Long-term efficacy and safety of a bioresorbable polycaprolactone-based injectable in female stress incontinence

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Ethics approval and consent to participate: due to the retrospective nature of the study, participants were not subjected to any study treatments or actions. The medical information used was registered as the standard of care in the medical records of the patients. Therefore, the Medical Research Involving Human Subjects Act does not apply, and no informed consent was obtained. However, during the screening of patients, the medical records were carefully checked for objections to medical research. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. This study was granted approval from the Etichal committee of General Hospital Sibensk-kninske Country, reference number 01-13541/1-23.

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Abstract

A fully bioresorbable polycaprolactone (PCL)-based bulking agent was evaluated for safety and efficacy in female patients with mild to moderate stress urinary incontinence (SUI) who attempted and failed prior pelvic floor muscle training. A total of 44 adult female subjects with mild or moderate SUI (median age 60 and 57, respectively) were treated by transurethral sub-mucosal injection. Safety was evaluated at 6-, 12-, and 24-month follow-up visits. Efficacy was assessed at the same intervals with the Stamey grading system (SGS). SGS improvement was shown in both the mild and moderate SUI groups. At 24 months, most participants were continent: 78.1% in the mild SUI group and 66.7% in the moderate SUI group. All participants in the moderate SUI group showed an improvement in the SGS grade, and most participants were continent. The study shows that the PCL-based bioresorbable bulking agent treatment seems to be a safe and effective treatment option for women with mild to moderate SUI who attempted and failed prior pelvic floor exercises.

Introduction

The long-term complications of midurethral sling (MUS) surgery, such as urethral obstruction, tape erosion, and refractory chronic pain,[1] have sparked interest in patients and physicians for less invasive treatment options for stress urinary incontinence (SUI) without major risks for complications.[2] The increasing interest in less invasive treatments for SUI has resulted in a growing interest in bulking agents.[3] The use of these bulking agents in SUI could bridge the gap between non-surgical therapy (pelvic floor training, change in fluid intake, and drug therapy) and surgical treatment [MUS procedure; the retropubic (TVT) or the transobturator sling].[4,5] A promising addition to the possible bulking agents suitable for urethral injection is a polycaprolactone (PCL)-based bioresorbable bulking agent (Urolon®, AQLANE Medical B.V., Oisterwijk, Netherlands).[6-10] Although this product is a new option for SUI, the mid- to long-term safety and efficacy results are promising.[9,10] In a recent publication by our research group, we evaluated its safety and efficacy in a group of 50 women treated in three different centers. The mid- to long-term results of this study show the product to be safe and effective in the treatment of mild to moderate SUI.[10] In addition, a prior study of this group shows the results of a single center 12-month follow-up in 47 women with mild, moderate, and severe SUI [Stamey grading system (SGS) 1-3], showing particularly good results in the participants with mild to moderate SUI.[9] The results in this study show an update of the study presented in the publication by Mojsovic and Koldewijn,[9] containing the long-term (24-month follow-up data) efficacy and safety results for urethral injection using a PCL-based bioresorbable bulking agent in treatment for female subjects with mild to moderate SUI.

Materials and Methods

All patients in this retrospective case series were treated at the General Hospital in Šibenik (Croatia) between April 2019 and July 2020. Patients were suitable for treatment if there was an SUI SGS of 1 or 2. Patients with an SGS of 3 were excluded from the case series since the product is less effective for this category of patients. Patients with prior treatments for SUI were included in the study. Primary outcome measurements were the return of continence, the duration of the continence period using the SGS, as well as the complication rate. The outcome measurements were recorded in the patient's medical records. The data was collected retrospectively from the patients' medical records.

Bulking agent

The patients were treated using the medical polymer PCL-based bulking agent (Urolon®, AQLANE Medical B.V., Oisterwijk, Netherlands) because of its bioresorbability and neocollagenesis characteristics. The treatment procedure is described in our earlier publication.[9]

The PCL-based bulking agent consists of 30% PCL microspheres and 70% aqueous carboxymethylcellulose gel carrier. The PCL microspheres are smooth and spherical-shaped and have optimal biocompatibility for use as a particle-based bulking agent.[6-8] Moreover, the particles have previously been shown to stimulate (type I) collagen formation,[11-13] potentially restoring lost collagen and supporting long-term effectiveness after the microspheres have been bioresorbed.

Follow-up

Data on the continence and complications experienced by the patients was collected during outpatient follow-up appointments. The continence level of patients was scored using the SGS, in which: grade 0 = continent; grade 1 = loss of urine with a sudden increase in abdominal pressure such as from coughing, sneezing, or laughing; grade 2 = leaks with lesser degrees of physical stress such as walking, standing erect from a sitting position, or sitting up in bed; grade 3 = total incontinence, urine is lost without any relation to physical activity or position.[14] Patients were asked to evaluate their continence before treatment, at 6 months, 12 months, and 24 months post-procedure. The treatment was a success if the patients' continence improved to SGS 0. The duration of the continence period ended when patients scored >0 on the SGS. If patients opted for re-treatment using the PCL-based bulking agent due to loss of continence, the follow-up for this study would end, as these results would cloud the effectiveness of a single treatment.

Data analysis

Efficacy analysis was performed using a per-protocol (PP) approach on all subjects. Safety evaluations were recorded throughout the study *via* any reported adverse events (AE). Frequency statistics were calculated for all nominal results. The median and interquartile range (IQR) were calculated for the participants' age, and a Kaplan-Meijer survival curve was generated for the duration of continence post-intervention. Data analysis was performed using SPSS Statistics v28 (IBM, Armonk, NY, USA).

Informed consent

Due to the retrospective nature of the study, participants were not subjected to any study treatments or actions. The medical information used was registered as the standard of care in the medical records of the patients. Therefore, the Medical Research Involving Human Subjects Act does not apply, and no informed consent was obtained. However, during the screening of patients, the medical records were carefully checked for objections to medical research. This study was granted approval from the Etichal committee of General Hospital Sibensk-Kninske Country, reference number 01-13541/1-23.

Results

The patient characteristics of this case series are presented in Table 1. The median age of women who were treated varied between the mild SUI and moderate SUI groups [60, interquartile range (IQR) 20 *versus* 57, (IQR 23), respectively]. All subjects had given vaginal birth to at least one child, with a maximum of five children. Six patients had received prior treatment for SUI (13.6%),

Table 1. Baseline characteristics.

	Mild SUI (SGS 1) n=32	Moderate SUI (SGS 2) n=12
Age, median (IQR)	60 (20)	57 (23)
No of births (vaginal)		
1 (%)	2 (6.3)	1 (8.3)
2 (%)	20 (62.5)	8 (66.7)
3 (%)	6 (18.8)	3 (25.0)
4 (%)	3 (9.4)	0
5 (%)	1 (3.1)	0
Prior treatments		
Urodex (%)	2 (6.3)	0
Urolastic (%)	0	1 (8.3)
TVT (%)	2 (6.3)	1 (8.3)
Co-morbidities		
Urge incontinence (%)	4 (12.5)	0
Prior gynecological surgery (%)	6 (18.8)	1 (8.3)
Chronic cystitis (%)	5 (15.6)	0
Spinal hernia surgery (%)	2 (6.3)	2 (16.7
Diabetes mellitus (%)	2 (6.3)	0
Adipositas (BMI>30) (%)	2 (6.3)	0
Retreatment (%)	3 (9.4)	3 (25.0)

SUI, stress urinary incontinence; SGS, Stamey grading system; IQR, interquartile range; TVT, retropubic transobturator; BMI, body mass index.

half of whom had received prior bulking injections using other products, and the other half had received a TVT procedure. A large number of participants in both groups had comorbidities that could influence continence; the results are presented in Table 1.

Treatment efficacy

The PP efficacy analysis for the SGS scores is shown in Table 2, and the duration of continence for all participants is specified in *Supplementary Table 1*. The results of the mild SUI group (SGS 1) show almost all participants improve their continence after treatment; these continence rates are stable in the first 12 months; at 13 months, a return of incontinence is seen in three extra women returning to an SGS score of 1. At 14 months after treatment, an additional two participants return to their baseline incontinence level of SGS 1. In addition, two participants reported the return of their incontinence at months 15 and 19 after treatment. The remaining 25 participants (78%) in this group stayed continent for at least 24 months after treatment. In the moderate SUI group (SGS 2), all participants improved their continence after treatment. After 13 months, two participants suffered from mild SUI (SGS 1). At 14-month follow-up, this increased to three participants with an SGS of 1, and finally, at 20 months, a total of four participants (33.3%) showed mild SUI symptoms. None of the participants in the moderate SUI group returned to their baseline level of incontinence within the first 24 months after treatment; 66% of the participants in this group stayed continent for at least 24 months after treatment. A total of six participants [SGS 1: three participants (9.4%), SGS 2: three participants (25.0%)] received re-treatment after they experienced a return of the incontinence. The data after this re-treatment is not used in this manuscript since the follow-up ends when the participants receive a re-treatment.

Duration of continence

Supplementary Table 1 details the duration of continence for each participant. Based on this data, the continence results of both the mild and moderate SUI groups have been plotted in the Kaplan-Meijer curve presented in Figure 1. Indeed, figure 1 shows the continence in both groups is stable for the first 13 months, after which the proportion of incontinent participants slowly increases until 20 months post-treatment. The remaining proportion of participants (SGS 1: 0.78, SGS 2: 0.66) was continent at the follow-up visit at 24 months past treatment. The Kaplan-Meijer curve shows the majority of participants treated in this study remain continent for at least 24 months after treatment.

Treatment safety

Six subjects reported a total of six AE. The majority of AE reported consisted of urinary tract infections (UTI) (four AE). All UTI were mild in nature and resolved by providing appropriate medication. One subject experienced transient urinary retention, which was mild in nature and was resolved with the use of a catheter for 48 hours. One subject reported a chronic UTI, which was managed using long-term treatment consisting of antibiotic prophylaxis. At 6-, 12-, and 24-month follow-ups, no additional AE were reported by the participants in this study. Table 3 details the post-operative AE.

Discussion

The study aimed to evaluate the long-term safety and efficacy results of a PCL-based bioresorbable bulking agent used for the treatment of mild to moderate SUI in female subjects treated in a single hospital by a single physician. In this study, the 2-year follow-up results are presented.

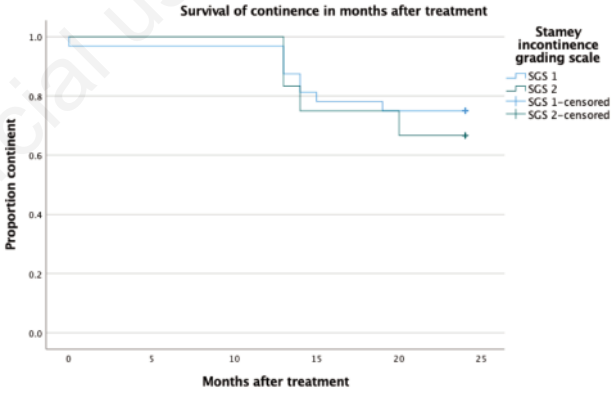

Figure 1. Kaplan-Meijer curve showing survival of continence. SGS, Stamey grading system.

Table 2. 24-month efficacy follow-up data.

	Mild SUI (SGS 1) n=32				Moderate SUI (SGS 2) n=12			
	Baseline	6 Mo (%)	12 Mo (%)	24 Mo (%)	Baseline	6 Mo (%)	12 Mo (%)	24 Mo (%)
Continent (SGS 0)	0	31 (96.9)	31 (96.9)	25 (78.1)	0	12 (100)	12 (100)	8 (66.7)
Mild SUI (SGS 1)	32	1 (3.1)	1 (3.1)	7 (21.9)	0	0	0	4 (33.3)
Moderate SUI (SGS 2)	0	0	0	0	12	0	0	0

SUI, stress urinary incontinence; Mo, month; SGS, Stamey grading system.

Table 3. Post-operative adverse events.

	Mild SUI (SGS 1) (%)	Moderate SUI (SGS 2) (%)
UTI	3 (9.4)	1 (8.3)
Chronic UTI	0	1 (8.3)
Urinary retention	1 (3.1)	0

SUI, stress urinary incontinence; SGS, Stamey grading system; UTI, urinary tract infections.

Treatment safety

This study shows that the treatment is safe for women suffering from mild to moderate SUI. AE were few and mostly mild in nature, consisting of five UTI. One AE consisted of urinary retention. All AE were resolved by providing relevant medication and/or catheterization. None of the AE needed surgical intervention to be corrected.

The results of the case series treated in this study are comparable to the results of this research group's previous publication on 50 patients treated by different physicians.[10] This study supports the claim of our previous study, which stated that the use of this bioresorbable bulking agent is a safe alternative for the treatment of mild to moderate SUI compared to permanent bulking agents,[15,16] and MUS treatment.[17,18]

Although in this case series, no 12-month follow-up cystoscopy was performed there is no reason to expect a different result from the prior publication which showed no complications at 12 months post-treatment.[10] The results of the long-term follow-up data in this study show the treatment using the PCL-based bioresorbable bulking agent is both safe during short- and long-term follow-up. A large retrospective study in dermatology has found a low complication rate in the use of PCL-based bulking agents as dermal fillers; the complications that occurred were mild in nature.[19]

In this study, a total of six participants (13.6% of all participants) received re-treatment after their return to incontinence. This result is lower than the results from the earlier study in the Netherlands/Belgium using the same product, which showed a 33.3% re-treatment rate. When compared to permanent bulking agents, the re-treatment rate was significantly lower in this study.[16,20]

The results of these studies show that re-treatment is common practice when using bulking agents in the treatment of SUI. The issue with re-treatment with permanent fillers is the accumulation of product in the treated area. These permanent materials will remain forever in the tissue as foreign bodies, with the potential risk of a delayed inflammatory response years after injection.[21] This is a well-known issue in equivalent permanent bulking agent materials used in dermal tissue, which are especially difficult to treat.[21,22] The bioresorbability of the PCL-based bulking agent should be an advantage over permanent fillers since the accumulation of product is expected to be limited as the injected product is replaced by collagen.[11,13] Based on the safety results of this study, we believe the data supports our claim about the role bioresorbable bulking agents play in bridging the gap between a conservative approach and more invasive surgical intervention.[10]

Treatment efficacy

Almost all patients in this study reported an improvement in the severity of incontinence (SGS). One out of 44 patients reported failure of treatment directly after treatment. All other patients reported at least an improvement in their SGS score (one patient) or a cure of incontinence (42 patients) at 6 months post-treatment. Over time, the curation rate slowly decreased in the mild SUI (SGS 1) group from 96.9% cured at 6 and 12 months post-treatment to 78.1% cured at 24 months post-treatment. The decrease in curation rate is slightly larger in the moderate SUI (SGS 2) group, from 91.7% cured at 6 months post-treatment to 66.7% cured at 24 months post-treatment. Although in this group 33.3% had a recurrence of incontinence, none of the participants in this group relapsed to an SGS score of 2. In this study, a total of six participants (13.6% of all participants) received re-treatment after their return to incontinence. This result is less than the results from the earlier study in the Netherlands using the same product, which showed a 33.3% re-treatment rate. Although comparing between studies is difficult due to differences in the study setup, the efficacy results of this study compete with those of permanent bulking agents with higher re-treatment rates.[16] A direct comparative study of multiple products in the future could give more insight into the differences in efficacy between different products. In the previous study, using the same product in the Netherlands showed lower efficacy results in the Stamey grade score improvement in mild to moderate SUI patients.[10] This could be the result of the multiple (three) physicians who did the treatment on 50 patients in the aforementioned study. Since there could be a learning curve,[23] the superior results in this study could be the result of the physician overcoming the initial learning curve. Future studies with larger participant numbers are needed to give more clarification on the efficacy of PCL-based bulking agents in SUI.

Conclusions

In conclusion, the results of the study underline our previous claim that treatment of mild-to-moderate SUI with a bioresorbable PCL-based bulking agent is a safe and effective alternative to permanent bulking agents and an intermediate treatment option before the use of the permanent MUS.

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Online supplementary material:

Supplementary Table 1. Duration of continence for each participant.