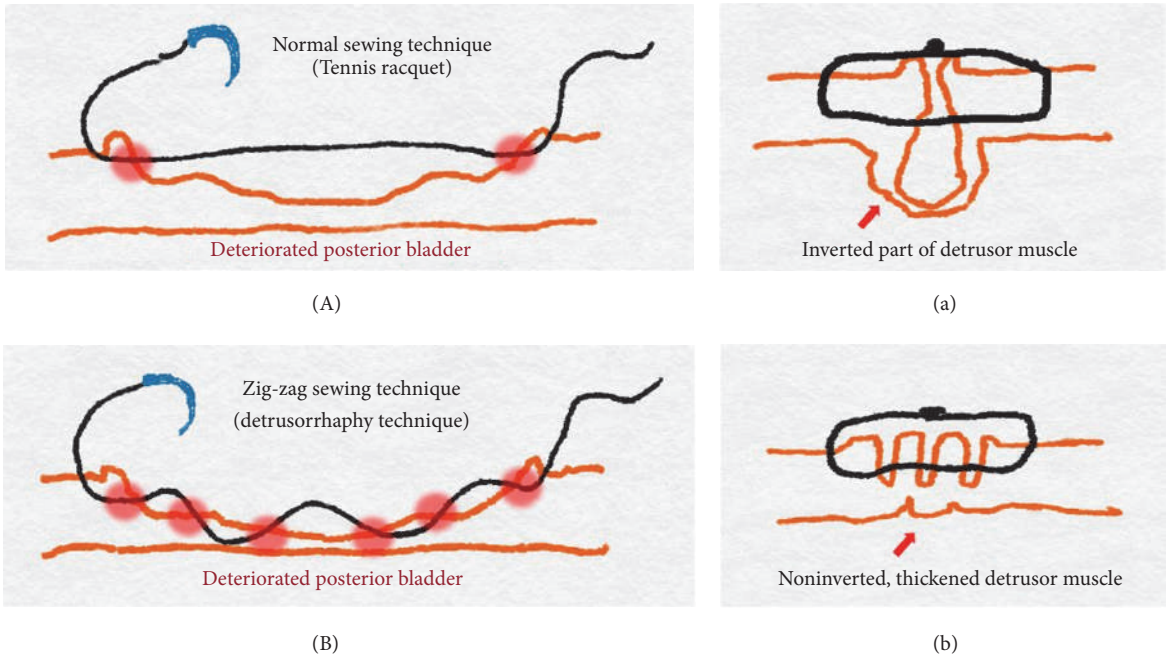

Figure 4: Schematic illustrations of the detrusorrhaphy technique. (A) In the standard narrowing technique, which simply sutures both wings of the dissected bladder and (a) some of the sutured detrusor muscles are inverted and do not contribute to continence recovery and may be discarded. (B) The point of the detrusorrhaphy technique is "zigzag" suturing and (b) this aims to reconstruct a physiologically and anatomically ideal form to thicken and strengthen the deteriorated muscles of detrusor during the posterior dissection of the bladder.

3. Results

3.1. Demographics. This study included 95 patients. Their baseline demographic and clinical data are summarized in Table 1. No significant between-group differences were observed regarding preoperative demographic and clinical data.

3.2. Operative Outcomes and Complications. Mean operative times in groups 1 and 2 were 250 and 220 min, respectively. The median operating time was comparable in the two groups. The estimated blood loss, blood transfusion rates (groups 1 and 2: 4 and 6.7%, respectively), mean number of days with urinary catheter, and overall complication rates were similar between the groups (Table 2).

Table 1: Preoperative data in group 1 (detrusorrhaphy) and group 2 (no detrusorrhaphy).

	Group 1	Group 2	p value
Patients, number	50	45	
Age, median (IQR), year	63.5 (53.0-78.0)	65.5 (58.0-79.0)	0.684
BMI, median (IQR), kg/m^2	25.4 (24.4-27.7)	25.8 (23.8-28.0)	0.957
ASA score, median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	0.873
TRUS, median (IQR), cc	38.6 (21.0-105)	36.5 (22.5-70.5)	0.425
PSA, median (IQR), ng/ml	8.9 (3.2-42.0)	9.5 (4.3-52.5)	0.070
Biopsy Gleason score, median (IQR)	7 (6-9)	7 (6-9)	0.895
IPSS score, median (IQR)	12 (3.0-21.0)	13.5 (2.0-20.0)	0.472
IIEF-5 score, median (IQR)	18.0 (13.5-22)	18.5 (12.5-21.0)	0.775
D'Amico risk group (%)			
(i) Low risk	35 (70)	28 (62.2)	0.065
(ii) Intermediate risk	10 (20)	9 (20)	0.855
(iii) High risk	5 (10)	8 (17.8)	0.073

IQR: interquartile range; BMI: body mass index; ASA score: American Society of Anesthesiologist score; TRUS: transrectal ultrasound; PSA: prostate-specific antigen; IPSS: International Prostate Symptoms Score; IIEF: International Index of Erectile Function.

Table 2: Perioperative and histopathologic data in group 1 (detrusorrhaphy) and group 2 (no detrusorrhaphy).

	Group 1 (n=50)	Group 2 (n=45)	p value
Operative time, median (IQR), min	250 (180-300)	220 (150-300)	0.275
Blood loss, median (IQR), ml	200 (80-400)	200 (100-600)	0.895
Nerve sparing (%)			
(i) Bilateral	30 (60)	24 (53.3)	0.085
(ii) Unilateral	12 (24)	12 (26.7)	
(iii) None	8 (16)	9 (20)	
PLND (%)	40 (80)	38(84.4)	0.125
Complications (%)			
(i) Clavien grade 1			
(ii) Clavien grade 2	2 (4)	3 (6.7)	0.089
(iii) Clavien grade 3	0	0	
Pathologic stage (%)			
(i) pT2	35 (70)	23 (51.1)	0.084
(ii) pT3a	10 (20)	12 (26.7)	0.126
(iii) pT3b	5 (10)	10 (22.2)	0.074
Pathologic Gleason score (%)			
(i) <6	10 (20)	9 (20)	
(ii) 7	30 (60)	24 (53.3)	0.245
(iii) >8	10 (20)	12 (26.7)	0.125
Positive surgical margins (%)	13 (26)	10 (22.2)	0.095
(i) pT2	5 (10)	5 (11.1)	0.185
(ii) pT3	8 (16)	5 (11.1)	0.07
Positive PLND (%)	0	0	

IQR: interquartile range; PLND: pelvic lymph node dissection.

Intraoperative complications were not encountered in any patient. During postoperative 12-month period, none of the patients had urinary retention. Moreover, there were no complications such as hematoma or lymphocele that required further procedures.

3.3. Continence Outcomes. Continence rates in groups 1 and 2 were 68% and 0% at 0 day, 78% and 17.8% at 1 week, 86% and 64.4% at 4 weeks, 92% and 73.3% at 8–12 weeks, and 100% and 91.1% at 6 months follow-up after catheter removal, respectively (Table 3). Up to 12 weeks, the continence recovery rate in group 1 was significantly higher than that in group 2 ($p < 0.05$). Regarding the learning curve analysis, a progressive change in the number of continent patients and operative time in groups 1 and 2 at each time point was not recorded. We also evaluated continence using

Table 3: Continence data at various follow-up points in group 1 (detrusorrhaphy) and group 2 (no detrusorrhaphy).

Time	Patients achieving continence, n (%)		p value
	Group 1 (n=50)	Group 2 (n=45)	
0 day	34 (68.0%)	0 (0%)	< 0.001∗
1 week	39 (78.0%)	8 (17.8%)	< 0.001∗
4 weeks	43 (86.0%)	29(64.4%)	< 0.001∗
8-12 weeks	46 (92.0%)	33 (73.3%)	0.043∗
6 months	50 (100%)	41 (91.1%)	0.089
12 months	50 (100%)	43 (95.6%)	0.115

∗ significant at $p < 0.05$

the IPSS score. There were no significant between-group differences regarding preoperative IPSS scores (12 and 13.5, respectively). At the 1-, 3-, and 6-month postoperative follow-ups, the IPSS scores were comparable in the two groups (11.2 and 12.7; 10.3 and 12.1; and 6.7 and 8.2, respectively; $p > 0.1$) (Figure 5).

Univariate analysis revealed a statistically significant difference in the recovery of continence at the time of catheter removal in relation to the complete nerve sparing technique difference ($p = 0.036$). The D'Amico risk classification appeared to influence the continence recovery at 1 week, 4 weeks, and 8–12 weeks ($p < 0.05$).

Multivariate analysis in group 1 showed that the patients in the D'Amico low risk and a bilateral complete nerve sparing technique group had a statistically significant advantage in terms of continence recovery at the time of catheter removal ($p = 0.025$). At 1 week and 4 weeks, a prostate volume < 60cc and the D'Amico low risk group indicated patients with continence recovery ($p = 0.042$ and $p = 0.012$, respectively). However, at 12 weeks, the only independent predictor variable was a low or intermediate D'Amico risk group ($p = 0.028$).

3.4. Pathologic Findings. Histopathologic data are presented in Table 2. The two groups had no significant differences in their pathologic stage, frequency of positive surgical margin (groups 1 and 2: 26% and 22.2%, respectively; $p > 0.05$), and Gleason score of the surgical specimen. However, the positive margin rate in the cohort of pT2-staged patients decreased to 10% and 11.1% in groups 1 and 2, respectively.

4. Discussion

Robotic prostate surgery in the pelvic cavity confers several advantages in terms of technical operative procedures and postoperative functional results. Thus, the oncological and functional outcomes of robotic prostatectomy may be superior to those achieved with traditional surgical methods [18]. Nevertheless, erectile dysfunction and postprostatectomy incontinence are common adverse effects of robotic prostatectomy. Postoperative incontinence is a particularly common complication that significantly affects the QoL of patients. The numerous potential causes of incontinence after RARP are associated with the disruption of normal anatomic contributors to continence [19]. These include shortening and thinning of the membranous urethra, devascularization or partial sphincter excision, bladder hypermobility and pelvic floor descent, posterior support disruption, and nerve injury. The physiological mechanisms related to postprostatectomy urinary continence are still not completely understood.

Several surgical adaptations to improve the QoL of patients have been described. Various techniques, such as the "Rocco stitch," nerve sparing technique, preservation of the bladder neck and maximum length of the urethra, preserving the puboprostatic ligament and endopelvic fascia, anterior reconstruction, posterior rhabdosphincter reconstruction, and total anatomical reconstruction for incontinence, have been introduced as long as oncological outcomes are not compromised [8–11]. The mechanism of continence recovery after surgery is complex and not completely understood. However, it is universally accepted that maximal preservation of the original anatomic structures associated with the prostate is the key to ensure continence recovery.

At our medical center, we have employed several techniques to reduce postoperative incontinence over the last 10 years. However, we did not achieve satisfactory results. Therefore, we identified key surgical steps and established standard perioperative protocols during RARP.

We particularly focused on the detrusorrhaphy technique. This procedure is specially designed for thickening and strengthening of detrusor muscles from the posterior bladder neck to the bilateral dissected pedicles area. The "zigzag" suturing of the detrusorrhaphy technique has a morphologically fundamental difference from the traditional tennis racquet procedure, which has been simply used to reconstruct the wide-opened bladder neck. Our hypothesis aims to reconstruct a physiologically and anatomically ideal form of the detrusor muscles. In the standard narrowing techniques, which simply suture both wings of the dissected bladder, some of the sutured detrusor muscles are inverted; these muscles do not contribute to continence recovery and may be discarded. Previous reconstructions are not anatomically perfect.

First, the zigzag suture is characterized by setting the suture direction according to the contraction direction of the detrusor muscle, thereby increasing the thickness and strength of the muscle and seeking to rebuild the bladder so as not to distort its original shape. Second, the zigzag suture has been proven to be a safe and feasible procedure in that no single ischemic necrosis has occurred. Third, we searched previous literature regarding detrusor cuff reinforcement. Normally, the puboperinealis muscle forms a dynamic cuff that pinches and angulates the urethra. This cuff is often

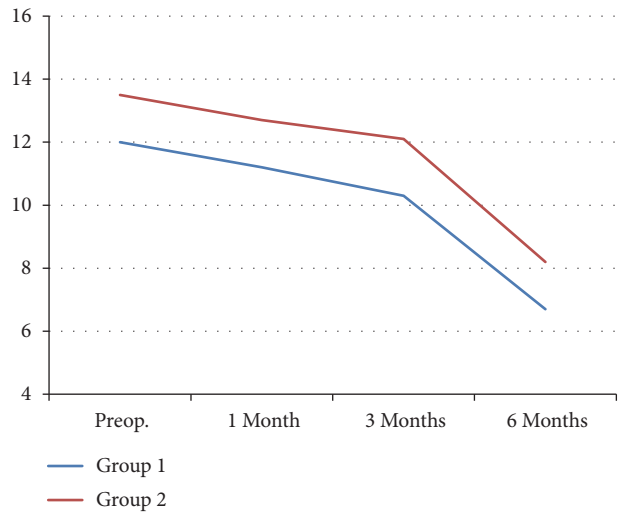

Figure 5: Comparison of the IPPS score between group 1 (detrusorrhaphy) and group 2 (no detrusorrhaphy) at preoperative, 1-, 3-, and 6-month follow-ups.

disrupted during posterior apical dissection, which weakens this support. The fourth novel aspect of the detrusorrhaphy technique involves dynamic detrusor cuff detrusorrhaphy, which supports the proximal urethra and bladder neck with contractile detrusor tissue and constricts this outlet [20]. Reconstruction of this detrusorrhaphy technique is thought to reduce stress urinary incontinence by preventing hypermobilization of the bladder neck area and is believed to be very important for continence recovery.

Our technique aimed to achieve an even earlier return to no pad state continence (≤ 12 weeks) with the potential for immediate continence. The detrusorrhaphy technique is founded on a simple assumption. The reinforcement of the posterior bladder neck correlates with functional normalcy. We attempted to reconstruct the pelvic anatomy after RARP with the goal of improving the postoperative functional status and specifically to achieve early continence.

Our results showed very early continence rates of 68%, 78%, 86%, 92%, and 100% at 0 day, 1 week, 4 weeks, 8–12 weeks, and 6 months follow-up after catheter removal, respectively. Our results are consistent with those of other studies that showed the benefits of early urinary incontinence recovery, although surgical techniques and continence definitions vary. In a nonrandomized single-arm study, Porpiglia et al. [11] achieved similar continence rates (71.8%, 77.8%, 89.3%, 94.4%, and 98.0% at 24 h and 1, 4, 12, and 24 weeks, respectively, after catheter removal).

Our study aimed to determine whether the detrusorrhaphy technique with additional surgical techniques including the use of a meticulous urethral approach for retaining the maximum length of the urethra, preservation of the puboprostatic ligament, and other factors such as nerve sparing and D'Amico risk groups could further improve the continence rate. As seen, in the multivariate analysis, the nerve sparing technique, D'Amico risk groups, and prostate volume were involved in the early recovery of urinary continence because they reasonably affected the preservation of anatomical structures and the involvement of the sacral plexus.

None of our patients developed urinary leakage or stenosis at the site of anastomosis. These findings suggest that meticulous urethrovesical anastomosis and posterior bladder neck reconstruction ensure a watertight anastomosis without a concomitant increase in the risk of stricture. Moreover, the new technique did not seem to affect the oncological results. While the overall positive surgical margin rate (groups 1 and 2: 26% and 22.2%, respectively) was higher in the previously reported study [21]. However, the positive margin rate in the cohort of pT2-staged patients (groups 1 and 2: 10% and 11.1%, respectively) was similar to or lower than the other reported study [22].

Some limitations of the present study should be acknowledged. These include the small sample size, the single-institution scope of the study, and the fact that only one surgeon was performing RARP. The continence outcomes of our study may be influenced by the extensive experience of the surgeon. Preexisting comorbidities, such as diabetes mellitus and smoking history, which could potentially affect the continence status, were not recorded. Therefore, we should perform multivariate analysis using the various factors described above in future studies.

5. Conclusions

Our study showed significantly better outcomes than those achieved with the standard technique in terms of urinary incontinence. The use of the detrusorrhaphy technique during RARP is simple, safe, and feasible. Although our findings need to be validated further, the technique described is relatively simple and reproducible and may be applicable for RARP.

Abbreviations and Acronyms

RARP: Robot-assisted radical prostatectomy
QoL: Quality of life
DVC: Dorsal vein complex

PSA: Prostate-specific antigen
IPSS: International Prostate Symptom Score
IQR: Interquartile range.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

The study was not funded.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Clinical Study

Association between the Urinary Bladder Volume and the Incidence of "De Novo" Overactive Bladder in Patients with Stress Urinary Incontinence Subjected to Sling Surgeries or Burch Procedure

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Aim. The aim of the study was to compare the incidence of "de novo" overactive bladder (OAB) after sling surgeries and Burch procedure and to analyze the effect of the preoperative bladder volume on the incidence of this condition. *Methods.* This prospective trial included 290 female patients with stress urinary incontinence (SUI) who were subjected to sling surgeries (TOT or TVT, n=170) or Burch procedure (n=120). Urodynamic testing was performed prior to the surgery and 6 months thereafter. The presence of OAB was diagnosed on the basis of subjective symptoms and urodynamic parameters. *Results.* The incidence of OAB 3 at 6 months postsurgery was the highest in patients who were subjected to the Burch procedure (14.2% and 17.5%, respectively). The incidence of OAB at 6 months turned out to be significantly higher in patients subjected to the Burch procedure with preoperative bladder volumes greater than 353 ml. We observed the significant postoperative decrease in the bladder volume of women who developed this complication following the Burch procedure. *Conclusions.* Among surgeries for stress urinary incontinence, Burch procedure is associated with the greatest risk of overactive bladder development. Probably, one reason for the higher incidence of overactive bladder after Burch procedure is the intraoperative reduction of the urinary bladder volume.

1. Introduction

Stress urinary incontinence (SUI) is defined as an unintentional, uncontrolled loss of urine through the urethra. This happens when vesical pressure exceeds the urethral sphincter pressure during coughing, sneezing, or physical exercise. The presence of SUI does not alter the frequency of micturition during the day and night and, contrary to the overactive bladder, is not associated with an urgent need to urinate [1].

According to the ICS definition published in 2002, overactive bladder (OAB) is a multisymptomatic disorder manifested with sudden urgency with or without urinary incontinence. It is usually associated with an increased frequency of micturition during the day and nocturia. Polyuria is currently defined as a subjective impression of excessive urination during the day, and nocturia as more than one micturition during the night [2–4]. Importantly, nocturia can be diagnosed only if one had to wake at night for voiding and fell asleep afterwards [1, 5–19]. It needs to be stressed that OAB can be diagnosed only after exclusion of other factors explaining the abovementioned symptoms, such as urinary tract infection, interstitial cystitis, tumors, urolithiasis, and neurological disorders [20]. Due to such definition of OAB, diagnosis of this condition does not

necessitate urodynamic testing. Nevertheless, the evidence of phasic or terminal detrusor overactivity (i.e., an increase in the detrusor pressure above 15 cm H_2O) constitutes an objective diagnostic criterion of OAB. It needs to be stressed that only approximately 40-60% of patients with the OAB-characteristic symptoms present with the detrusor overactivity on urodynamic testing [21]. The latter is usually accompanied by other, less characteristic symptoms, such as a sudden increase in the vesical pressure after administration of even small amount of infusion fluid, increase in myogenic activity, and spastic or terminal contractions. The presence of overactive bladder is not necessarily associated with urinary incontinence. Therefore, an urgent need to urinate with resultant urinary incontinence is classified as the "wet" OAB, whereas the sudden urgency without urinary incontinence is referred to as the "dry" OAB.

In this study, we focused on the incidence of "de novo" overactive bladder as a complication of sling surgeries (TOT and TVT) and Burch procedure. These procedures constitute the most popular methods of surgical treatment of stress urinary incontinence, and overactive bladder represents one of their most prevalent complications, markedly diminishing quality of life during postoperative period. Sling surgeries and Burch procedure are equally efficient in the treatment of SUI. The incidence of OAB after these procedures ranges between 3% and 66% [22], but according to some authors may reach even up to 75% [23]. If "de novo" sudden urgency is observed immediately after the surgery, one should exclude its other potential causes, such as incorrect placement of tension-free tape, e.g., inside the bladder or too close to its neck, postmicturition urinary retention, and urinary tract infection [24]. Similarly, in the case of late postoperative manifestation of OAB-like symptoms, a number of other potential causes should be considered. Finally, it needs to be emphasized that in many patients who present with overactive bladder after surgical treatment of stress urinary incontinence, the exact etiology of OAB remains unknown.

Due to their established high effectiveness, sling surgeries and Burch procedure are most common surgical treatments of SUI [25–27]. We hypothesized that selection of the most adequate surgical procedure for given patient might not only maximize the effectiveness of SUI treatment, but also minimize the risk of postoperative OAB. Therefore, the aim of the study was to compare the incidence of "de novo" OAB after sling surgeries and Burch procedure and to analyze the effect of the bladder volume on the incidence of this condition.

2. Materials and Methods

This prospective trial included 290 female patients who were operated on due to pure SUI in the Department of Fertility and Gynecology, Pomeranian Medical University in Szczecin. The presence of SUI was confirmed on the basis of a survey with the Gaudenz questionnaire [28], physical examination, and urodynamic testing. The study group was predominated by patients qualified to sling surgeries: TOT or TVT (n=170, 58.62%). The exact type of the sling procedure was chosen on a random basis. The remaining 120 patients (41.38%) were qualified to Burch procedure. The indication to the latter procedure was necessity of simultaneous laparotomic resection of benign endometrial or adnexal lesions.

The inclusion criterion of the study was presence of pure grade II or III SUI confirmed on urodynamic testing. The exclusion criteria were (1) preoperative evidence of OAB and mixed urinary incontinence, (2) grade I SUI, (3) stage 3 or 4 genital prolapse, (4) pre- and/or postoperative retention of more than 50 ml of urine and bladder outlet obstruction documented on urodynamic testing, (5) presence of early or late, direct postoperative complications, (6) incorrect placement of TOT or TVT tape confirmed on postoperative urogynecological ultrasonography, (7) history of surgical treatment for SUI, (8) urinary fistulae, (9) congenital and/or acquired defects of the urethra and bladder, (10) urinary tract infections, (11) hormone replacement therapy prior to and after the procedure, (12) cardiovascular conditions (arterial hypertension, ischemic heart disease, arrhythmia), (13) type 1 or 2 diabetes mellitus, and (14) deformation of the lumbosacral spine (spina bifida, posttraumatic and/or degenerative lesions).

Shortly before the surgery the patients were surveyed with the Gaudenz questionnaire [28] and subjected to gynecological examination and urodynamic testing with determination of the bladder volume. Urodynamic testing was performed after confirming normal result of urinalysis. All urodynamic tests were performed by the same investigator. The MMS Libra System (Medical Measurement Systems B.V.) was used to determine vesical (P_{ves}), abdominal (P_{abd}), and detrusor (P_{det}) pressure. Moreover, the first sensation of bladder filling (FS), first desire to void (FD), and strong desire to void (SD) were recorded during the filling phase. Also cough stress test and Valsalva maneuver were performed after administering the first 50 ml of fluid and repeated after every additional 100 ml. The micturition phase started after maximum filling of the bladder. The patient voided to a container placed on a scale, and uroflow curve and residual urine volume were determined. The presence of OAB was diagnosed on the basis of subjective symptoms reported by a patient and such urodynamic parameters as reactivity of the bladder, FS, ND, SD, and detrusor pressure. The survey with the Gaudenz questionnaire was repeated 3 and 6 months postsurgery, and urodynamic testing with determination of the bladder volume was performed at 6 months.

The protocol of the study was approved by the Local Bioethics Committee at the Pomeranian Medical University (decision no. BN-001/16/06), and written informed consent was obtained from all the participants.

Statistical analysis was conducted with Statistica 10 package (StatSoft, United States). Statistical characteristics of continuous variables were presented as arithmetic means, standard deviations, medians, minimum and maximum values, and the characteristics of qualitative variables as numbers and percentages. The normality of continuous variable distribution was verified with Shapiro-Wilk test. The effects of surgery type were compared with a two-way repeated measure ANOVA surgery (3: TOT, TVT, Burch procedure) x time (2: prior to surgery and 6 months thereafter). The Tukey's post hoc test was used for multiple comparisons.

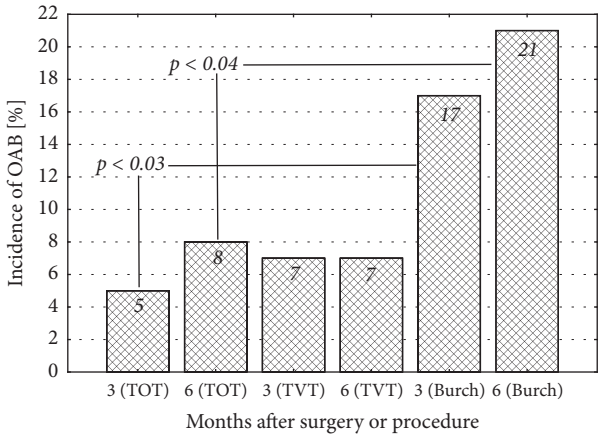

Figure 1: Incidence of overactive bladder 3 and 6 months after sling surgeries (TOT and TVT) and Burch procedure.

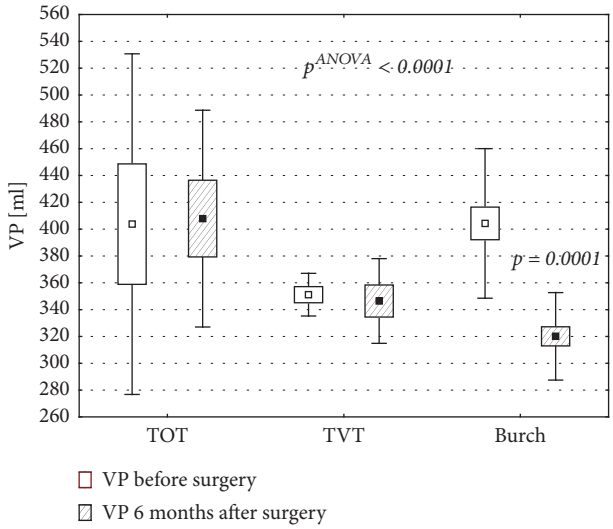

Figure 2: Mean urinary bladder volume of patients who developed OAB, determined prior to a sling surgery or Burch procedure and 6 months thereafter. Vp: urinary bladder volume; p-value of the Tukey's test.

Due to small sample size, relationships between pairs of qualitative variables were tested with the Pearson's chi-square test with Yates' correction or Fisher exact test. Moreover, some continuous variables were transformed into discrete variables on the basis of their median values. The threshold of statistical significance of all the tests was set at $p \leq 0.05$.

3. Results

The incidence of overactive bladder 3 and 6 months postsurgery was the highest in patients who were subjected to Burch procedure (14.2% and 17.5%, respectively) and the lowest in women operated on according to TOT protocol (4.6% and 7.4%, respectively). The incidence of OAB in these two groups differed significantly at both three (p=0.03) and six months (p=0.04) postsurgery. The incidence of OAB in patients operated on according to TVT protocol did not differ significantly when compared to the remaining groups (Figure 1).

In all patients, the urinary bladder volume prior to the surgery and 6 months thereafter ranged between 102 ml and 636 ml. While the patients who developed OAB after TOT or TVT surgeries did not show significant postoperative changes in the bladder volume, we observed the significant decrease in the bladder volume of women who developed this complication following Burch procedure (p=0.0001, Figure 2).

Six months postsurgery, the incidence of OAB in patients who were subjected to Burch procedure with preoperative bladder volumes greater than 353 ml turned out to be significantly higher than in the remaining women operated on with the same surgical technique (Figure 3). We did not document similar relationships in the TOT- and TVT-operated patients, but the size of these two subgroups might be too small to draw any firm conclusions.

Analysis of correlation between the pre- and postoperative bladder volumes showed only slight postoperative changes of this parameter or complete lack thereof in most of the women who developed OAB following a sling surgery (Figures 4 and 5). In contrast, a postoperative decrease in the

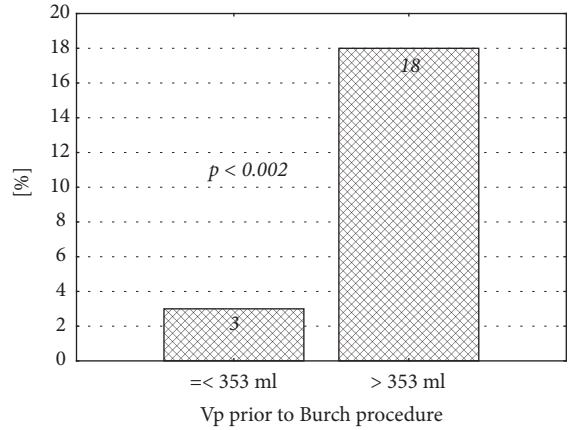

Figure 3: Incidence of overactive bladder 6 months after Burch procedure, stratified according to the preoperative urinary bladder volume.

urinary bladder volume was observed in all but two patients who developed OAB as a consequence of Burch procedure (Figure 6).

4. Discussion

TOT and TVT surgeries and Burch procedure constitute currently the most popular methods for surgical treatment of SUI. Regardless of the surgical method, the outcomes of the treatments are good. The effectiveness varies according to the follow-up time, from approximately 90% after one year to ca. 70% at five years after the surgery [25–27]. Unfortunately, some patients operated on for SUI may develop OAB which is detrimental for their quality of life in many dimension. It is unclear whether presence of SUI impairs quality of life to a larger extent than OAB with severe nocturia. Our study

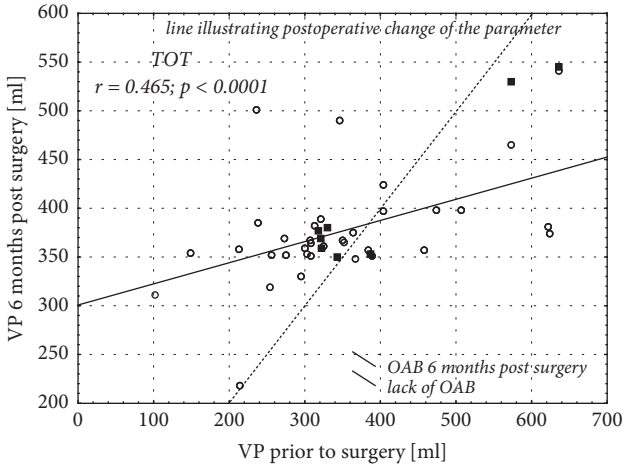

Figure 4: Correlation between urinary bladder volumes determined prior to surgery according to TOT protocol and 6 months thereafter.

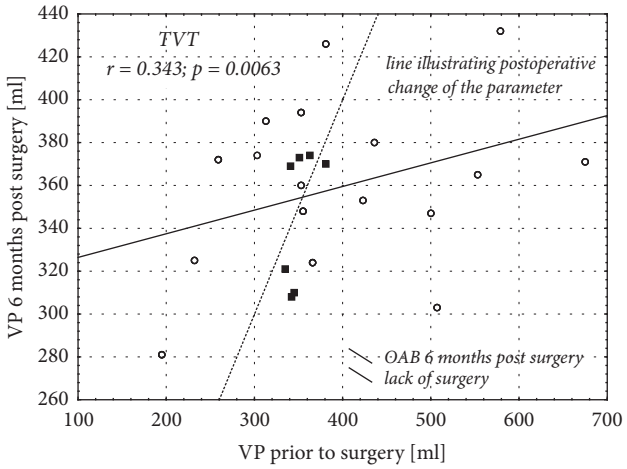

Figure 5: Correlation between urinary bladder volumes determined prior to surgery according to TVT protocol and 6 months thereafter.

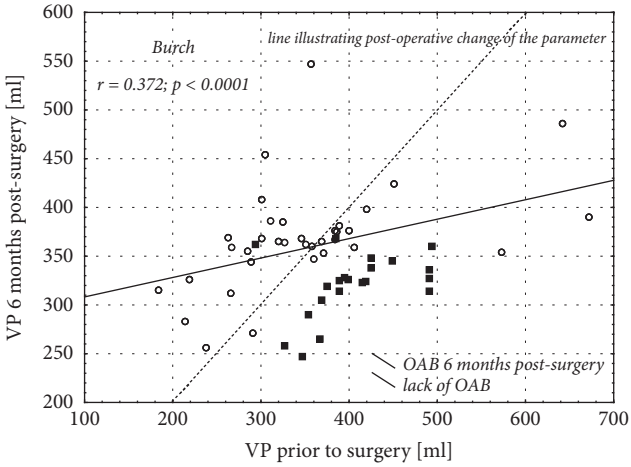

Figure 6: Correlation between urinary bladder volumes determined prior to Burch procedure and 6 months thereafter.

revealed that the incidence of OAB, both 3 and 6 months postsurgery, was the highest after Burch procedure (14.2% and 17.5%, respectively). The incidence of OAB documented 3 and 6 months after TVT surgery was similar, amounting to ca. 11%. The complication turned out to be least frequent 3 and 6 months after TOT procedure, amounting to 4.6% and 7.4%, respectively. According to other authors, OAB may occur in 3-66% [22] or even 75% of patients after surgical treatment of SUI [23].

Due to specific structure of its wall, urinary bladder is highly flexible and can substantially change its volume. According to various authors, the volume of the urinary bladder ranges between 350 ml and 650 ml [1]. Theoretically, the factors that impair the bladder's flexibility may also interfere with the detrusor function [29]. Only few authors analyzed the influence of the surgical treatment of SUI on the bladder volume and relationship between postoperative changes in this latter parameter and incidence of OAB. A subanalysis of postoperative changes in the bladder volume of our patients who developed OAB 6 months postsurgery showed a significant decrease in this parameter of women who were subjected to Burch procedure. We did not observe this relationship in the remaining subgroups of patients. Moreover, we showed that larger volume of the bladder prior to Burch procedure was associated with significantly higher incidence of OAB 6 months after the surgery. Similar association was not documented in the case of women who were operated on according to TOT and TVT protocols. Probably, the patients whose bladder volume was significantly reduced as a result of Burch procedure were more likely to develop "de novo" OAB after the surgery. Also the fact that this procedure is associated with a reduction of the bladder volume at the level of its neck and resultant change of the urethrovesical angle, is worth noticing. This hypothesis seems to be supported by our finding on lower incidence of this complication after TOT and TVT surgeries. To the best of our knowledge, none of the previous studies analyzed a relationship between the bladder volume and incidence of "de novo" OAB. Wang et al. [30] compared the outcomes of TVT and Burch surgeries in patients with stress urinary incontinence and analyzed the influence of these procedures on the bladder volume and residual urinary volume. However, they did not analyze the association between the bladder volume and incidence of OAB. Instead, they only showed that the bladder volume of patients subjected to Burch procedure decreased significantly, contrary to persons who were operated on according to TVT protocol [30]. The treatment outcomes in patients with stress urinary incontinence were also studied by Han et al. [31]. Among the parameters analyzed by these authors were the bladder volumes determined one month, one year, and five years after the procedure. The authors did not document significant changes in the bladder volume of patients subjected to TVT surgery [31]. Our findings seem to be consistent with this observation. Overall, these data point to a necessity of preoperative assessment of the bladder volume in patients with SUI and appropriate selection of the surgery type in order to prevent excessive postoperative reduction of this parameter.

5. Conclusions

Among surgeries for SUI, Burch procedure is associated with the greatest risk of overactive bladder development. Probably, one reason for the higher incidence of overactive bladder after Burch procedure is the intraoperative reduction of the urinary bladder volume.

Data Availability

Dataset connected to this study is available from the corresponding author upon a reasonable request.

Conflicts of Interest

None of the authors has conflicts of interest. The authors did not receive any support from enlisted companies to conduct the study.

Acknowledgments

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Research Article

The Effect of Pelvic Floor Muscles Exercise on Quality of Life in Women with Stress Urinary Incontinence and Its Relationship with Vaginal Deliveries: A Randomized Trial

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Introduction. Urinary incontinence (UI) is a health problem affecting the quality of women's lives (QOL) at various life stages. Stress urinary incontinence (SUI) can be caused by previous vaginal deliveries and is especially likely to occur in the perimenopausal period. The most commonly recommended first-choice treatment methods involve exercises for the pelvic floor muscles (PFM). The aim of this study was to assess the impact of isolated PFM exercises and combined training of the PFM and the m.transversus abdominis (TrA) muscle on the QoL of patients with SUI with regard to the number of vaginal deliveries. *Material and Methods*. 137 women with SUI were qualified for analysis (mean age 53,1 ± 5,5). To assess the effectiveness of PFM training QOL questionnaire was used (ICIQ-LUTS qol). PFM training for groups A (PFM+TrA) and B (PFM) was intended for 12 weeks. Statistica v. 12.0 PL, StatSoft, USA, was used for statistical calculations. *Results*. The analysis demonstrated that conservative treatment based on the A training program (PFM + TrA) yielded statistically significantly better results than the B program (PFM), with the improvement observed in such QoL domains as the performance of household duties, physical activity and travelling, social limitations, emotions, sleep problems and fatigue, the frequency of changing panty liners, fluid intake control, and embarrassment. *Conclusion*. Both the combined training of the PFM and the synergistic (TrA) muscle and the isolated PFM exercises improve the QoL of women with SUI. Nonetheless, the combined PFM and TrA muscle physiotherapy is more effective. The exercises for the PFM and the synergistic muscle give better results in women who have given birth fewer than three times than isolated PFM exercises.

1. Introduction

Urinary incontinence (UI) is a health problem affecting the quality of women's lives at various life stages. According to the data, the incidence of urinary incontinence ranges from 30% to 60%. The International Continence Society (ICS) singles out stress urinary incontinence (SUI), overactive bladder (OAB), overflow incontinence (OI), and functional incontinence (FI). SUI is especially likely to occur in the perimenopausal period, when tissue resilience decreases as a result of lower estrogen levels. This type of urinary incontinence can be caused by previous vaginal deliveries. During natural childbirth, the birth canal tissues are excessively stretched, and damage to the levator ani muscle and the visceral pelvic fascia may happen [1]. Despite the mechanisms of tissue regeneration in this area, researchers indicate reduction abilities of female bodies after three or more deliveries compared with those of nulliparous and women who have given birth only once [2]. Another complication that can arise during vaginal delivery is damage to neurological structures of this area. It can especially happen in the second phase of labor, when the presenting part of the

fetus is getting through the birth canal, pressing the nearby nerves. Suspended on the tendinous arch, the levator ani muscle is tightened and stretched. The pubourethral fascia, rectovaginal septum, and perineal body are strained and may even be ruptured. At the end of the second phase of the labor, the pudendal nerve damage is sometimes observed [3]. The study of 384 women conducted by Pereira with the use of surface electromyography (sEMG) demonstrated that the ability of the pelvic floor muscles (PFM) to be properly tensed varies depending on the life stage. The greatest recruitment of the motor units of the PFM is noted in nulliparas, then primiparas, women after C-section, women after vaginal delivery, and finally climacteric and postmenopausal women [4].

The most commonly recommended first-choice treatment methods, especially for stage 1 SUI, involve exercises for the PFM. Many publications emphasize good effects of this type of conservative treatment, thus indicating that it is appropriate noninvasive management of the mildest—stage 1—SUI. Doing these exercises leads to stabilization of the urethra through an increase in muscle mass. Positive results, patients achieve only after about 6-8 weeks of regular exercises and are manifest themselves in a higher assessment of the QoL [5]. Some researchers indicate the possibility of combining exercises for the PFM and the TrA muscle. According to Stapsford, the TrA muscle is a synergistic muscle, showing natural activity during PFM contractions [6, 7].

The International Consultation Incontinence Questionnaire Lower Urinary Tract Symptoms quality of life (ICIQ-LUTSqol) is a questionnaire measuring the QoL of patients with urinary incontinence [8]. The International Urogynecological Association (IUGA), the ICS, and the International Consultation on Urologic Diseases (ICUD) underline that it is important for questionnaires to use clear, simple language so that patients with different perceptions can complete them on their own [9]. The ICIQ-LUTSqol includes questions concerning the influence of urinary incontinence on particular life domains, namely, physical activity, social contacts, sexual contacts, emotional state, and sleep. Other questions concern activities and feelings that patients experience due to urinary incontinence, among them wearing panty liners, fluid intake control, changing wet underwear, and anxiety associated with unpleasant smell. All items are rated on a four-point scale: never or not at all (1 point), a little or sometimes (2 points), often or moderately (3 points), and very or all the time (4 points). The total score ranges from 19 to 76 points. The ICIQ-LUTSqol has been developed on the basis of King's Health Questionnaire (KHQ) [10, 11].

The aim of this study was to assess the impact of isolated PFM exercises, and combined training of the PFM and the TrA muscle on the QoL of patients with SUI with regard to the number of vaginal deliveries.

2. Material

A urodynamic test was performed by means of the Libra device (Medical Measurement System B.V. MMS, Enschede, the Netherlands, 2001). From among 300 patients 150 were qualified for the study; based on the urodynamic test results, an interview was carried out with the Gaudenz questionnaire and gynecological examination unambiguously indicating stage 1 SUI. The qualifying examinations for the study were performed at the Department of Gynecology, Endocrinology and Gynecologic Oncology, Pomeranian Medical University in Szczecin.

The criteria for inclusion in the study were stage 1 SUI without urinary urgency, the 45-60 years age-bracket, at least one vaginal delivery, and the patient's written consent to take part in the study. The criteria for exclusion from the study were higher stage SUI, types of urinary incontinence other than SUI, prolapse according to the Pelvic Organ Prolapse Quantification (POP-Q) system, diabetes, age below 45 and above 60 years, no vaginal deliveries, and no patient's consent for inclusion in the study. The project was approved by the Bioethical Commission of the Pomeranian Medical University in Szczecin (decision no. KB0012/142/13 of 30 September 2013).

3. Method

To assess the effectiveness of conservative treatment for stage 1 SUI according to Ingelman-Sundberg scale. In this scale the incontinence severity is graded according to the circumstances or physical activities provoking urinary leakage: grade I: urinary incontinence while coughing or sneezing, grade II: urinary incontinence while running or picking up heavy objects, and grade III: incontinence while walking or climbing stairs [12].

The patients (n = 150) were assigned to two groups by a computer draw—group A (n = 75) and group B (n = 75). As the first step, an interview was carried out using the Polish version of the standardized validated ICIQ-LUTSqol. Next, training programs for group A and group B were designed. For both groups intravaginal estrogen therapy was recommended. After three months, the ICIQ-LUTSqol was used again to assess the patients' QoL. In group A, seven patients did not complete the training: four patients underwent transvaginal tape (TVT) surgery, and three patients did not turn up for the follow-up examination. In group B, six patients did not turn up for the follow-up examination. Eventually, 68 patients from group A and 69 patients from group B were qualified for analysis.

The initial and final QoL assessments were performed by means of the ICIQ-LUTSqol, developed on the basis of the KHQ. This standardized validated questionnaire includes questions concerning such spheres of life as the performance of household duties and outside home activities (Q3), physical limitations (Q4a), social limitations (Q4b), interpersonal limitations (Q5), emotions (Q6), languidness and vitality associated with urinary incontinence (Q7), the performance of such activities as: changing panty liners, restricting fluid intake, changing wet underwear (Q8), and embarrassment (QW). When completing the questionnaire, patients tick one of the four answers: not at all (1 point), a little (2 points), moderately (3 points), and very (4 points).

Table 1: The features of group A (PFM + TrA) and group B (PFM).

		Group A n=68 PFM + TrA	Group B n=69 PFM	p
Age ($\overline{x}$+SD, years)		53,2 ± 5,4	53,1 ± 5,6	0,813*
BMI ($\overline{x}$+SD, kg/m^2)		27,3 ± 4,7	27,3 ± 5,1	1,0*
Number of vaginal deliveries	Group 0 (<3)	53	57	0,492
	Group 1 (≥3)	15	12	
Place of residence (%)	city	74,6	76,2	0,842
	village	26,4	23,8	
Physical activity (%)	sitting	11,9	17,7	0,616
	active	31,1	26,5	
	mixed	57,0	55,8	
Menopausal status (%)	before	47,1	61,4	0,09
	after	52,9	38,6	
Smoking (%)	yes	13,9	12,4	0,8
	no	86,1	87,6	

The possible scores range from 19 to 79 points. The scores for this questionnaire were calculated in accordance with the guidelines described in Keller's article, following the example of the base questionnaire—the KHQ—calculation principles [13]. The reliability of the applied survey methods was evaluated by calculating Cronbach's alpha for pre- and posttreatment scores. High pre- and posttreatment values of Cronbach's alpha (0.717 and 0.844, respectively) point to a high reliability of the scale.

The training program for group A (PFM + TrA) was intended for 12 weeks. The exercises were performed four times a week according to the following pattern: three series of 10 repetitions of PFM contractions (6-8 seconds) with the strength of 60-70% MVC (maximum voluntary contraction) and two series of 10 repetitions of PFM contractions with the strength of 30-60% MVC. All contractions were correlated with exhalations and simultaneous TrA muscle contractions and performed in a lying-back position with the legs bent and feet on the ground. Additionally, "the Knack Maneuver" was recommended in case of increased intra-abdominal pressure (IAP) during coughing, sneezing, laughing, and lifting heavy objects. The training program for group B was analogous, but the patients were instructed not to tense the TrA muscle during PFM contractions.

Statistical characteristics of quantitative variables were presented as arithmetic means, standard deviations, medians, minimum, and maximum values as numbers and percentages. Normal distribution of continuous variables was verified with Shapiro-Wilk test. Statistical significance of differences between the study groups was verified with Student t-test and Pearson chi-square test. The effect of number of vaginal deliveries on QOL scores was analyzed with factorial ANOVA: training program (A vs. B) x co-variate (group 0- number of vaginal deliveries <3 vs. group 1- number of vaginal deliveries ≥3), with Tukey post hoc test. All calculations were carried out with Statistica 12 package (StatSoft, USA). $P < 0.05$ was considered statistically significant.

4. Results

The original survey developed by the authors was used to collect such characteristics of the study subjects as age, body mass index, number of vaginal deliveries, place of residence, level of physical activity, menopausal status, and smoking (Table 1.).

Table 2 shows the impact of an interfering factor (the number of vaginal deliveries) on the results of conservative treatment applied in women with stage 1 SUI according to the A training program (PFM + TrA) and the B training program (PFM). The significance of differences in the treatment results between the groups was analyzed in order to estimate the impact of this factor.

The analysis results after exercise training demonstrated that conservative treatment based on the A training program (PFM + TrA) yielded statistically significantly better results than the B program (PFM), with the improvement observed in such QoL domains as the performance of household duties and outside home activities (Q3), physical activity and the possibility of travelling (Q4a), and social limitations: interpersonal contacts and the possibility of meeting friends (Q4b), emotions (Q6), sleep problems and fatigue (Q7), the frequency of changing panty liners, fluid intake control, changing wet underwear, anxiety associated with unpleasant smell (Q8), and embarrassment (QW). The analysis of the sum scores of the ICIQ-LUTSqol revealed that a statistically significant change was only reported by the women who had given birth naturally fewer than three times (group 0) and who applied the A training program (PFM + TrA).

5. Discussion

The true pelvic floor fulfills numerous functions in a female body. Changes in this area occur not only as a result of a menopause-related drop in hormone levels or hormonal changes in pregnancy, but also a consequence of vaginal

Table 2: The effect of pelvic floor muscles exercise on quality of life in group A (PFM + TrA) and B (PFM). The relationship with number of vaginal deliveries—results of post hoc test after exercise training.

Score	groups	NVD Group 0 (<3) Group 1 (≥3)	$\overline{x}$ ± SD	test *post hoc* Tukey
Q3	A	0	18,4 ± 20,1	A_0 vs B_0 p=0,025 A_1 vs B_1 p=0,789 A_0 vs A_1 p=0,935 B_0 vs B_1 p=0,964
		1	11,1 ± 19,2	
	B	0	30,2 ± 20,1	
		1	33,3 ± 21,1	
Q4a	A	0	19,9 ± 15,1	A_0 vs B_0 p=0,010 A_1 vs B_1 p=0,442 A_0 vs A_1 p=0,892 B_0 vs B_1 p=0,807
		1	11,1 ± 9,6	
	B	0	32,8 ± 20,9	
		1	41,7 ± 25,3	
Q4b	A	0	6,6 ± 9,8	A_0 vs B_0 p<0,001 A_1 vs B_1 p=0,848 A_0 vs A_1 p=0,999 B_0 vs B_1 p=0,313
		1	11,1 ± 0,0	
	B	0	21,5 ± 15,8	
		1	27,8 ± 25,1	
Q5	A	0	14,9 ± 25,3	A_0 vs B_0 p=0,482 A_1 vs B_1 p=0,638 A_0 vs A_1 p=0,999 B_0 vs B_1 p=0,810
		1	16,7 ± 16,7	
	B	0	24,2 ± 25,5	
		1	22,4 ± 22,1	
Q6	A	0	11,6 ± 14,4	A_0 vs B_0 p<0,001 A_1 vs B_1 p=0,708 A_0 vs A_1 p=0,999 B_0 vs B_1 p=0,139
		1	7,4 ± 6,4	
	B	0	27,8 ± 19,6	
		1	29,6 ± 33,5	
Q7	A	0	19,6 ± 20,1	A_0 vs B_0 p=0,006 A_1 vs B_1 p=0,963 A_0 vs A_1 p=0,624 B_0 vs B_1 p=0,997
		1	22,3 ± 19,2	
	B	0	33,9 ± 19,5	
		1	38,9 ± 13,6	
Q8	A	0	24,9 ± 17,9	A_0 vs B_0 p<0,001 A_1 vs B_1 p=0,125 A_0 vs A_1 p=0,997 B_0 vs B_1 p=0,687
		1	11,1 ± 12,7	
	B	0	42,4 ± 17,5	
		1	48,6 ± 15,3	
QW	A	0	14,9 ± 21,1	A_0 vs B_0 p=0,034 A_1 vs B_1 p=0,685 A_0 vs A_1 p=0,991 B_0 vs B_1 p=0,996
		1	11,1 ± 19,2	
	B	0	30,2 ± 26,4	
		1	44,8 ± 23,1	
Suma scores	A	0	116,0 ± 87,6	A_0 vs B_0 p<0,001 A_1 vs B_1 p=0,111 A_0 vs A_1 p=0,999 B_0 vs B_1 p=0,970
		1	90,7 ± 13,1	
	B	0	212,8 ± 88,1	
		1	269,9 ± 113,5	

NVD: number of vaginal deliveries (NVD).
group A [NVD = 0 (<3) n = 53; NVD = 1 (≥3) n = 15].
group B [NVD = 0 (<3) n = 57; NVD =1 (≥3) n = 12).

deliveries. This may be due to damaged fascias, ligaments, and a part of the peripheral nerves, as well as poor PFM functioning [14]. The comparison between women who have given one natural childbirth and those after one C-section suggests that those delivering vaginally may be at an 8%-12% higher risk of urinary incontinence and reproductive organ prolapse.

We assumed that the number of vaginal deliveries ≥ 3 contributes to the insufficiency of the true pelvic floor, including SUI in the perimenopausal period. This hypothesis

is supported by numerous studies describing the connection between urinary incontinence and the number of deliveries. In the study of Lassere et al. [15] the odds ratio for women delivering more than three times was 4.1 and for women delivering only twice 3.0. Also the results obtained by Özdemir et al. [16] are worth mentioning. These authors analyzed 233 women with urinary incontinence in terms of their QoL and the PFM strength. They found that higher numbers of natural childbirths entailed statistically significantly decreased QoL and worse PFM function.

In our study, the numbers of deliveries in the groups were as follows: women after ≥ 3 vaginal deliveries constituted 22% of group A and 17% of group B. The women after < 3 deliveries were substantially more numerous and constituted 78% of group A and 83% of group B.

Tukey's *post hoc* test demonstrated significance only in the group of women who had given birth fewer than three times (group 0). The A training program (PFM + TrA) was significantly more effective than the B training program (PFM) only in this group of women. Similar results were reported by Pereira et al. [4], who analyzed the impact of group PFM exercises (G), individual PFM exercises (I), and exercises performed by the control group (C). The numbers of deliveries in these groups were as follows: 1.46 ± 1.50 (G), 1.26 ± 1.27 (I), and 2.13 ± 1.45 (C). Both group and individual training programs included exercises to be performed in one-hour sessions twice a week for 6 weeks. The exercises were done in a lying-back position, a sitting position, and a standing position. About 100 tonic and phasic PFM contractions were performed during one session. The control group did not do any exercises in this period. Both group and individual exercises resulted in substantial improvement in the performance of household duties and outside home activities (Q3). It should be emphasized that the training was only recommended for the PFM. The analysis of other domains of the KHQ, employed by these researchers, shows that despite a small number of deliveries in the studied groups, significant improvement was only observed in the abovementioned domain and the domains of emotions (Q6), sleep problems (Q7), and the frequency of changing panty liners, restricting fluid intake, and changing wet underwear (Q8).

A significant upturn in the performance of household duties (Q3) was also confirmed by Fitz et al. [17], who assessed effects of the three-month training in 36 women with SUI. The principles of the PFM training performed three times a week were as follows: three sessions of 10 slow contraction repetitions, and 3-4 quick contraction repetitions in a lying-back position, a sitting position, and a standing position. The mean number of deliveries in the study group was 2.5 ± 2.2. The authors demonstrated significant differences in all QoL domains assessed by the KHQ.

The study of Nascimento-Correia et al. [18] involved 30 patients who performed group PFM exercises in a lying-back position and in a sitting position for one hour once a week over a 12-week period. The mean number of deliveries in the study group was 1.47 ± 1.51, and in the control—not exercising—group: 2.13 ± 1.46. In this study, the patients only reported improvement in the performance of household duties (Q3), sleep problems (Q7), and the frequency of changing panty liners, fluid intake control, and changing underwear (Q8).

The results described by Hirakawa et al. [19], who compared the effectiveness of classic PFM exercises and PFM exercises combined with biofeedback therapy in 46 women with SUI, show a different distribution of statistically significant differences in the QoL domains. The patients doing only PFM exercises reported improvement in the ability to perform household duties (Q3), physical activity and travelling (Q4a), and SUI related emotions (Q6), as well as the lesser necessity of controlling fluid intake and changing panty liners (Q8). In this group, the mean number of vaginal deliveries was 2.1 ± 0.6.

Kashanian et al. [20] analyzed a group of 91 women to compare the results of PFM exercises and PFM exercises performed using the "Kegelmaster" device. The authors employed the Incontinence Quality of Life (I-QOL) questionnaire and the Urogenital Distress Inventory (UDI) for general QoL assessment after completed treatment. The study was carried out over 12 weeks, during which the patients performed 6-8-second PFM contractions with a 6-second break for 15 minutes twice a day. The mean numbers of births in the groups were 3.56 ± 1.95 and 3.20 ± 1.00 respectively. Kashanian et al. reported the general QoL improvement after completed conservative treatment in the patients doing isolated PFM exercises. A significant upturn was confirmed by two questionnaires.

In their investigation, Kim et al. [21] performed the Valsalva maneuver in three groups: nulliparous, women who had given birth naturally, and women who had a C-section. The authors performed ultrasound measurement of the muscle thickness, simultaneously assessing intravaginal pressure by means of a perineometer. The examination demonstrated substantial differences in the TrA muscle thickness during pushing between the three groups. The thickness of this muscle was smallest during pushing in women after natural childbirth. There was also a significant difference in the external abdominal oblique muscle between the groups. The authors claim that low intravaginal pressure after natural childbirth and after C-section confirms that pregnancy and labor contribute to the ability of TrA to contract. This conclusion may suggest that the greater number of pregnancies, and thus natural childbirths, worsens the functioning of the TrA muscle and contributes to the effectiveness of the PFM + TrA training program. The results presented in our study show that in the case of patients who have delivered fewer than three times, the A training program (PFM + TrA) is significantly more effective than the B training program (PFM). This confirms that the number of deliveries contributes to the effectiveness of the training.

6. Conclusions

Both the combined training of the PFM and the synergistic (TrA) muscle, and the isolated PFM exercises improve the QoL of women with SUI. Nonetheless, the combined PFM and TrA muscle physiotherapy is more effective. The exercises

for the PFM and the synergistic muscle give better results in women who have given birth fewer than three times than isolated PFM exercises.

7. Limitations

The study involved 137 patients. Considering a huge number of women who experience SUI, it is necessary to conduct further research on their QoL levels. In the future, the strength of the PFM could be assessed using a perineometer—an instrument for measuring intravaginal pressure produced by PFM contractions.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

The research was conceived and designed by Magdalena Ptak. Samples were collected, prepared, and analyzed by Magdalena Ptak under the supervision of Agnieszka Brodowska, Sylwester Ciećwież, Jolanta Nawrocka-Rutkowska, and Esther D. Mohedo. Data analysis and interpretation were completed by Magdalena Ptak and supervised by Agnieszka Brodowska and Sylwester Ciećwież. The manuscript was drafted by Magdalena Ptak and was proofread and corrected by Iwona Rotter and Andrzej Starczewski.

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Research Article

Injectable Bulking Agent to Treat Postprostatectomy Urinary Incontinence: A Safety and Effectiveness Pilot Study

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Objectives. To evaluate the safety and effectiveness of the injectable bulking agent Opsys® (Promedon, Cordoba, Argentina) for treating minimal postprostatectomy stress urinary incontinence (SUI). *Patients and Methods*. Single-centre, pilot study on ten male patients with SUI, < 30 g urine loss/ 24 h, more than 1 year after radical prostatectomy. Patients were treated by endoscopic transurethral injections of bulking agent in the presphincteric zone of the urethral submucosa. The results were evaluated using a pad weight test to quantify the differences in urine loss at 1, 3, and 6 months after intervention. Subsequently, the results of treatment were also evaluated by International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), Incontinence Impact Questionnaire (IIQ-7), Urogenital Distress Inventory Short Form (UDI-6-SF), and the Patient Global Impression of Improvement (PGI-I) at 1, 3, and 6 months after intervention. *Results*. The primary outcome was the absolute result of the 24-hour pad weight test after treatment. Treatment success was defined as <3 g urine loss/24 h, improvement as ≥50% decrease in urine loss/ 24h, failure as <50% decrease in urine loss/24 h, or worsening of urine loss. Success was demonstrated in one, improvement in one, and failure in eight patients one month after treatment. One patient improved and 9 failed 3 and 6 months after treatment. The median 24-hour pad weight test was higher at all three moments of follow-up (1, 3, and 6 months after treatment). The median 24-hour pad weight test was before treatment 17.3g (6.4-20.9) and 1, 3, and 6 months after treatment, respectively, 40.3g (5.9-130.6) p= 0.038, 38.3g (18.3-202.1) p= 0.014, 55.0g (16.5-314.6) p= 0.028. The ICIQ-SF was significantly higher at 3 and 6 months, respectively 15.0 (12.0-18.5) p= 0.007 and 16.0 (12.5-17.5) p=0.012 versus 10.0 (9.0-12.0) before injection. No significant differences were found between IIQ-7, UDI-6-SF, and PGI-I before and after injection. Complications occurred in four patients: two patients reported spontaneously resolved haematuria and two patients reported urinary frequency. All complications were classified as Clavien–Dindo 1. *Conclusion*. Injection therapy with Opsys® bulking agent is not an effective treatment option for male SUI after radical prostatectomy. It is not a safe treatment option, due to worsening urine loss after treatment.

1. Introduction

Urinary incontinence after radical prostatectomy has a high impact on patients' quality of life. The current guidelines on postprostatectomy urinary incontinence stated that surgical treatments can be considered for men who fail conservative treatment [1]. The artificial urinary sphincter is still considered the gold standard for treating postprostatectomy incontinence [2]. The male sling and Proact balloons, however, have proved to be good alternative treatment options for patients with mild postprostatectomy incontinence [3]. However, there is still no appropriate minimal invasive intervention available for minimal postprostatectomy incontinence (<30 g urine loss/24-hour pad test), though injection of a bulking agent might be a solution. Multiple bulking agents have been used for treatment of female stress urinary

incontinence (SUI) with inconsistent results on effectiveness [4]. The Opsys® (Promedon, Cordoba, Argentina) bulking agent seemed to be safe and effective for treating female SUI and can be offered as a minimally invasive procedure with quite durable clinical results and minimal complications [5]. Opsys® is made of a polyacrylate polyalcohol copolymer, and it is a nonabsorbable biomaterial which is also used in children to treat vesicoureteral reflux [6]. The biocompatibility and nonmigration characteristics as well as long term bulking stability in the injection site of Opsys® have been studied in in-vivo and in-vitro studies [7]. Various kind of bulking agents have been used to treat male incontinence, the outcome was variable, and the reintervention rate of 52.9% was high [8]. However, there are no scientific data regarding the efficacy and safety of Opsys® for treating postprostatectomy incontinence [8]. We hypothesised that injection of the bulking agent Opsys® might be an appropriate minimal invasive treatment for patients with minimal SUI after prostatectomy. The expectation was that bulking agents could replace the more invasive and more comorbidity-related implantation of slings and Proact balloons for these patients. We present a pilot study that evaluated the safety and efficacy of the injectable bulking agent Opsys® for treating postprostatectomy SUI.

2. Materials and Methods

2.1. Inclusion and Exclusion Criteria. All patients gave their written informed consent before inclusion in the study. The study was approved by the local ethics committee and registered in the Dutch Trial registration as number NL.57054.044.15. Patients were included in this pilot study and treated with Opsys® bulking agent between October and December 2016. Inclusion criteria were minimal SUI (<30 g/day loss during the 24-hour pad weight test), at least 12 months after radical prostatectomy, and being refractory to conservative treatment, such as pelvic floor muscle training. Patients remained dry at night and could voluntarily stop micturition. Patients with a history of radiation treatment for prostate carcinoma, bladder neck sclerosis, urethral stricture, urgency urinary incontinence, detrusor overactivity during urodynamic evaluation, and/or urinary tract infection were excluded from the study.

2.2. Bulking Agent. Opsys® consists of particles of polyacrylate polyalcohol copolymer which is a nonabsorbable biomaterial. It has a very high molecular mass (~10,000 kDa) and comes in the form of sterile pyrogen-free particles. The macroparticles have an average diameter of 300 μm and the carrier is a 40% glycerol solution. This substance can be manually injected easily through small needles (21-gauge). Once implanted, the glycerol solution is eliminated by the reticuloendothelial system without metabolizing it and is excreted through the kidneys, leaving the particles behind for permanent bulking [7].

2.3. Injection Procedure. Broad-spectrum antibiotics were administered. General or regional anaesthesia was given based on patients' preference. All procedures were performed in the operating room. Opsys® was implanted using a video endoscope with 6-French working channel, 0° optics, and a 21-gauge transurethral injection needle. All procedures were video-recorded. The bulking agent was injected in a transurethral manner into the presphincter zone of the urethral submucosa. Injections of about 1.0 mL of bulking agent around all quadrants in the urethra were executed. The bladder was emptied after the procedure by a single use catheter 12 French.

2.4. Follow-Up. All patients were assessed prior to treatment via their medical history, physical examination, and endoscopic- and urodynamic evaluations including postvoid residual volume. All patients were assessed again 1, 3, and 6 months after treatment. Pretreatment and posttreatment SUI were evaluated using two 24-hour pad weight tests. Posttreatment success was defined as a maximum of 3 g of urine loss during the 24-hour pad weight test. Improvement was defined as a ≥50% reduction of urine loss during the 24-hour pad weight test. Failure was classified as <50% reduction or increased urine loss during the 24-hour pad weight test.

Uroflowmetry and postvoid residual volume was measured each post treatment visit.

The following validated questionnaires were administered preoperatively and at every follow-up visit: International Consultation on Incontinence Questionnaire Short Form (ICIQSF), Incontinence Impact Questionnaire (IIQ-7), and Urogenital Distress Inventory Short Form (UDI-6-SF). In addition, the Patient Global Impression of Improvement (PGI-I) was assessed postoperatively [1]. Complications were assessed and classified using the Clavien–Dindo classification [9].

2.5. Statistical Analysis

2.5.1. Power Calculation. A total of 30 subjects were planned to be included in this clinical study, distributed among two research centres. The inclusion of 30 patients within the given time period was feasible for the two centres. Injection of Opsys® was expected to result in a success percentage of 30-50%. The sample size calculation was based on the two-sided confidence interval formula (Score (Wilson)) for one proportion. This was calculated using PASS 11. A sample size of 30 produces a two-sided 95% confidence interval with a width equal to 0.337 when the sample proportion is 0.500: 0.332 to 0.668.

2.5.2. Follow-Up Data. Continuous normally distributed variables are reported as means with standard deviation (SD), and continuous nonnormally distributed variables are presented as medians with interquartile range (IQR). The preoperative and postoperative (1, 3, and 6 months) 24-hour pad weight test ICIQ-SF, IIQ-7, UDI-6-SF, and PGI-I scores were compared using the Wilcoxon signed-rank test. To analyse the PGI-I score at 1, 3, and 6 months, we adapted a baseline value of 4.0, which indicated no change.

A p-value <0.05 was considered to be statistically significant. All data were analysed using SPSS version 23.0.

Table 1: Baseline characteristics.

Variable	N=10
Age (years), mean ± SD	67.0 ± 6.1
BMI (kg/m^2), mean ± SD	29.7 ± 6.3
Mode of previous prostate surgery, n (%)	
Open radical prostatectomy	5 (50)
Robot-assisted radical prostatectomy	4 (40)
Laparoscopic radical prostatectomy	1 (10)
Anaesthesia, n (%)	
Spinal	5 (50)
General	5 (50)
Operation time (min), mean ± SD	14.1 ± 3.8
Number of injections, mean ± SD	4.7 ± 1.1
Total injected volume (mL), mean ± SD	2.3 ± 1.5

3. Results

Ten patients were included in the pilot study. The calculated power of 30 patient was not accomplished due to an inclusion stop after interim analysis of the effectiveness and safety results of the first 10 patients. Table 1 summarizes the baseline characteristics. The mean patient age was 67.0 years (range 55–77 years). The mean BMI was 29.7 kg/m^2 (range 21-44 kg/m^2). The following comorbidities were present: hypertension (n=4), diabetes mellitus (n=3), hypercholesterolemia (n=2), sleep apnoea syndrome (n=1), and chronic obstructive pulmonary disease (n=1). Three patients did not have significant comorbidities. The postvoid residual volume was in all patients < 50 mL.

The mean number of transurethral injections per patient was 4.7 (range 3–7). The mean total injected volume of bulking agent was 2.3 mL (0.3–5.0 mL).

Complications occurred in four patients. Two patients had light haematuria for 2–4 days after the injection that resolved by itself. Two patients reported urinary frequency, one patient for 1 day after the injection and one patient for 2 months. All complications were classified as Clavien–Dindo 1.

The results after 1 month showed one patient with success, one with improvement, and eight with failure (Table 2). At 3 and 6 months' follow-up, none of the patients showed a successful outcome: one patient exhibited improvement and nine patients showed failure. The median 24-hour pad weight test was significantly higher 1, 3, and 6 months after injection of the bulking agent, respectively, 40.3 g (5.9-130.6) p= 0.038, and 38.3 g (18.3-202.1) p= 0.014, 55.0 g (16.5-314.6) p= 0.028, compared with baseline, 17.3 g (6.4-20.9). Posttreatment clinical examination/interview demonstrated no signs of urge incontinence. Posttreatment residual volume was in all patients below 50 mL.

The ICIQ-SF was significantly higher after 3 months, 15.0 (12.0-18.5) p= 0.007, and 6 months, 16.0 (12.5-17.5) p=0.012, compared with baseline, 10.0 (9.0-12.0) (Table 2). No significant differences were found between the IIQ-7, UDI-6-SF, and PGI-I scores before and after injection.

4. Discussion

SUI greatly affects patients' quality of life. The minimally invasive procedure that entails injecting the bulking agent Opsys® in patients who have minimal SUI failed in 9 of the 10 patients. Consequently, the inclusion of patients in the study was stopped before the calculated power of 30 patients was reached. Furthermore, the follow-up in the study was shortened by 6 months instead of 12 months in the initial protocol. So, patients were able to get another treatment for incontinence. Subsequently, one patient was treated with an artificial urinary sphincter and two patients with a male sling. All three patients were dry after this reintervention. The remaining 6 patients who did not improve after injection treatment refused an additional treatment. A major weakness of this study is the small sample size and the lack of an appropriate control group. However, it is also important to publish these results and to suggest explanations for the poor outcome of the injection of the bulking agent Opsys®.

First, three independent urologists expert in male urinary incontinence evaluated the recorded videos of the endoscopic injection procedures of the patients. They provided a blinded prediction of the functional outcome of each injection procedure. There was no correlation between any of the predicted results and the real-time outcomes. The experts concluded that all injection procedures were performed according to the technical description in the protocol. The independent urologist checked for the following eight steps of injection procedures: (1) The endoscope was introduced in the bladder and the injection needle in the endoscope till the tip of the needle was seen; (2) the endoscope and the tip of the needle removed backward up to the presphincter zone; (3) the needle was injected at a 30°-45° angle with regard to the urethral mucosa; (4) the endoscope was placed at a 0° angle, parallel to the urethra; (5) the position of the needle was checked injecting a small amount of product, which demonstrated bulkiness in the urethral submucosa and around 1 mL Opsys® was injected; (6) the needle was removed from the injection site after 15-30 seconds; (7) the clinician injected at four quadrants in the urethral submucosa or till bulkiness and closing of the urethral lumen was observed; (8) the endoscope

Table 2: Postoperative results. P-values correspond to the Wilcoxon signed-rank test for comparing baseline with 1, 3 and 6 months follow-up. ICIQ-SF = International Consultation on Incontinence Short Form; IIQ-7 = Incontinence Impact Questionnaire; UDI-6-SF = Urogenital Distress Inventory Short Form; PGI-I = Patient Global Impression of Improvement. ∗∗ n.c. = no change; for statistical analysis we adopted a baseline value of 4.

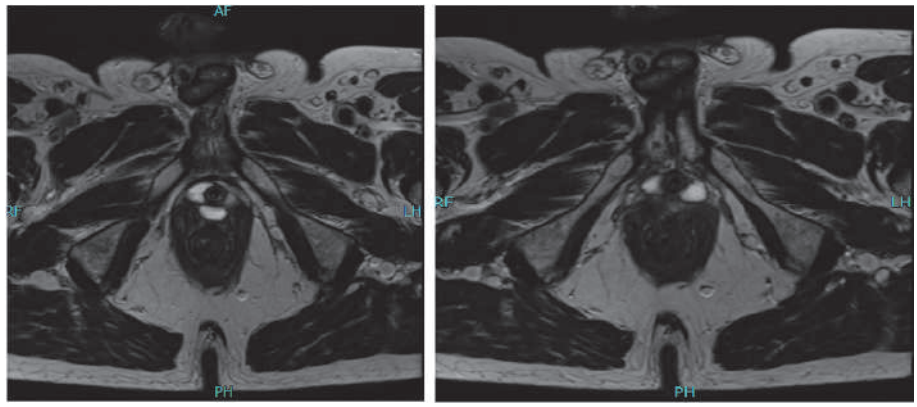
	Baseline	1 month (n=10)	P	3 months (n=10)	P	6 months (n=10)	P
Treatment outcome, n (%)							
Success		1 (10)		0 (0)		0 (0)	
Improvement		1 (10)		1 (10)		1 (10)	
Failure		8 (80)		9 (90)		9 (90)	
24-h pad weight test (g), median (IQR)	17.3 (6.4 – 20.9)	40.3 (5.9 – 130.6)	0.038	38.3 (18.3 – 202.1)	0.014	55.0 (16.5 – 314.6)	0.028
ICIQ-SF score, median (IQR)	10.0 (9.0 – 12.0)	16.0 (11.8 – 18.0)	0.109	15.0 (12.0 -18.5)	0.007	16.0 (12.5 – 17.5)	0.012
IIQ-7 score, median (IQR)	26.5 (13.0 – 41.5)	38.0 (34.5 – 50.3)	0.122	49.5 (17.8 – 67.0)	0.413	36.0 (15.5 – 62.0)	0.528
UDI-6-SF score, median (IQR)	33.0 (20.8 – 40.3)	36.0 (26.5 – 44.0)	0.553	39.0 (17.0 – 58.5)	0.552	39.0 (28.0 – 47.0)	0.766
PGI-I score, median (IQR)	n.c.∗∗	5.5 (4.8 – 6.0)	0.102	4.5 (3.8 – 6.0)	0.121	5.0 (3.5 – 5.0)	0.206

was not moved forward through the injection site, since this could deform injected material bulkiness.

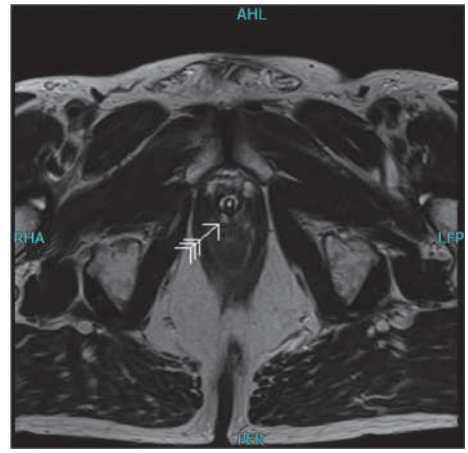
Second, we used magnetic resonance imaging (MRI) of the pelvis/urethra to evaluate the anatomical positioning of the bulking agent after injection. Postinjection MRI was not part of the protocol. However, we performed postinjection MRI in all patients to investigate the poor outcome after injection. A radiologist of the study centre and two authors of this manuscript assessed the MRI results. It showed no correlation between the demonstrated MRI bulking agent around the urethra and the number of injections, volume of the injections, location of injections, or functional outcome (Figure 1). The differences between location/volume of injection and the MRI results are difficult to explain. There should be no risk of migration around the injection site or to other parts of the body because of the 300 μm average diameter of the polyacrylate polyalcohol copolymer particles. Because these macroparticles are flexible, irregularly shaped, and highly deformable by compression, they may be extruded using 21-gauge needles. Once implanted, macroparticles enlarge the volume of the tissue, generating little fibrotic growth around them (i.e., 70–125 μm thick) [7]. Subsequently, MRI evaluation of the injection technique and the anatomical position of the bulking agent did not result in an explanation of failure or even worsening of the urinary incontinence. The results of our study were therefore disappointing compared with the former results of Opsys® in women with SUI [5]. Hence, we must address the causes of the failed treatment of male SUI after radical prostatectomy.

Figures 1(a) and 1(b) MRI views demonstrated different location and amount of bulking agent on 3.5 mm slides. Both patients had 5 injections with bulking agent. The urethra can be recognized by the transurethral catheter.

Postprostatectomy urinary incontinence is due to damage of the anatomic support and pelvic innervation. The anatomic support consists of the urethral sphincter complex for passive and active continence and the anterior and posterior support structures around the urethra and the pelvic floor [10]. Women also have internal sphincter deficiency, but the aetiology of urinary incontinence is different between the sexes. In men, pelvic surgery leading to neurovascular and anatomic support damage is the main cause, while birth-related trauma is the main cause in women. The trauma that induces urinary incontinence in men tends to occur at an older age (sixties onwards) than in women (childbearing age). The collagen tissue surrounding the urethra might be less supportive in older patients, especially if there is neurovascular damage. The bulking agent around the urethra might have further diminished the vascularisation of the urethra due to obstruction by the bulk material. Our results compare unfavourably to earlier results with Opsys® in the treatment of female SUI and other published results on bulking agents in the treatment of male SUI. One patient showed increased incontinence (>1000mL / 24 hours) and was additionally treated by an artificial urinary sphincter implant. To our knowledge, this worsening of incontinence after bulking agent injection was never published. The former published studies on transurethral injection of collagen demonstrated a short-term success rate of 44–58%. None of those studies, however, were randomised or placebo-controlled. A subsequent review published in 1996 concluded that transurethral injection with collagen has a limited role in the management of urinary incontinence [11]. Macroplastique injections demonstrated a success rate of 43% and even dry rates up to 80% in a selected group of patients with minimal incontinence [12, 13]. Chughtai et al. evaluated all interventions for SUI or mixed incontinence in male patients during 2000–2011 [8]. This study showed that the use of bulking agent has decreased from 52.2% to 16.4% in favour of sling surgery, which increased from 14.8% to 51.4%. One of the reasons for this might be the higher reintervention rate during the first year following surgery in patients treated with bulking agents (40.1%) compared with the sling (9.7%) and an artificial urinary sphincter (7.1%). Our hypothesis regarding the failure of Opsys® bulk injection in the present study is that postprostatectomy urinary incontinence has multifactorial causes, including anatomic support and pelvic innervation damage. These multifactorial causes are not resolved by injecting this bulking agent.



(a) Patient with 5 submucosal urethral injections at 1, 3, 5, 7, and 9 o'clock, total amount of Opsys® injected is 2.5 mL. Two transverse views. Lateral and dorsal of the urethra are white spots which shows bulking agent



(b) Patient with 5 submucosal urethral injections at 2, 5, 6, 8, and 10 o'clock, total amount of Opsys® injected is 4.0 mL. Only 1 transverse view on MRI shows a white spot which shows the bulking agent

FIGURE 1: **Magnetic resonance imaging (MRI∗) views of bulking agent.** ∗*1.5 T Siemens Avanto MRI:T2 Blade 3,5mm sagittal, T1 space coronal 0.9mm, T2 TSE transversal 3.5mm, T2 TSE coronal oblique 3.5mm, and T2 TSE coronal 3.5mm. Technical aspects: Field Of View 240mm, distance 30%, phase right to left, resolution 320, and phase resolution 86%.*

5. Conclusions

Injection of Opsys® bulking agent is not a safe and effective treatment option for male SUI after radical prostatectomy. The treatment resulted in worsening of the minimal SUI. We could not find an evident explanation for these results. So, we could not suggest adaptions to improve the treatment with Opsys® bulking agent in male SUI.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

Dr. Cornel reports personal fees from Promedon, outside the submitted work.

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Research Article

Predictors for De Novo Overactive Bladder after Readjustable Mid-Urethral Sling Procedure in Women with Stress Urinary Incontinence due to Intrinsic Sphincter Deficiency

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Purpose. This study identified noninvasive factors that predict overactive bladder (OAB) after readjustable mid-urethral sling surgery (Remeex system) in women with stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD). *Materials and Methods*. We retrospectively reviewed the medical records of 130 women with SUI due to ISD [Valsalva leak-point pressure (VLPP) <60 cm H_2O] who underwent the Remeex procedure between February 2011 and March 2017. Patients were classified according to OAB symptoms before and 6 months after the Remeex procedure: Group 1, without preoperative and postoperative OAB (n=46); Group 2, without preoperative OAB and with postoperative OAB (de novo OAB, n=15); Group 3, with preoperative OAB and without postoperative OAB (n=25); Group 4, with preoperative and postoperative OAB (n=44). Noninvasive clinical and urodynamic factors were evaluated as predictors of de novo OAB. *Results*. The four groups significantly differed with respect to age (p=0.036), peak urinary flow rate (PUFR) one month after surgery (post-PUFR, p=0.001), and postvoid residual (PVR) one month after surgery (post-PVR, p=0.005). No significant differences were detected for body mass index, diabetes, multiparity, menopause, previous hysterectomy, previous incontinence surgery, previous pelvic organ prolapse surgery, pyuria, preoperative PUFR, preoperative PVR, maximal cystometric capacity, VLPP, maximum urethral closure pressure, detrusor pressure at PUFR, and detrusor overactivity (p>0.05). Post-PUFR decreased significantly compared with preoperative PUFR in Groups 1, 2, and 4 (p=0.002, p=0.001, and p=0.001, respectively). Pairwise comparisons of post-PUFR and post-PVR revealed statistically significant differences between Group 2 and other groups (p<0.0125). Multivariate logistic regression analyses showed that post-PUFR was the only significant predictor of de novo OAB (odds ratio = 0.823, 95% confidence interval 0.727-0.931, p=0.002). *Conclusions*. Reduced PUFR after the Remeex procedure is a promising predictor of risk for de novo OAB. This metric is noninvasive and easy to measure.

1. Introduction

Patients with stress urinary incontinence (SUI) display a spectrum of urethral characteristics ranging from a highly mobile urethra with good intrinsic function to an immobile urethra with poor intrinsic function [1]. The definition of urethra with poor intrinsic function is imprecise [2, 3], but this condition is considered to have intrinsic sphincter deficiency (ISD), which is recognized as a risk factor for failure of the mid-urethral sling procedure [4–6]. The 12-month success rates of the mid-urethral sling procedure in 72 patients with SUI were 91% in the tension-free vaginal tape (TVT) group and 89% in the transobturator tension-free vaginal tape (TVT-O) group [7]. The 5-year objective cure rate of 254 patients with SUI was 84.7% in the TVT group and 86.2% in the TVT-O group [8]. By contrast, ISD patients have a 6-month cure rate of only 79% in the TVT group and 55% in the TVT-O group [9].

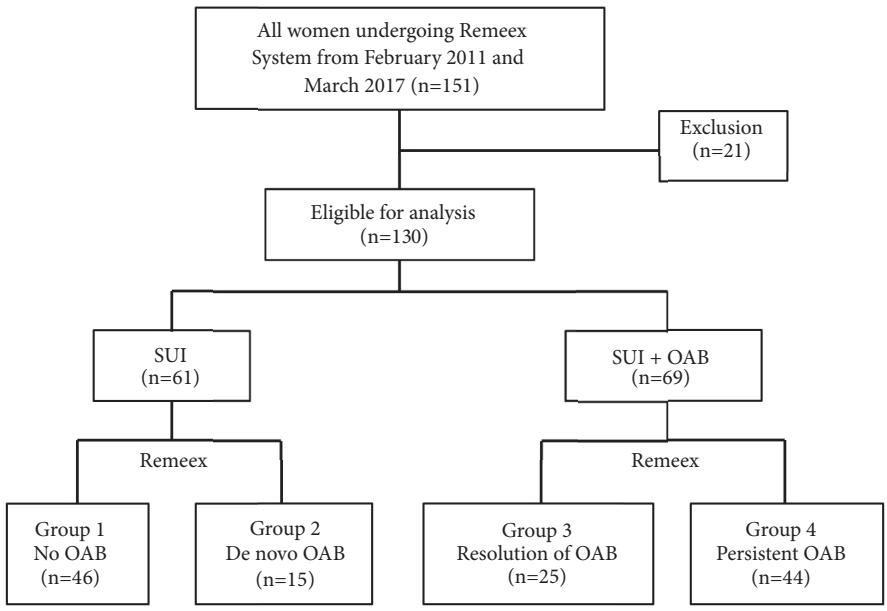

Figure 1: **Study cohort and distribution of women according to the presence of overactive bladder (OAB) symptoms before and 6 months after the Remeex procedure**. Group 1, without preoperative and postoperative OAB; Group 2, without preoperative OAB and with postoperative OAB; Group 3, with preoperative OAB and without postoperative OAB; Group 4, with preoperative and postoperative OAB.

The readjustable mid-urethral sling (Remeex system; Neomedic International, Terrassa, Spain) has the advantages of regulating of sling tension postoperatively and avoiding urinary obstruction or persistent SUI due to inappropriate sling tension [10]. The Remeex procedure has good efficacy even in ISD patients. Among 102 women with previous failed surgery or ISD, 91 (89%) patients were cured and 6 (6%) were improved at 27 months of mean follow-up [11]. Sling tension readjustment was needed in 14 patients (14%). Among 50 SUI patients with ISD, 45 (90%) patients were cured and 3 (6%) were improved at 7 years of mean follow-up [12]. Sling tension readjustment was needed in three patients (6%).

Urinary obstruction or persistent SUI is no longer serious conditions since the readjustable mid-urethral sling was introduced; however, de novo overactive bladder (OAB) or worsening preexistent OAB symptoms continue to be challenging. These symptoms may reduce patient satisfaction after the mid-urethral sling procedure and adversely affect health-related quality of life more than other forms of urinary incontinence [13]. Postoperative urinary tract infections, bladder outlet obstruction, urinary tract perforation, and idiopathic urgency have been suggested as possible causes of de novo OAB after sling surgery. The aim of this study is to identify noninvasive clinical parameters that can be used to predict OAB in women with SUI due to ISD following the readjustable mid-urethral sling surgery.

2. Materials and Methods

2.1. Patients. We obtained approval for this study from the Institutional Review Board at CHA Bundang Medical Center (approval number: 201810038). The medical records of 151 women with SUI due to ISD who underwent the Remeex procedure between February 2011 and March 2017 were reviewed. The following inclusion criteria were used: (1) aged ≥18 years, (2) Valsalva leak-point pressure (VLPP) <60 cm H_2O measured by urodynamic studies, and (3) more than 1 year of follow-up after readjustable mid-urethral sling surgery. A total of 130 patients met the inclusion criteria (Figure 1). Exclusion criteria included the presence of lower urinary tract pathology such as urinary tract calculus, bladder tumors, interstitial cystitis, clinically significant bladder outlet obstruction, and symptomatic or recurrent urinary tract infections. Subjects who had a neurogenic cause underlying OAB also were excluded.

Women with SUI due to ISD were classified into one of the following four groups according to the presence of OAB symptoms before and 6 months after the Remeex procedure: Group 1, without preoperative and postoperative OAB (n=46); Group 2, without preoperative OAB and with postoperative OAB (de novo OAB, n=15); Group 3, with preoperative OAB and without postoperative OAB (n=25); Group 4, with preoperative and postoperative OAB (persistent OAB, n=44) (Figure 1).

2.2. Preoperative Examination. The preoperative examination included a detailed medical and surgical history, physical examination, a 3-day bladder diary using a 5-point urgency rating scale, urine analysis and culture, stress test, and urodynamic study, which included the maximal cystometric capacity, VLPP, maximum urethral closure pressure (MUCP), detrusor pressure at peak urinary flow, uroflowmetry, and postvoiding residual measurement. The results of uroflowmetry were accepted when voided urine volume was more than

150 ml, PUFR was measurable, and an adequate voiding curve was generated. Women who did not void greater than 150 ml were asked to repeat the test after drinking water. ISD was defined as VLPP <60 cm H_2O. Women who displayed urinary frequency (≥8 voids/24 h), urinary urgency (≥6 episodes/3 d), or urge incontinence (≥3 episodes/3 d) were considered as OAB patients.

2.3. Surgical Procedures. The readjustable mid-urethral sling surgery was performed using the Remeex system. The Remeex device consisted of a suburethral polypropylene prosthesis that was linked to a pressure adjusting device (varitensor) by two traction threads. The varitensor was implanted permanently in the abdominal rectus muscle fascia, and the postoperative sling tension was adjusted by connecting the manipulator to the varitensor.

The surgical procedure was performed under spinal anesthesia with the patient placed in the dorsal lithotomy position. A 4 cm abdominal transverse incision was made 2 cm above the symphysis pubis, and the dissection was continued until the rectus sheath was exposed. The anterior vaginal wall was incised from the middle urethra to the urethrovesical junction (approximately 2 cm) and then dissected from the underlying periurethral tissues to the endopelvic fascia. A needle was passed through the retropubic space to perforate the abdominal muscle fascia at the lateral margins of the transverse incision from the vaginal to the abdominal plane. A cystoscopy was performed to ensure that the bladder had not been perforated. Then, the traction threads were passed through a needle-eye and drawn upward on each side until it appeared at the abdominal incision. A polypropylene mesh was placed at the mid-urethral level. The traction threads were inserted into the varitensor and knotted together. The manipulator was then rotated clockwise until the varitensor lay on the rectus sheath without tension. The vaginal and abdominal incisions were closed with the manipulator protruding through the abdominal incision.

Patients were examined the day after surgery. They were asked whether they could urinate without any difficulty, and they were asked to perform a cough test or any activity that would generally result in SUI. If there was a urine leak, the manipulator was rotated to tighten the sling until no further leakage occurred without significant residual urine. The manipulator was removed after the patient had reached continence.

2.4. Follow-Up. Follow-up visits were scheduled at 1, 3, 6, and 12 months, and then every 12 months thereafter. Each follow-up examination included uroflowmetry, postvoid bladder scanning, and a stress test to measure the degree of incontinence. If urine leak was detected, the Remeex system was adjusted as follows. The patient was placed under local anesthetic, the manipulator was reattached to the varitensor through a previous abdominal incision, and the sling tension was readjusted. A 3-day bladder diary using a 5-point urgency rating scale was performed at 6 months after the surgery.

2.5. Statistical Analysis. The following nine clinical parameters were evaluated as potential predictors of de novo OAB: age, body mass index (BMI), diabetes, multiparity, menopause, previous hysterectomy, previous incontinence surgery, previous pelvic organ prolapse surgery, and pyuria. The following nine urodynamic parameters were evaluated as potential predictors of de novo OAB: preoperative peak urinary flow rate (pre-PUFR), preoperative postvoid residual (pre-PVR), maximal cystometric capacity (MCC), VLPP, MUCP, detrusor pressure at peak urinary flow (PdetQmax), detrusor overactivity (DO), peak urinary flow rate one month after surgery (post-PUFR), and postvoid residual one month after surgery (post-PVR). The potential predictive factors were compared among the four groups using the Kruskal-Wallis test and Chi-square test. To identify significant factors that affect de novo OAB, univariate and multivariate logistic regression analyses were performed. Regression analysis results are presented as odds ratio (OR) and 95% confidence interval (CI). Statistical analyses were performed using SPSS 24.0 (IBM Corp., Armonk, NY). Data are presented as the mean ± standard deviation. A p value less than 0.05 was considered as statistically significant.

3. Results

The study enrolled 130 patients. The mean age was 59 ± 11 years (range 33-86 years, Table 1). The four groups differed significantly with respect to age (p=0.036), post-PUFR (p=0.001), and post-PVR (p=0.005, Table 1). By contrast, there were no significant differences among the four groups with respect to BMI, diabetes, multiparity, menopause, previous hysterectomy, previous incontinence surgery, previous pelvic organ prolapse surgery, pyuria, pre-PUFR, pre-PVR, MCC, VLPP, MUCP, PdetQmax, and DO (p>0.05). The post-PUFR decreased significantly compared with pre-PUFR in Groups 1, 2, and 4 (p=0.002, p=0.001, and p=0.001, respectively) (Figure 2). There were no significant differences between pre-PUFR and post-PUFR in Group 3 (p=0.269).

Pairwise comparisons of age, post-PUFR, and post-PVR indicated that post-PUFR and post-PVR significantly differed between Group 2 and the other groups (p<0.0125, Table 2). Post-PUFR was significantly lower in Group 2 than in other groups. Post-PVR was also significantly higher in Group 2 than in other groups.

Table 3 presents the results of univariate and multivariate logistic regression analyses of clinical and urodynamic factors as predictors of de novo OAB. Among 130 women with SUI due to ISD, 15 patients had de novo OAB. Multivariate logistic regression analyses indicated that post-PUFR was the only significant predictor of de novo OAB after the Remeex procedure (OR = 0.823, 95% CI 0.727-0.931, p=0.002). Multivariate analyses indicated that age and post-PVR were not predictive of de novo OAB.

4. Discussion

We found that post-PUFR decreased significantly after surgery with the Remeex system, and the post-PUFR of

Table 1: Comparison between women according to preoperative and postoperative OAB after the Remeex procedure for stress urinary incontinence with intrinsic sphincter deficiency (data are means ± standard deviation).

Potential predictive variable		Total	Group 1	Group 2	Group 3	Group 4	*P* value∗
		n=130	*n*=46	*n*=15	*n*=25	*n*=44	
Clinical variables							
Age (year)		59±11	57±10	60±15	55±11	62±9	0.036[a]
BMI (kg/m^2)		24.6±3.3	24.4±2.8	24.9±4.2	24.6±3.1	24.7±3.6	0.979[a]
Diabetes	Present	18	3	2	4	9	0.286[b]
	Absent	112	43	13	21	35	
Multiparity	Present	61	25	4	8	24	0.080[b]
	Absent	69	21	11	17	20	
Menopause	Present	93	33	9	17	34	0.605[b]
	Absent	37	13	6	8	10	
Previous hysterectomy	Present	31	9	6	7	9	0.371[b]
	Absent	99	37	9	18	35	
Previous incontinence surgery	Present	32	7	3	9	13	0.196[b]
	Absent	98	39	12	16	31	
Previous POP surgery	Present	10	3	1	3	3	0.847[b]
	Absent	120	43	14	22	41	
Pyuria	Present	9	1	0	3	5	0.167[b]
	Absent	121	45	15	22	39	
Urodynamic variables							
Pre-PUFR (ml/sec)		25.1±6.3	24.7±6.2	25.7±2.9	23.0±5.8	26.6±7.4	0.104[a]
Pre-PVR (ml)		14±25	15±25	7±11	11±18	18±32	0.306[a]
MCC (ml)		297±46	297±61	305±14	294±52	296±31	0.799[a]
VLPP (cm H_2O)		45±10	45±9	47±9	44±12	43±9	0.381[a]
MUCP (cm H_2O)		57±25	58±27	51±19	53±23	61±25	0.516[a]
PdetQmax (cm H_2O)		18±9	19±9	20±11	16±8	17±8	0.415[a]
DO	Present	26	9	1	9	7	0.105[b]
	Absent	104	37	14	16	37	
Post-PUFR (ml/sec)		20±8	20.7±8.1	13.2±3.8	22.3±6.6	21.7±8.3	0.001[a]
Post-PVR (ml)		43±67	29±40	97±113	40±67	41±63	0.005[a]

BMI = body mass index; POP = pelvic organ prolapse; pre-PUFR = preoperative peak urinary flow rate; pre-PVR = preoperative post-void residual; MCC = maximal cystometric capacity; VLPP = Valsalva leak point pressure; MUCP = maximal urethral closing pressure; PdetQmax = detrusor pressure at peak urinary flow; DO = detrusor overactivity; post-PUFR = peak urinary flow rate at one month after the Remeex procedure; post-PVR = post-void residual at one month after the Remeex procedure.

∗$p<0.05$ was considered as statistically significant.

[a]Kruskal-Wallis test.

[b] Chi-square test.

Group 2 (de novo OAB) had the largest decrease compared with the other three groups. Statistical analyses indicated that the post-PUFR decrease was significantly associated with de novo OAB after surgery with the Remeex system. We anticipated this result because obstruction of the bladder outlet was hypothesized as the possible cause of de novo OAB. Other possible causes of de novo OAB after anti-incontinence surgery include postoperative urinary tract infection and foreign bodies such as mesh or suture materials with or without adherent calculus [14]. Among these possible causes, bladder outlet obstruction could alter receptor function, myogenic denervation, and neurotransmitter balance, leading to detrusor overactivity [15].

Although decreased post-PUFR does not correspond exactly with bladder outlet obstruction, maximum urinary flow rate ≤15 ml/sec appeared to be the most discriminating parameter of female bladder outlet obstruction in neurologically intact women [16]. Patients in Group 2 were considered to have bladder outlet obstruction after the Remeex procedure because their mean PUFR decreased from 25.7 ml/sec to 13.2 ml/sec. Mean post-PUFR was <15 ml/sec in Group 2 after the Remeex procedure. The bladder outlet obstruction index (BOOI) was developed to diagnose benign prostatic obstruction in older men [17]. BOOI can be calculated from PdetQmax and PUFR, which are measured by urodynamic studies. However, to obtain BOOI, the urodynamic study should be performed again after mid-urethral sling surgery. Some patients feel discomfort throughout the urodynamic study. In a survey to query patient responses to the urodynamic study, of 314 patients who completed the questionnaire (60%

Table 2: Pair wise comparisons of age, post-PUFR, and post-PVR among four groups.

Variable	Group 1	Group 2	Group 3	Group 4	*P* value∗ [a]	*P* value∗ [b]					
						G1 vs G2	G1 vs G3	G1 vs G4	G2 vs G3	G2 vs G4	G3 vs G4
Age	57±10	60±15	55±11	62±9	0.036	0.756	0.329	0.036	0.543	0.300	0.004
post-PUFR	20.7±8.1	13.2±3.8	22.3±6.6	21.7±8.3	0.001	0.001	0.402	0.654	0.001	0.000	0.689
post-PVR	29±40	97±113	40±67	41±63	0.005	0.001	0.287	0.104	0.009	0.011	0.807

Post-PUFR = peak urinary flow rate at one month after the Remeex procedure; post-PVR = post-void residual at one month after the Remeex procedure.
∗$p<0.05$ was considered as statistically significant.
[a] Kruskal-Wallis test.
[b] Post-hoc least significant difference test.

Table 3: Logistic regression analysis of predictive factors for overactive bladder at 6 months after the Remeex procedure in women with stress urinary incontinence due to intrinsic sphincter deficiency.

Predictive factor*	Univariate			Multivariate		
	P	OR	95% CI	*P*	OR	95% CI
Age (year)	0.648	1.012	0.963-1.063	0.365	0.974	0.921-1.031
Post-PUFR (ml/sec)	0.001	0.821	0.734-0.919	0.002	0.823	0.727-0.931
Post-PVR (ml)	0.007	1.008	1.002-1.015	0.121	1.005	0.999-1.012

*All parameters were analyzed as continuous variables per unit.
OR = odds ratio; CI = confidence interval; post-PUFR = peak urinary flow rate at one month after the Remeex procedure; post-PVR = post-void residual at one month after the Remeex procedure.

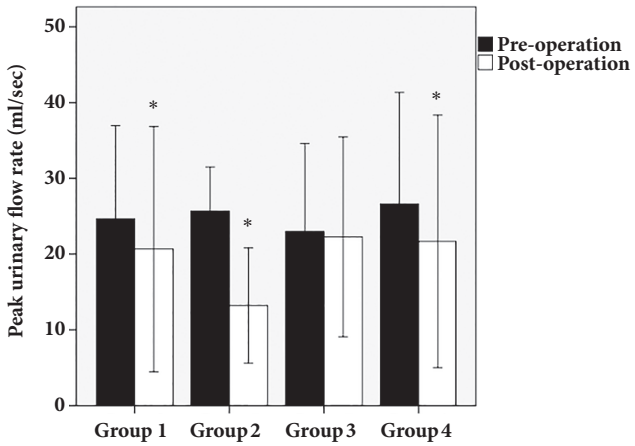

Figure 2: **Comparison of changes in peak urinary flow rate (PUFR) between the four groups before and 1 month after the Remeex procedure**. The post-PUFR decreased significantly compared with pre-PUFR in Groups 1, 2, and 4. $*p < 0.05$.

response rate), 29.0% and 12.4% of respondents reported physical and emotional discomfort, respectively, although half of the respondents did not feel discomfort [18]. Patients who had undergone previous anti-incontinence surgery reported significantly higher pain levels during the urodynamic study [19]. Based on these data, we consider routine follow-up urodynamic study to be unreasonable and invasive, and recommend noninvasive methods to assess poor urinary stream. Therefore, the measurement of urinary flow rate provides a promising metric to screen for de novo OAB because it is noninvasive and easy to perform.

Several possible predictors associated with de novo OAB symptoms after mid-urethral sling procedure have been investigated. Lee et al. reported that ISD, previous stress incontinence surgery, concomitant apical prolapse operation, previous prolapse surgery, and preexisting DO were important predictors of de novo OAB symptoms [20]. Marcelissen and Van Kerrebroeck identified the following risk factors of OAB symptoms after mid-urethral sling surgery in women: urgency, use of anticholinergic medications, previous incontinence surgery, older age, and urodynamic signs of OAB such as DO, lower bladder capacity, and elevated detrusor pressure [21]. In the present study, these aforementioned predictors did not significantly differ among the four patient groups, possibly because our subjects were ISD patients in whom reduced PUFR was the only parameter significantly associated with de novo OAB. Detrusor pressure on voiding was significantly lower in ISD patients than in non-ISD patients. Therefore, the effect of bladder outlet obstruction on de novo OAB may be more significant in ISD patients after the Remeex procedure [22].

It is important to determine when OAB symptoms should be evaluated because lower urinary tract symptoms that arise after mid-urethral sling surgery often disappear with increasing time after surgery [23, 24]. Liang et al. reported that most OAB symptoms resolved without intervention by 3 months after surgery in patients treated with transobturator sling procedures [23]. Rechberger et al. reported that the majority of undesired lower urinary tract symptoms spontaneously resolved within the first 6 months after mid-urethral sling surgery. In general, the number of urgency episodes significantly declined by 6 months after surgery compared with baseline. Therefore, we evaluated de novo OAB symptoms during the 6-month follow-up examination after the Remeex procedure.

This study has some limitations. First, this was a retrospective study, so we did not perform postoperative urodynamic tests to confirm the bladder outlet obstruction. However, we think that it will be possible to distinguish female bladder outlet obstruction from neurologically intact women using the parameter of maximum urinary flow rate ≤15 ml/sec instead of the urodynamic study. Second, although post-PUFR decrease after the Remeex procedure was the most prominent predictor in the de novo OAB group (Group 2), it was not easy to obtain good cut-off values for de novo OAB because post-PUFR also decreased in other groups and the current study was statistically under-powered (insufficient patient numbers in each group). Further studies with prospective designs and large cohorts are needed to confirm our findings.

5. Conclusions

We found that post-PUFR significantly decreased in the de novo OAB group, and it was the only significant predictor of de novo OAB after the Remeex procedure in women with SUI due to ISD. Our results show that a decrease in PUFR after the Remeex procedure is a promising metric indicating that the patient should be screened for de novo OAB. This metric can be easily and noninvasively determined.

Abbreviations and Acronyms

BOOI: Bladder outlet obstruction index
DO: Detrusor overactivity
ISD: Intrinsic sphincter deficiency
MCC: Maximal cystometric capacity
MUCP: Maximum urethral closure pressure
OAB: Overactive bladder
PdetQmax: Detrusor pressure at peak urinary flow
post-PUFR: PUFR one month after surgery
post-PVR: PVR one month after surgery
PUFR: Peak urinary flow rate
PVR: Postvoid residual
SUI: Stress urinary incontinence
TVT: Tension-free vaginal tape
TVT-O: Transobturator tension-free vaginal tape
UDS: Urodynamic study
VLPP: Valsalva leak-point pressure.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Research Article

Should We Always Use Antibiotics after Urodynamic Studies in High-Risk Patients?

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Aim. The aim of this observational study was to evaluate the effectiveness of a phytotherapic drug (Canephron N) in preventing urinary tract infection (UTI) in high-risk women undergoing urodynamic studies (UDS). *Methods*. The study protocol was approved by the local institutional ethical committee. Adult women with at least one risk factor for acquiring UTI (defined as: age over 70, elevated postvoid residual urine>100 ml, recurrent UTI, pelvic organ prolapse (POP) ≥II in POP-Q scale, and neurogenic bladder) had received after UDS either a single oral dose of fosfomycin trometamol (FT) (3 grams) or a phytodrug containing centaury herb, lovage root, and rosemary leaves (5 ml taken orally three times daily for one week). All patients included in the study had no pyuria according to urine dipstick (nitrite and/or blood and/or leukocyte esterase) and negative urine culture (CFU $< 10^3$/ml) before UDS. Urine samples were also tested 7 days after UDS. *Results*. Seventy-two high-risk participants completed the study. Seven days after urodynamic studies UTI symptoms, pyuria (nitrite and/or blood and/or leukocyte esterase) and bacteriuria with *E. coli* occurred in two patients (one (2.8%) in the FT and one (2.7%) in the phytodrug group, respectively). No statistical differences in UTI incidence were found between both treatment groups. We did not observe any additional adverse events in both groups. The major disadvantage of prophylaxis with the phytodrug as compared to FT was the necessity of continuing therapy for 7 days. *Conclusion*. Prophylaxis of UTI with a phytodrug (Canephron N) may be considered a good alternative to antibiotic prophylaxis use after UDS in high-risk female patients.

1. Introduction

Urodynamic studies (UDS) are especially used to evaluate lower urinary tract function in patients with bladder outlet obstruction, urinary incontinence, and neurogenic bladder dysfunction [1]. Urodynamic studies consist of series of tests, which can be helpful in proper recognition of abnormalities in the lower urinary tract. It has been already published that UDS, in many cases, significantly changed the ordering clinician's clinical impression of the patient's diagnosis for stress urinary incontinence and for urgency urinary incontinence [2]. UDS can also help in the better understanding of dysfunctions in patients with neurologic disorders, and in comprehending the changes in lower urinary tract functions in patients with pelvic gynaecologic cancer before and after radical treatment [3, 4]. UDS are an invasive procedure that involves catheterization; therefore, urinary tract infection (UTI) or bacteriuria may be observed after UDS, with an incidence of bacteriuria ranging from 1.5 to 30% [5].

The main value of prophylaxis is to decrease the risk of serious infection complications in patients after invasive procedures caused by the presence of bacteriuria. There is still no consensus on whether antibiotic prophylaxis is necessary for patients undergoing UDS. In the randomized study conducted on 270 patients published by Hirakauva *et al.*, antibiotic prophylaxis before UDS did not reduce the incidence of UTI in women [5]. In the past, Cundiff *et al.* came to the same conclusion in their research. There was no statistically significant difference in bacteriuria between female patients receiving two doses of nitrofurantoin 100 mg

and patients receiving placebo after combined urodynamics and cystourethroscopy [6]. On the other hand, Latthe *et al*., based on the results of randomized controlled studies, noticed a 40% reduction in the risk of significant bacteriuria with the administration of prophylactic antibiotics of different dose, type, and duration after UDS [7]. Therefore, it seems reasonable to reduce bacteriuria with antibiotic prophylaxis, because its rate correlates with the rate of infectious complications after invasive procedures [8].

Due to growing antibiotic resistance and weak evidence for routine antibiotic use in UDS prophylaxis, Tsai *et al*. investigated 261 patients and recommended that prophylactic antibiotics should be given only to high-risk patients [9]. Furthermore, Nadeem *et al*. also suggested giving antibiotics only to high-risk patients [10]. Unfortunately, it is still unclear which patients should be treated as high risk when it comes to UDS. Some potential risk factors are, however, considered in urogenital operations, including female gender [1], older age, diabetes mellitus, multipara (>3) [9], advanced organ prolapse, hypothyroidism, and body mass index >30 [11]. Although Cameron *et al*. did not recommend routine antibiotic prophylaxis in patients with diabetes mellitus, they did define risk factors for the development of UTI after UDS. These are neurogenic lower urinary tract dysfunction, elevated postvoid residual urine (PVR), asymptomatic bacteriuria, immunosuppression, age >70, and patients with an indwelling catheter [12]. Indeed, the use of prophylactic antibiotics is still controversial due to their many adverse effects and because of the increase of resistance of bacterial uropathogens. It is important, hence, to find a balance between the symptoms and risk associated with UTI, and with costs, adverse effects, and growing resistance to antibiotics [13].

Canephron N (Bionorica, Germany) is a phytotherapeutic drug with diuretic, spasmolytic, anti-inflammatory, antibacterial, and nephroprotective properties. The main ingredients of Canephron N are century herbs, lovage roots, and rosemary leaves. It is recommended for both adults and children. Moreover, it may also be used during pregnancy and breast feeding [14]. Because of Canephron's safety and positive impact on inflammatory processes within the urinary tract, we have decided to assess this phytodrug as a potential alternative to the use of antibiotics after UDS in high-risk patients.

The aim of this study was to evaluate the effectiveness of Canephron N in comparison to routine prophylaxis with fosfomycin trometamol (FT) (Zambon, Italy) in preventing UTIs in female patients undergoing urodynamic studies.

2. Materials and Methods

The protocol of this observational study was approved by the local institutional ethical committee. Urodynamic testing, including cystometry with bladder catheterisation, was conducted in women with mixed urinary incontinence, neurogenic bladder, or unclear lower urinary tract symptoms (LUTS). All participants were informed about the potential adverse events of FT and phytodrug and then gave written informed consent. In the study, women with at least one risk factor for acquiring UTI (defined as: age over 70, elevated postvoid residual urine (PVR)>100 ml, recurrent UTI, pelvic organ prolapse (POP) ≥II in POP-Q scale [15], and neurogenic bladder) received alternately after UDS, either a single oral dose of fosfomycin trometamol (3 grams) or a phytodrug (Canephron N) containing centaury herb, lovage root, and rosemary leaves (5 ml taken orally three times daily for one week). Simple randomization was used from pseudorandom numbers generated by a computer to allocate patients into the study groups in a ratio of 1:1.

All patients included in the study had no pyuria (nitrite and/or blood and/or leukocyte esterase) according to urine dipstick tests and negative urine culture (CFU $< 10^3$/ml) before UDS. Standard aseptic procedure of catheterization during UDS was performed in all participants. Urine samples collected from clean-catch midstream were also tested with dipstick 7 days after UDS. All patients were also informed to contact the hospital immediately in case of any UTI symptoms if they occurred before scheduled visit.

The primary endpoint was the presence of UTI symptoms and/or positive dipstick for pyuria (nitrite and/or blood and/or leukocyte esterase) and/or bacteriuria (CFU$>10^3$/ml) at follow-up visit. Secondary endpoint included the assessment of potential adverse events during the follow-up period.

Statistical analysis was performed with Statistica StatSoft, version 10 package, using the unpaired or paired t test and the $\chi 2$ test, as appropriate. A p value < 0.05 was considered statistically significant throughout.

3. Results

To the best of our knowledge, our study is the first, which compares the efficacy of phytodrug (Canephron N) to fosfomycin trometamol (3g) in preventing bacteriuria or symptomatic UTI after UDS. Baseline demographic characteristics were similar between both groups (Table 1).

Seventy-two women completed treatment and the follow-up visit conducted at week 1 after UDS (see flowchart - Figure 1). Eleven patients with well-controlled diabetes mellitus type 2 were included in the study (5 in the FT and 6 in the phytodrug group, respectively). No statistical differences in incidence of diabetes mellitus were found between both treatment groups. In seven patients (3 in the FT and 4 in the phytodrug subgroup, respectively) menopausal hormone therapy (MHT), local or systemic, was continued during the study. There was no statistically significant difference in MHT administration between both groups.

In our study, seven days after urodynamic studies, UTI symptoms and pyuria (nitrite and/or blood and/or leukocyte esterase) according to urine dipstick tests occurred in two patients, one (2.8%) in the FT and one (2.7%) in the phytodrug group, respectively. The patient with urinary tract infection in the FT group had recurrent UTI in her medical history, whilst the participant in the phytodrug group presented POP-Q stage III in her gynaecological assessment, as well as increased PVR (180 ml). In both patients, urine culture was assessed, and *E. coli* (CFU/ml 10^6) was recognized as a pathogen responsible for UTI development. We did not observe any additional adverse events in both groups.

Table 1: Demographic characteristics of patient groups.

Variable	Prophylaxis with fosfomycin trometamol (n=35)	Prophylaxis with phytodrug (n=37)	p
Age (years)	62.7 ±11.2	63.8 ±10.8	NS
BMI (kg/m^2)	30.1 ±3.8	30.2 ±4	NS
Parity	2.1 ±1.12	2.3 ±0.97	NS
Menopause	28 (80%)	31 (83.7%)	NS

Continuous variables are presented as the mean±SD; categorical variables are presented as number and %.

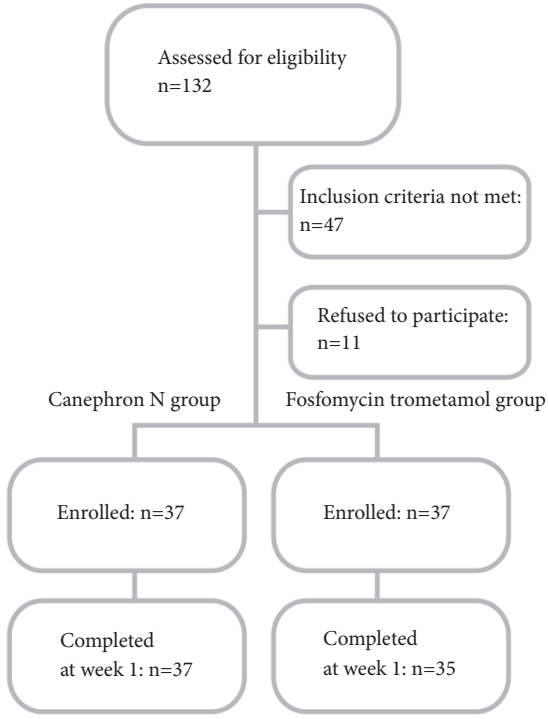

Figure 1: Flowchart of the participants in the study.

Indeed, no statistical differences in UTI incidence were found between both treatment groups; however 10 patients in phytodrug group reported the necessity of continuing therapy for 7 days as the major disadvantage of such prophylaxis.

4. Discussion

During urodynamic testing, there is a need to place a catheter into the bladder; therefore, it can result in UTI, and the incidence of UTI after urodynamic testing may vary from 1% to 30% [16–18]. The presence of UTI may also exacerbate urinary incontinence and other LUTS [19]. Hence, it is reasonable to find out if a patient truly requires antibiotic prophylaxis of UTI after UDS and to assess the efficacy of alternative pharmacotherapy options.

In the study published by Nóbrega *et al.,* multivariate analysis with multiple logistic regression was conducted to assess the risk factors which are associated with bacteriuria and UTI after UDS. Based on the results collected from 232 women who underwent UDS, the authors found that body mass index (BMI) >30, advanced pelvic organ prolapse, and hypothyroidism are responsible for significant increase of risk bacteriuria, whilst only BMI >30 was associated with greater incidence of UTI after UDS [11].

Cameron *et al*., based on a literature review and the expert opinions, recommended antibiotic prophylaxis before urodynamic testing for patients with such medical conditions as known relevant neurogenic lower urinary tract dysfunction, increased PVR, asymptomatic bacteriuria, immunodeficiency, and age >70. Their recommendations also suggest antibiotic prophylaxis for patients with any indwelling catheter or who perform clean intermittent self-catheterization. As a first choice of antimicrobial agents before UDS in high-risk patients, they recommended a single dose of trimethoprim-sulfamethoxazole; however, the choice of prophylactic antibiotic should also include local pathogen resistance patterns [12]. We built upon these studies and recommendations in our recognition of high-risk patients in our study. Our choice of antibiotic prophylaxis was also associated with knowledge of local resistance of *E. coli* to trimethoprim-sulfamethoxazole (which exceeds 22%), and, therefore, in our region, this antibiotic should be avoided in prophylaxis [20].

Antimicrobial resistance epidemiology is still changing and so should empiric treatment implications. In the study conducted by Naber *et al*. during a three-year period (from 2003 till 2006) in 10 different countries, 4264 patients were analyzed in terms of epidemiology and antimicrobial susceptibility of uropathogens. The results revealed that the most common bacteria, *Escherichia coli,* had a prevalence of 76.7%, and it showed the *E. coli* susceptibility rate to methicillin of 95.8%, nitrofurantoin of 95.2%, and ciprofloxacin of 91.8%. The lowest rate was found for ampicillin (45.1%) [21]. In a similar study conducted by Miotla et al., also in a three-year period (from 2013 till 2015) 4453 patients were evaluated. Herein, the most common uropathogens cultured from urine samples were *E. coli* with a slightly lower prevalence of 65.5%. The resistance rate of *E. coli* strains for antibiotics mentioned earlier was slightly higher. Direct comparison between the ARESC study and our results shows mainly an increase of *E. coli* resistance to ciprofloxacin (10.7% and 22.7%, respectively, in the premenopausal and the postmenopausal groups) [22].

In UTI treatment, resistance rates should always be taken into consideration. For example, resistance of *E. coli* varies considerably within Europe; thus, ciprofloxacin is only recommended for empirical therapy when the resistance rate of *E. coli* is lower than 10-20% [22]. For these reasons (high resistance rates to trimethoprim-sulfamethoxazole and fluoroquinolones), in our study, we chose fosfomycin trometamol (3g) as a prophylaxis in high-risk patients. Furthermore, the

choice of phytodrug as a comparator was associated with the concerns of antimicrobial resistance, which is considered to be a major health threat. Our first dosage started after the intervention according to our local guidelines and previously published analyses considering antibiotic proxylaxis after UDS [23, 24].

Multidrug-resistant bacteria infections are associated not only with highest costs of treatment, but also with increased patient mortality and morbidity. Whether reduced antibiotic consumption can restore antibiotic susceptibility, Sundgvist *et al*. performed a very interesting intervention in which the use of trimethoprim was decreased by 85% due to voluntary restriction of its use in a certain area for 24 months. The results of the study were very promising, but the effect was rather disappointing. There was no statistically significant change in resistance of E. coli against trimethoprim. This study showed that, once bacterial resistance is established, it has a low possibility of reverting itself [25]. Nevertheless, it seems reasonable to encourage reduced use of antibiotics even if the only benefit would be slowing down the rate of increasing resistance [26]. Therefore, to ascertain the effect of avoidance of unnecessary antibiotic consumption, we decided to use a Canephron N as a comparator for this study.

Gürbüz *et al*. assessed the efficacy of ciprofloxacin in a single dose (500 mg) taken orally 1 hour before UDS (n=141) vs. a single dose of FT (3 g) taken approximately 12 hours before the procedure (n=137) and vs. no treatment group (n=133). Herein, a significant bacteriuria developed in 12 female patients during the first week after UDS. Broken down, the rate of detection was 6 (4.3%) participants from the fluoroquinolone groups, 3 patients (1.6%) from the FT group, and 3 (2.3%) women from the no-prophylaxis subgroup. *E. coli* was cultured in half the UTI cases. The authors concluded that previous urogenital surgeries and female gender were associated with statistically increased risk for bacteriuria after UDS; however, via multiple logistic regression analysis, only past urogenital surgeries were responsible for the presence of bacteriuria [1]. The incidence of UTI in our FT (2.8%) and phytodrug (2.7%) was similar to the results published in the abovementioned study.

Foon *et al*. conducted a review study of nine randomized controlled trials (RCTs), which included 973 patients between the ages of 18 and 82. Patients in their study received different types of antibiotics either 24 hours before or up to 72 hours after UDS. The authors observed (in 5 RCTs) less incidence of UTI in participants who received prophylactic antibiotics in comparison to no-treatment groups (20% vs. 28%, respectively), with no statistical significance of this finding. Moreover, adverse events (AEs) were reported only in 2 RCTs; however, the rate of AEs did not reach 1.5% of all participants. Based on their results, they calculated that, statistically, 13.4 women needed to receive antibiotic prophylaxis to prevent one case of bacteriuria. Therefore, one of the final conclusions of that meta-analysis was the statement that prophylactic antibiotics can reduce the risk of bacteriuria after UDS, whilst data considering reduction of symptomatic UTIs are limited [13]. Interestingly, not all of the patients included in that analysis fulfilled restricted criteria for recognition as a high-risk group, and, what is more, the incidence of UTI in both groups was much higher when compared to the results of our study, 2.8% and 2.7% in the FT and the Canephron N groups, respectively. In prophylactic treatment, nonantimicrobial preventative methods should be considered first, as antibiotic prevention is risky in terms of resistance [27]. Gürbüz et al. postulated that FT seems to be a first choice of prophylaxis in patients at higher risk of UTI development after urodynamic study [1]. The results of our study showed that the efficacy of Canephron N seems to be similar to FT in the prevention of UTI after UDS.

The major limitations of our study include the relatively small group of participants and lack of male patients. The strengths of the study include very restricted inclusion criteria used for the recognition of high-risk patients and the very good follow-up achieved.

5. Conclusions

Prophylaxis of UTI with Canephron N may be considered a good and safe alternative to antibiotic prophylaxis used after UDS in high-risk female patients. Moreover, the usage of a phytodrug might be helpful in decreasing antibiotic consumption, as well as in the prevention of growing antibiotic resistance.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

Pawel Miotla is the speaker for Angelini and Bionorica. Sara Wawrysiuk has no conflicts of interest. Kurt Naber is the speaker for Zambon, Apogepha, and Bionorica. Ewa Markut-Miotla has no conflicts of interest. Pawel Skorupski has no conflicts of interest. Tomasz Rechberger is the speaker for Angelini and Bionorica. The authors did not receive any support from enlisted companies to conduct the study.

Authors' Contributions

Pawel Miotla and Sara Wawrysiuk contributed equally to this work.

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