Treatment of mild to moderate stress urinary incontinence with a novel polycaprolactone-based bioresorbable urethral bulking agent

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Abstract

A fully bioresorbable polycaprolactone-based bioresorbable bulking agent was evaluated for safety and efficacy in female patients with mild to moderate stress urinary incontinence who attempted and failed prior pelvic floor muscle training. Fifty female subjects were treated by transurethral sub-mucosal injection. Safety was evaluated over a 24-monts follow-up period. At the 12-months visit, a cystoscopy was performed for visual inspection of the injected area. Efficacy was assessed with the same intervals with the Stamey Grading System (SGS) among others. Only 6/50 subjects reported transient mild adverse events. The results show for the SGS grade more than 55% of the participants had an improvement in SGS grade, 40% of whom were cured within the first 12 months after treatment. During the second year of follow-up the effect seems to falter with an improvement of 50% of the subjects of whom 25% were cured. The results of the study suggest that treatment of mild-to-moderate stress urinary incontinence with a bioresorbable PCL-based bulking agent is a safe and effective alternative to permanent bulking agents and intermediate treatment option before the use of the permanent midurethral sling.

Introduction

There is a wide range of treatment options available for Stress Urinary Incontinence (SUI), including non-surgical therapy (pelvic floor muscle training, electric stimulation, change in fluid intake and drug therapy) and surgical treatment. The most widely used surgical treatment for SUI is the Midurethral Sling (MUS) procedure; the Retropubic (TVT) or the Trans Obturator Sling (TOT).[1,2]

With the recent safety concerns and suggested underestimation of complications such as urethral obstruction requiring surgery, vaginal, bladder and/or urethral erosion requiring surgery, and refractory chronic pain associated with MUS procedures,[3] there is a growing interest for alternative less invasive treatment options for SUI without major risks for complications.

One of such alternative minimally invasive treatment option for SUI is the urethral injection of a bulking agent.[4] A promising Polycaprolactone (PCL)-based bulking agent for the treatment of SUI has recently been introduced (Urolon™; AQLANE Medical, The Netherlands).[5-7] The equivalent of the PCL-based bulking agent, a CE-marked soft-tissue filler, has already been shown to have an excellent safety and efficacy profile in the field of soft tissue augmentation.[8-10] Furthermore, PCL and CMC individually have a proven biocompatibility profile and have been used successfully in numerous FDA approved and CE-marked medical devices, such as oral and maxillofacial surgery, wound dressings, controlled drug delivery systems and its use as a bioresorbable tracheal splint for the treatment of tracheobronchomalacia.[11-18] This study intended to evaluated if the PCL-based bioresorbable bulking agent may be a safe and effective treatment options for female subjects with mild to moderate (Stamey grade 1 and 2) SUI who attempted and failed pelvic floor muscle training.

Materials and Methods

In this multicenter study, female subjects of 18 years and older were eligible for inclusion. Inclusion criteria consisted of subjects who suffer from predominantly SUI as determined by the Questionnaire for Urinary Incontinence Diagnosis (QUID); Total Stress Score (Sum Q1-3) of ≥4 and Total Urge Score (Sum Q4-6) of <6. Subjects must have attempted or failed prior pelvic floor exercises while incontinent, suffer from mild to moderate SUI as confirmed by the Stamey Grading Scale (SGS) 1 or 2, able to comply with trial follow-up procedures, schedule, and are willing to provide written informed consent for their participation in the trial.

Exclusion criteria included: previous

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Contributions: ELK: protocol development, data collection, data analysis, manuscript writing; SDW: protocol development, data collection, data analysis, manuscript editing; DJAJO: protocol development, data collection, data analysis, manuscript editing; MJAMDW: protocol development, data collection, manuscript editing; VV: protocol development, data collection, data analysis, manuscript editing; AB: data analysis, manuscript editing. All authors have reviewed and are in agreement with the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work

Conflict of interest: This study was sponsored by AQLANE Medical BV, The Netherlands and was performed in collaboration with the Clinical Research Organization Medpace (Maastricht, The Netherlands). ELK and DJAJO have received honoraria for speaking at symposia for AQLANE Medical BV.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate: Ethical Committee approval was obtained in The Netherlands and Belgium: Trial Registration: Reference NL5760 (NTR6002) (Netherlands); Reference 80M0633 (Belgium). The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. All patients participating in this study signed a written informed consent form for participating in this study.

Informed consent: Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Further information: Preliminary data of this study has been presented at the annual ICS meeting in Philadelphia (USA; August 2018; poster), the UKCS meeting in Manchester (UK; April 2019; oral presentation) and the annual ICS meeting in Gothenburg (Sweden; September 2019; poster).

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bulking agent implantation in the submucosa of the urethra or any form of surgery to treat SUI, morbid obesity (BMI ≥40 kg/m2), post void residual volume ≥100mL, a neurogenic bladder dysfunction, allergies to antibiotics, pregnant (or within 12 months postpartum) or lactating, known connective tissue disease, an active infection of any kind at the time of enrollment, allergies to topical, injectable, or general anesthetics, having been treated with chemotherapy agents or systemic corticosteroids within 3 months prior to enrollment, urethral or bladder neck strictures, non-viable tissue, *e.g.*, history of significant pelvic irradiation, multiple pelvic surgeries, *etc.*, and enrollment in another investigational clinical trial

Subjects were selected and treated in three different hospitals, each subject enrolled in the trial received a treatment and returned to the trial site at 3, 6, 12, 18, and 24 months for safety and efficacy assessments.

Treatment/intervention

Prior to treatment the Stamey Grade was assessed to determine the level of complaint and a non-invasive cough-test was performed. Before treatment a prophylactic antibiotic (1g Cefuroxime) was administered intravenously. Topical anesthesia or propofol sedation was used at the discretion of the physician. All urologists administering the treatment were trained in performing urethral injections prior to the start of the study. All urologists who participated in the study were instructed on correct placement and volume use. Multiple injections (at the recommended 2, 6, and 10 o'clock positions) were administered in a way that optimal coaptation of the urethral mucosa was achieved. Injections were placed in the urethra (1.0–1.5 cm distal from the bladder neck) with the transurethral injection technique using the Williams Cystoscope Needle (3G, 35cm, Cook Medical, Ireland) under cystoscopic guidance. Post-treatment and before discharge a non-invasive cough-test is performed. Subjects are discharged after spontaneous voiding.

Subjects were instructed to adhere to the post treatment instructions as described in Figure 1. The treatment was defined as a "success" if the subject was dry after the intervention. Only one re-treatment per subject was allowed after the 3-month follow-up time point if the subject was not dry after the initial treatment.

Bulking agent

The agent used for the urethral bulking was a Polycaprolactone (PCL)-based bulking agent (Urolon™) developed by AQLANE Medical, The Netherlands. The PCL-based bulking agent consists of 30% PCL microspheres and 70% aqueous Carboxymethylcellulose (CMC) gel carrier. The PCL microspheres are smooth and spherical-shaped and have optimal biocompatibility for use as a particle based bulking agent.[5-7] Moreover, the particles have previously shown to stimulate (type I) collagen formation,[19,20] potentially restoring lost collagen and supporting long-term effectiveness after the microspheres have been bioresorbed.

Follow-up

During the visits at the 3-, 6-, 12-, 18-, and 24-month follow-up time points participants were asked to complete multiple questionnaires (designed to SUI symptoms and Quality of Life) and a non-invasive cough test. Treatment safety via subjects reported AE/SAE's and an additional cystoscopic examination at 12 months follow-up.

SUI symptoms and treatment success were assessed with the Stamey Grading System (SGS), Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Improvement (PGI-I). The SGS and PGI-S results were obtained at baseline and during subsequent follow-up visits. The PGI-I was obtained only during the follow-up visits since this is a subject reported level of improvement compared to their complaints prior to treatment. PGI-I improvement was calculated as the percentage of subjects at follow-up that had a score of 1 "very much better", 2 "much better" or score 3 "a little better". Furthermore, Quality of life (QoL) was assessed with the International Consultation on Incontinence Questionnaire – Short Form (ICIQ-SF) and Incontinence Quality of Life (I-QOL) scale. The ICIQ-SF severity was divided into the following four severity categories: slight (1 – 5), moderate (6 – 12), severe (13 – 18) and very severe (19 – 21) according to Klovning *et al.*[21]

Data analysis

A comparison for the mean I-QoL and ICIQ-SF between the 3-, 6- and 12-month data versus baseline was done using a paired-samples Student t-test with the online calculator (www.socscistatistics.com/tests/ttestdependent/Default2.aspx). Efficacy analysis was performed using a Per-Protocol (PP) approach on all subjects that completed follow-up visits. An additional analysis using a Last Observation Carried Forward (LOCF) was performed to account for subjects lost in follow-up to support the PP analysis. For the LOCF, the last observed value (non-missing value) was used to fill in missing values at follow-up in the study. All data were rounded to one decimal place. Safety evaluation was recorded throughout the study via any reported adverse events. At 12-month follow-up, an additional safety cystoscopy examination was performed to detect any abnormalities found at the injection sites.

Informed consent

This study was approved by the Medical Research Ethics Committees United (MEC-U) in the Netherlands and the Antwerp University Ethical Committee (EC UZA/UA. The ethics board approval numbers are NL55843.100.15 for the Netherlands and B300201627814 for Belgium. 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. Informed consent was obtained from all participants for being included in the study.[22]

Results

A total of 50 female subjects were treated. The mean age of these subjects was 47.5±12.2 ranging from 26-81 years with a median age of 47 years. Of the 50 treated

The following 'post – treatment instructions' are given to the subject prior to discharge from the hospital and recommended to be followed for 3 – 4 weeks post treatment:

1) Drink 1 – 2 liters every day, especially water.
2) Do not lift anything heavier than 5 kilograms.
3) Do not do any heavy exercise.
4) Take showers instead of baths.
5) Avoid thermal baths, or going to the sauna.
6) Prevent constipation by adapting your diet.
7) Avoid sexual activity with vaginal penetration for 1 month.

Figure 1. Post treatment instructions.

subjects, 49, 47, 39, 36 and 32 completed the 3, 6, 9 ,12, 18 and 24-month follow-up.

A re-treatment was received by 17/50 (34.0%) subjects. The loss of follow-up during the first 12 months of the study is shown in Figure 2. Another 7 subjects were lost in follow-up during the second year of the study.

Treatment parameters

The mean (±SD) initial injection volume was 1.5±0.5 cc with a median of 1.6 cc. The mean (±SD) re-treatment injection volume was 1.3±0.4 cc and a median of 1.3 cc. Total mean injection volume (n=50, initial volume + re-treatment) was 1.9±0.9 cc and a median of 1.6 cc (corrected for needle priming volume loss).

Treatment safety

Five subjects reported a total of 7 Adverse Events (AE) of which 3 were related to 1 subject (sensation of post-void urinary retention, a one-time urinary retention resolved by catheterization, and bladder cramps caused by catheterization). The other 4 subjects reported transient urge incontinence, urinary tract infection, hematuria and dysuria. All AE were mild in nature and resolved spontaneously by providing relevant medication and/or catheterization. One subject experienced transient urinary retention that required in-patient hospitalization and was therefore recorded as serious. However, the event itself was mild in nature and was resolved with the use of a catheter. At 12-month follow-up, all subjects received an additional cystoscopic examination but no abnormalities were found at the injection sites.

Treatment efficacy

The Per Protocol (PP) and Last Observation Carried Forward (LOCF) efficacy analysis for the different symptom scores and continence measurements are shown in Table 1.

The results of the PP analysis show for the SGS scale more than 55% of the participants an improvement (improvement + cure) in SGS grade after treatment within the first 12 months after treatment. Approximately 40% of the subjects report being dry on the SGS scale during this same period. During the second year of follow-up the effect seems to falter with an improvement (improvement + cure) in SGS grade of 50% of the subjects and 25% of the subjects being dry. Similar but slightly lower SGS results were found when using a LOCF analysis (Table 1).

Additional efficacy data were obtained with the PGI-S questionnaire, the PP analysis shows a consistent improvement on the PGI-S questionnaire in more than 63% of the participants during the entire follow-up period. At the 3-month follow-up visit more than 50% of the participants rated their urinary tract condition as being normal again (cured), this percentage reduces to approximately 40% at the 24-month follow-up visit. Similar but slightly lower PGI-S results were found when using a LOCF analysis (Table 1)

Treatment success as measured with the PGI-I shows a consistent majority of the participants (more than 74% during the 24 moths follow-up period) feel the treatment was successful. Similar but slightly lower PGI-I results were found when using a LOCF analysis (Table 1).

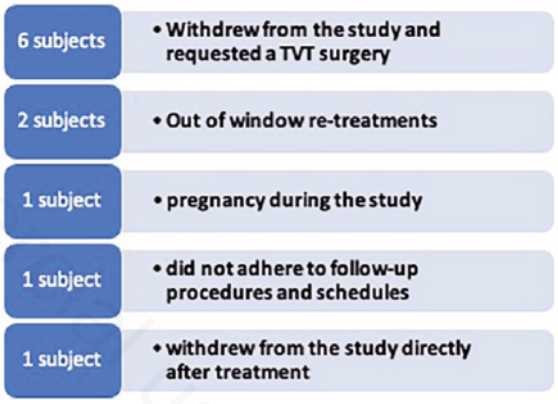

Figure 2. The loss of follow-up (11 out of 50 subjects) during the first 12 months of the study.

Table 1. Change at 3-, 6-, 12-, 18- and 24-months follow-up *vs* baseline.

	3-months *vs* baseline No. Pts/Total No. (%)	6-months *vs* baseline No. Pts/Total No. (%)	12-months *vs* baseline No. Pts/Total No. (%)	18-months *vs* baseline No. Pts/Total No. (%)	24-months *vs* baseline No. Pts/Total No. (%)
Stamey grade					
0 (dry)	21/49 (42.9)	19/46 (41.3)	15/38 (39.5)	9/36 (25.0)	8/32 (25.0)
Total Improvement (Inc. Dry)	31/49 (63.3)	25/46 (54.3)	22/38 (57.9)	17/36 (47.2)	16/32 (50.0)
0 (dry) - LOCF	21/50 (42.0)	19/50 (38.0)	16/50 (32.0)	10/50 (20.0)	9/50 (18.0)
Total Improvement (Inc. Dry) - LOCF	31/50 (62.0)	27/50 (54.0)	26/50 (52.0)	21/50 (42.0)	20/50 (40.0)
PGI-S					
1 (normal/cure)	26/49 (53.1)	20/47 (42.6)	17/38 (44.7)	16/36 (44.4)	13/32 (40.6)
Total Improvement (Inc. Normal)	37/49 (75.5)	34/47 (72.3)	24/38 (63.2)	27/36 (75.0)	23/32 (71.9)
1 (normal/cure) LOCF	26/50 (52.0)	20/50 (40.0)	21/50 (42.0)	18/50 (36.0)	15/50 (30.0)
Total Improvement (Inc. Normal) LOCF	37/50 (74.0)	35/50 (70.0)	33/50 (66.0)	34/50 (68.0)	34/50 (68.0)
PGI-I					
Improvement	42/49 (85.7)	35/47 (74.5)	31/39 (79.5)	29/36 (80.6)	26/32 (81.3)
Improvement LOCF	42/50 (84.0)	36/50 (72.0)	35/50 (70.0)	34/50 (68.0)	32/50 (64.0)

LOCF: Last Observation Carried Forward.

Quality of life (QoL) results

The Quality of life (QoL) results, measured with the ICIQ-SF and I-QoL are shown in Table 2. The results of the ICIQ-SF scores are shown in Table 2A. The baseline ICIQ-SF scores were moderate/severe (12/13) which were reduced to a moderate median ICIQ-SF score of 6/7 during the 24-month follow-up period. Furthermore, the mean differences (improvement) compared to baseline were significant improvements ($p<0.05$), and varied from 4.6 at the 24-month follow-up time point to 6.0 at the 6-month follow-up time point. Similar but slightly lower ICIQ-SF values were found when using a LOCF analysis (Table 2). I-QoL results show a significant ($p<0.01$) mean difference (improvement) compared to baseline of 13.8%, to 17.8% in I-QoL value during the 24-month follow-up period. Similar but slightly lower I-QoL values were found when using a LOCF analysis (Table 3)

Discussion

The aim of the study was to evaluate treatment safety and efficacy of a novel PCL-based bioresorbable bulking agent used for the treatment of mild to moderate SUI in female subjects. In this study the two-year follow-up results are presented.

Treatment safety

This study shows the treatment is a safe alternative to the commonly used TVT or TOT procedures. Adverse events were few and mostly mild in nature consisting of the sensation of post-void urinary retention, transient urge incontinence, urinary tract infection, hematuria, and dysuria. One serious adverse event was found consisting of urinary retention and bladder cramps caused by catheterization. All SAE/AE resolved by providing relevant medication and/or catheterization. No surgical intervention was needed to correct any of the SAE/AE. Comparing these results to the complication results of MUS treatment it shows a much lower occurrence of both standard and serious adverse events. This is expected due to the less invasive nature of this bulking agent.[23,24] When comparing the results of this bioresorbable bulking agent to permanent bulking agents the occurrence of AE and SAE's in the results of this study are significantly lower in both AE and SAE occurrence.[25,26]

This combined with the results of the 12-month follow-up cystoscopy results show the treatment using the PCL-based bioresorbable bulking agent is both safe during short- and long-term follow-up. As such, this bioresorbable procedure may have the potential to bridge the gap between a conservative approach and more invasive surgical intervention.

Treatment efficacy

For the subjects that completed the

Table 2. Change at 3-, 6-, 12-, 18- and 24-months follow-up *vs* baseline.

A) ICIQ-SF	Baseline	3-months (n=49)	6-months (n=47)	12-months (n=39)	18-months (n=36)	24-months (n=32)	Mean difference
Mean ± SD	12.3 ± 3.3	7.0 ± 4.9					5.3*
Mean ± SD	12.1 ± 3.3		6.1 ± 4.7				6.0*
Mean ± SD	12.0 ± 3.3			6.9 ± 3.9			5.2*
Mean ± SD	12.2 ± 3.2				7.2 ± 3.9		5.3*
Mean ± SD	11,9 ± 3.2					7.3 ± 3.8	4.6*
B) ICIQ-SF (LOCF)	**Baseline**	**3-months FU (n=50)**	**6-months FU (n=50)**	**12-months FU (n=50)**	**18-months FU (n=50)**	**24-months F U (n=50)**	**Mean difference**
Mean ± SD	12.2 ± 3.3	7.0 ± 4.9					5.2*
Mean ± SD	12.2 ± 3.3		6.6 ± 5.0				5.6*
Mean ± SD	12.2 ± 3.3			7.5 ± 4.4			4.7*
Mean ± SD	12.2 ± 3.3				8,0 ± 4.2		4.2*
Mean ± SD	12.2 ± 3.3					8.5 ± 4.2	3.7*

*Paired t-test, $p<0.01$.

Table 3. Change at 3-, 6-, 12-, 18- and 24-month follow-up vs baseline.

A) I-Qol	Baseline	3-months (n=49)	6-months (n=47)	12-months (n=39)	18-months (n=36)	24-months (n=32)	Mean difference
Mean ± SD	68.9 ± 17.5	84.2 ± 13.9					15.4
Mean ± SD	69.0 ± 17.8		85.0 ± 15.6				16.0
Mean ± SD	68.9 ± 18.1			84.4 ± 13.2			15.6
Mean ± SD	69.1 ± 18.4				86.9 ± 12.1		17.8
Mean ± SD	68.1 ± 18.7					81.9 ± 11.8	13.8
B) I-QOL (LOCF)	**Baseline**	**3-months FU (n=50)**	**6-months FU (n=50)**	**12-months FU (n=50)**	**18-months FU (n=50)**	**24-months FU (n=50)**	**Mean difference**
Mean ± SD	68.9 ± 17.5	84.1 ± 13.6					15.2*
Mean ± SD	68.9 ± 17.5		84.2 ± 15.5				15.3‡
Mean ± SD	68.9 ± 17.5			83.0 ± 14.4			14.1*
Mean ± SD	68.9 ± 17.5				84.4 ± 13.8		15.5
Mean ± SD	68.9 ± 17.5					81.3 ± 13.0	12.4

*Paired t-test, $p<0.05$. ‡Paired t-test, $p<0.01$.

study follow-up visits, the efficacy analysis shows that the treatment was experienced as successful by the subjects (PGI-I) and resulted in improvements on both the severity of the subject's incontinence (SGS), PGI-S as well on their Quality of Life (ICIQ-SF, I-QoL).

The subjects lost in follow-up partly show less or no beneficial effect of the procedure but not all can be considered as treatment failures. Of those subjects lost in follow-up, 6 withdrew from the study and requested a TVT surgery. Since the results of these subjects showed improvement on several individual efficacy data points (data not shown) it seems likely these subjects had a higher expectation of the treatment.

Due to the high level of loss to follow-up additional analysis was performed using an LOCF to support our PP analysis. The results of the LOCF analysis were similar to the PP analysis and no substantial differences were found. These results support the efficacy results found in the initial PP analysis.

One third of the subjects received a re-treatment which is similar or less than what is published for competing permanent bulking agents currently available on the market, with similar efficacies.[26,27] Because re-treatments are also common with permanent bulking agents,[26] the bioresorption of the PCL-based bulking agents is an advantage from a safety perspective. Re-treatments cause an accumulation of bulking agent material at the injection site over the years. With the PCL-based bioresorbable bulking agent the accumulation is expected to be limited as the injected product bioresorbs over time and is replaced by collagen. In contrast, (accumulated) permanent materials will remain forever in the tissue as foreign body, potentially eliciting a delayed inflammatory response years after injection.[28] This is a well-known and common sequela with equivalent permanent bulking agent materials used in dermal tissue. Hence, complications associated with permanent materials regularly become permanent problems and are especially difficult to treat.[28,29]

Besides the potential safety advantage of the PCL-based bulking agent described above, efficacy competes with that of permanent bulking agents with similar re-treatment rates.[26] However, it remains difficult to compare efficacies directly due to the variations in e.g. study setup, efficacy endpoints, inclusion/exclusion criteria and/or subjects demographics. This may be addressed by future directly comparative studies.

Also interesting to note is that 12 subjects that were dry (SGS 0) at 12-month follow-up did not receive a re-treatment. Moreover, when grouping all the subjects at the 12-month follow-up that were re-treated versus those that did not have a re-treatment, a better treatment outcome (PP and LOCF) was observed in the non-re-treated group (data not shown). The reason why the non re-treatment group performed better could not be established. However, it suggests that re-treatment not necessarily determines improved treatment success. Apparently other factors (such as urethra anatomy) contributed to the treatment success in these particular subjects and merits to investigate such factors in future studies.

In addition, a recent publication shows the physician skills (learning curve) were found to be a risk factor that showed an inferior efficacy for the first 20 bulking agent procedures performed. It is therefore likely that with additional training and experience the efficacy of this treatment can be optimized.[30] Moreover, it is also suggested that a better success rate can be achieved in subjects with an age ≥60 years and <2.5 daily stress incontinence episodes.[31] Although this could not be established in the current study, it does suggest that patient variability can be expected to impact results. Nevertheless, factors such as those described above, will become more evident when bulking agent treatments will increase, which e.g. in the UK has happened over the past few years with the changes in NICE guidelines on surgical meshes.[32] Moreover, Ong *et al.*[33] reported that when using a validated SUI Patient Decision Aid to help patient chose their preferred treatment, bulking agents were preferred over other options with none of the patients choosing for mesh-placement.

In conclusion, the results of the study suggest 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 intermediate treatment option before the use of the permanent MUS.

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