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Injectable Biological Bulking Agent to Treat Stress Urinary Incontinence in Women: A Feasibility Pilot Study

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Abstract

Background: Urinary incontinence mainly affects women regardless of age and, as it affects their quality of life, influences work, sex life and independence for activities of daily living. The treatment of stress urinary incontinence including urethral volume injection therapy can provide an intermediate option over non-surgical and surgical therapies. One of the mechanisms for stress continence depends on the effective coaptation of the urethra during the increase in intra-abdominal pressure. The bulking agents can be injected transurethral or periurethral retrogradely, using direct vision from a cystoscope. **Purpose:** To evaluate the feasibility and preliminary outcome performance of the bacterial polysaccharide gel used as biological bulking agent applied in female patients with stress urinary incontinence. **Methods:** A prospective clinical pilot study was performed, in a single institution, including female patients who were admitted to the urologic outpatient clinic with Stress Urinary Incontinence (SUI) without previous treatments and they were selected and underwent bulking agent procedure. The evaluation was performed at the time of enrollment and 6 months after treatment. The primary outcome was Quality of Life (QOL) using the ICIQ-SF Questionnaire. The amount of urine leakage measured by the 1-HOUR PAD-TEST was the second outcome. **Results:** Fifteen women (with an average age of 53 years) were submitted to the application of bacterial cellulose gel and she was analyzed. Only two patients presented unchanged incontinence. The study considered as primary outcome the improvement or disappearance of symptoms after six months of intervention. Post-intervention Quality of Life

(QOL) questionnaire indicated that all of these patients related a better quality of life (62.5%). Through the PAD-test it was possible to observe a decrease in urinary leak of 85% comparing the results pre and post-intervention (BCA—Bacterial Cellulose Application) with p-value equal to 0.000009. **Conclusions:** The results of this pilot study suggest that the use of biological bulking agent is a promising approach to treat stress urinary incontinence in female patients. **Trial registration:** Registration number and date of registration should be instated in this section.

Keywords

Bulking Agents, Urinary Incontinence, Stress, Biopolymers

1. Introduction

Urinary incontinence affects primarily women, regardless of age and by affecting quality of life, influences work, sex life and independence for various routine activities. Approximately half of these individuals suffer from stress urinary incontinence (SUI) and are directly influenced by risk factors such as obesity and diabetes [1].

Conventional treatments include a mid-urethral sling procedure that does not fit all patients or does not solve the problem of urinary incontinence [2]. For these problems, urethral expansion agents have been developed which are an alternative but still have varying clinical success rates. Many of these products have been developed in recent decades and most of them have had limited effectiveness or have problems with application such as local pain and even thromboembolism leading to death [3].

For this reason, an injectable bulking agent must be biocompatible, non-immunogenic and cause minimal fibrosis at the injected site. Several injectable bulking agents with synthetic or natural chemical composition have been developed in recent years [4]. However, injectable bulking agents such as tetrafluoroethylene (Teflon®) have been discontinued due to their high risk of particle resorption and migration to sensitive areas of the body [3]. The study and development of natural bulking agents that have positive immunogenicity factors, such as hyaluronic acid, dextranomer (Deflux®) and bovine collagen derivatives (Contigen®) have become references in the market [3] [4].

Bacterial Cellulose Gel (BC) is a highly crystalline biopolymer produced from sugarcane molasses [5]. A previous study showed that BC was not cytotoxic, genotoxic, or acutely toxic, in addition to being biocompatible and low cost [6]. In recent years, BC has been successfully used in several surgeries [7] [8] [9] [10] [11]. And for having a natural structure with easy availability and being toxicity-free, it is attracting attention in the treatment of urinary stress incontinence [12].

The BC gel was used in 2012 as an implant into rabbits' eviscerated eyes and

demonstrated that the BC was biocompatible and properly integrated into the surrounding tissues. In 2015, Lima and collaborators evaluated the biocompatibility of bacterial cellulose gel as a bulking agent in rabbit bladders. The study also demonstrated the physiological integration of BC gel application in the host tissue and resistance to the biodegradation process. These results obtained indicated that the BC gel may be an option for injectable therapy of stress urinary incontinence. [13] [14]. As the present study evaluated the use of BC gel in the treatment of stress urinary incontinence in women diagnosed with SUI.

2. Materials and Methods

Design and sample selection

A pilot study was realized from March 2019 to October 2021, female patients who were admitted to the urologic outpatient clinic with stress urinary incontinence (SUI) without previous treatments. The evaluation for the bulking agent procedure was performed at the time of enrollment and 6 months post-intervention. The sample size was calculated based on the population proportion estimation and the site sample size calculation was used.

The study followed the ethical recommendations of the National Health Council, the Helsinki Declaration and the Nuremberg Code for studies with human beings and was approved by the National Ethics in Research Committee (CONEP #1.650.992). We formally informed participants about the study and invited them to attend. All patients enrolled in the study signed an informed consent form (ICF). Exclusion criteria were: infravesical obstruction of a mechanical nature, neurogenic bladder arising from surgical treatment and patients with urethral hypermobility.

The primary outcome was quality of life (QOL) using the International Consultation on Incontinence Questionnaire in its short form (ICIQ-SF) that consists of three questions that assess the frequency, severity and impact of urinary incontinence, as well as a set of eight self-diagnosis items related to the causes or incontinence situations experienced by the patient [15]. In the test, the sum of the scores of the questions three, four and five and ranges from 0 to 21, where 0 corresponds to no UI impact on quality of life and 21 corresponds to a very severe impact of UI on the patient's quality of life.

The amount of urine leakage measured by the 1-HOUR PAD-TEST was the second outcome. This method is based on the weight gain of the pad during the test period under standard conditions. In this comparative test, the patients used the absorbent for 01 hour in the preoperative evaluation and six months after the implantation of the BC gel. The comparison of mean values was get with Wilcoxon signed-rank test (pre-post analysis). This test was considered statistically significant when P value < 0.05. The software used for analysis was SPSS Version 21.

Polysaccharide gel is an innovative product for Health Ltda which is produced from molasses biopolymer developed by POLISA's R&D and research team. The

gel was obtained by hydration of microcrystalline bacterial cellulose at a ratio of 0.8% cellulose in 99.2% water and sterilization by gamma ray [6].

The bacterial cellulose gel used for testing has a stable formulation with a concentration of 0.8% cellulose polysaccharide. The Bacterial Cellulose Application (BCA) in all patients was performed in the operating room, with patient sedated and submitted to urethrocystoscopy. The entire urethra and bladder cavity and subsequent identification of the injection site was evaluated. The material was injected at a distance of 1 cm below the vesicourethral junction with cystoscopic needle, at positions 3, 6, 9 and 12 hours, the total of 8 ml was injected into each patient. The bladder was emptied previously.

3. Results

Fifteen women were submitted to the application of bacterial cellulose gel and she was analyzed. The preliminary conditions were described in baseline characteristics (Table 1) and pre-intervention urodynamic data (Table 2).

The mean age of patients was 52.75 years, which characterizes this study population as relatively young, sexually active, and as productive workers.

After the endoscopic filling procedure, patient evolution was assessed every three months. The phases of bulking agent application were shown in different moments: (A) Aspect of the bladder neck pre-intervention. It is possible to observe

Table 1. Baseline characteristics.

Total Sample (N*)	15
Age (years)	40 - 68
Mean (years)	53
BMI* Kg/m^2	28.3 (21.3 - 31)
Obese (BMI** ≥ 30 kg/m^2), n (%)	5
Family Background	13
Previous Radical Pelvic Surgery, n (%)	4 (26.6)

*N = Number of patients **BMI = Body Mass Index.

Table 2. Pre-intervention urodynamic data.

VARIABLE	MEDIAN (Range)
FDTV, mL	180 (70 - 330)
CC, mL/s	407 (206 - 580)
Q_{max}, mL/s	24.78 (15.1 - 37.3)
Intravesical opening pressure, cmH_2O	23.4 (9 - 66)
$Pdet_{max}$ during voiding, cmH_2O	>60
$PdetQ_{max}$, cmH_2O	24.4 (8 - 60)

FDTV: first desire to void; CC: cystometric capacity; Q_{max}: maximum urinary flow; $Pdet_{max}$; maximum detrusora.

the damage to the urethra, where the spacing allows the constant loss of fluid. (B) Image of cystoscopy needle during intervention (the endoscopic needle-injected bacterial cellulose polysaccharide filling is shown). (C) Aspect of the bladder neck post-intervention. The ultravesical space is shown to be reduced, thanks to the filling agent procedure (**Figures 1(A)-(C)**).

Although the literature presents complications such as pelvic pain and urinary retention, in our sample only urinary retention was evident in some cases post-intervention. And these were resolved with the use of intermittent catheterization, only during the hospital stay.

The study considered as primary outcome the improvement or disappearance of symptoms after six months post-intervention. Polysaccharide gel has been used in various medical and biological applications. No variation in final volume was observed after tissue injection in different experimental trials with a standardized concentration at 0.8% [16] [17].

The urine leakage has been correlated with quality of life in the pre- and post-intervention, the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) was used. Quality of life analysis was the secondary outcome. According to ICIQ-SF Questionnaire answers from the patients, there was a 62.5% improvement in the quality of life of these women (**Table 3**).

Through the results of 1-Hour PAD-Test it was possible to observe an improvement in urinary leak and, the difference in the mean values of leak was statistically significant with p-value equal to 0.000009 (**Figure 2**).

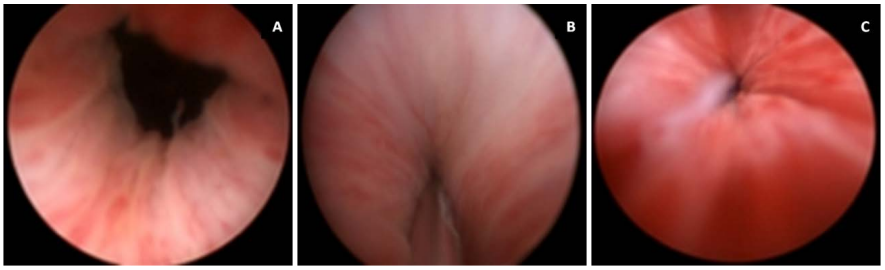

Figure 1. The phases of bulking agent application. (A) Aspect of the bladder neck pre-intervention (BCA); (B) Image of cystoscopy needle during intervention (BCA); (C) Aspect of the bladder neck post-intervention (BCA).

Table 3. ICIQ-SF score pre and post-intervention and percentage increase.

QUESTIONS	PRÉ-INTERVENTION (BCA)	POST-INTERVENTION (BCA)	PERCENTAGE INCREASE (%)
How often do you leak urine? (0 - 5)	4.2	2.9	31
We would like to know how much urine you think leaks. How much urine do you usually leak? (0 - 6)	4.7	2.6	43
Overall, how much does leaking urine interfere your everyday live? (0 - 10)	8.7	5.3	39
All questions (0 - 21)	17.6	10.8	62.5

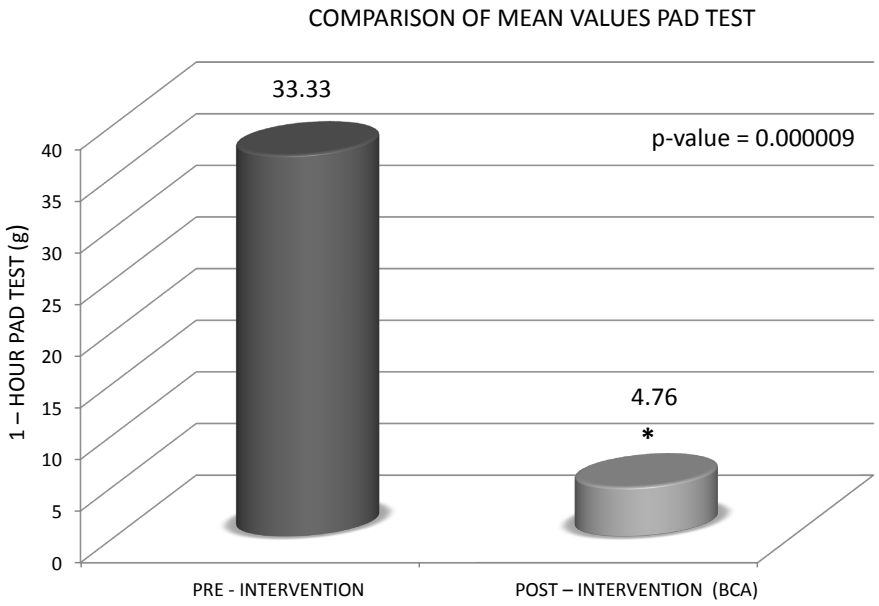

Figure 2. PAD-Test—Urinary losses pre and post-intervention (BCA).

4. Discussion

Despite the surgical treatment with a urethral sling is the common treatment for patients with stress urinary incontinence (SUI), urethral bulking agents have traditionally been offered as salvage procedures for recurrent this type of incontinence. However, there's a part of these patients who persist with incontinence or are not ideal candidates for surgical treatment [18].

Different bulking agents have been investigated for the treatment of SUI [19]. The parameters that distinguished an ideal bulking agent are that it should be non-immunogenic, non-migratory, non-erosive, non-inflammatory, and easily handled and stored. It should be permanent and the application should not cause pain, have long term side effects, and must provide clinical improvement [20] [21]. However, the urethral bulking agents currently being used do not fully fulfill these criteria; so, the search for the ideal agent is still ongoing which makes the results here presented with BC gel even more important. Another advantage of the present agent is its low cost and by coming from an inesgotable source in nature with makes the use very attractive.

The use of bulking agents in gel does not interfere with future procedures in the treatment of incontinence and is an extremely valid treatment in sexually active women who are planning new pregnancies or who have any comorbidity that may affect the use of anesthesia [22].

Previous studies related the application of biopolymer gel in rabbits' bladder submucosa showed that the agent did not present any inflammatory issue reaction, was well colonized by cell matrix and blood vessels indicating no body rejection of these materials [19]. In another application, the author tested the polysaccharide gel from bacterial cellulose in rats' bladder. The gel showed good stability remaining in place after implantation which characterized it as a satis-

factory bulking substance. These results allowed the testing in patients suffering from stress urinary incontinence without any improvement by previous conventional treatments [23].

Some studies have reported that the use of certain bulking agents caused some complications such as urinary retention, pain (dysuria, pain in injection site, pelvic pain) hematuria, infection in the urinary tract or vaginal injection [20]. Lower urinary tract symptoms such as incontinence, polyuria and urinary urgency have also been reported. Rare and severe complications, such as periurethral abscess, pseudocyst formation or granuloma of the injected material, fistula formation and erosion of the urethra or vagina, have also been reported in other studies with bulking agents [24] [25].

In our work, no major intra and post procedure complications were reported. Only two of the fifteen patients present urinary retention within 12 hours after the procedure which was overcome with the use of intermittent catheterization. No procedure related infection, painful symptoms or any of the other abovementioned problems related to bulking agents procedures were reported.

Researchers pointed out effectiveness ranging from 50% to 70% in terms of subjective improvement which confirms the results we obtained. One study has also stated that the use of coating agents is not suitable for long term treatment of patients. Our use of polysaccharide gel from bacterial cellulose is unprecedented with patients with SUI [19]. The positive results corroborate the use and indicate the necessity of further new studies to prove the long-term effectiveness of BC gel.

The results of the improvement in the ICIQ-SF test were similar to what has been found in the literature [4]. Even though some patients reported not staying absolutely dry, all of the patients reported a marked improvement in all domains of the applied questionnaire. Improvement in quality of life is related by not having to use pads or the decrease in the number used in a way that does not have repercussions on the patient's social or professional life.

The study's difficulties were only related to the population that fit the study's inclusion criteria. There were no difficulties with the procedure because it was performed in an outpatient clinic and the material used was only a cystoscope and needle, also indicating a low cost.

Bacterial cellulose polysaccharide gel is not only an efficient but extremely economical alternative. To provide an example of this: the most commonly used bulking agent to treat stress urinary incontinence, the Dextranomer Microspheres Plus Hyaluronic Acid gel has an average price of U$300.00 [26]. In our study, the bacterial cellulose polysaccharide gel only costs U$10.00. Polysaccharide gel could also be used for other conditions such as vesicoureteral reflux where bulking agents are the front line of treatment. Increased demand for the substance would lower the market cost.

A multicenter prospective study conducted with forty-seven patients treated with urethral bulking agents showed 3-year results with 81% of the sample declaring themselves cured [27]. This study showed that bulking agents are an ade-

quately effective and safe option for the treatment of recurrent SUI, corroborating the findings of the present study.

Therapy with the biopolymer gel is a beneficial and valuable alternative to surgical treatment in the rather heterogeneous group of stress urinary incontinence patients. The PAD-TEST showed that the patients were not completely dry after the injections, but losses were significantly improved and there was an important repercussion on the quality of life.

5. Conclusion

The use of natural bulking agent such as bacterial polysaccharide gel has shown to be a promising alternative for treatment of stress urinary incontinence in female patients. The majority of the treatments for SUI are invasive and most of the patients persist with this disease. The use of a natural bulking agent, such as bacterial polysaccharide gel, is a valuable alternative for patients with previous uncured surgeries or other invasive treatments.

Conflicts of Interest

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

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