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Safety and Efficacy of a Single Incision Sling for Treatment of Stress Urinary Incontinence in Women through 24-months

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Abstract: The objective of this study was to compare the safety and efficacy of a unique single-incision sling to mid-urethral retropubic and/or transobturator slings in adult female patients with stress urinary incontinence through 36-months. In this paper we present descriptive results through 24-months post-implant. Objective efficacy measures consisted of 24-hour pad weight, dryness (defined as pad weight ≤ 4.0 grams) and negative cough stress test. Subjective measures included: PGI-I, UDI-6 and IIQ-7. Safety measures included device- and/or procedure-related serious adverse events and relevant adverse events including observed rates of organ perforation, bleeding (including hemorrhage and hematoma), mesh exposure in the vagina, mesh erosion into the bladder, pelvic/urogenital (groin) pain, infection, de novo dyspareunia, urinary retention, recurrent incontinence, other urinary problems, neuromuscular problems, and revision/re-operation. Comparative efficacy and safety assessments between study arms occurred at 6, 12, 18, and 24-months. At 24-months, efficacy outcomes remain similar between arms with high objective and subjective results observed. Patient satisfaction is high with 91.2% and 91.3% of single incision and comparative-arm patients (respectively) responding "very much better" or "much better" to PGI-I. Relevant adverse events as well as serious procedure- and/or device-related adverse events are similar between arms.

Keywords: Stress urinary incontinence; single incision sling; midurethral sling; transobturator sling; retropubic sling

1. Introduction

The retropubic mid-urethral sling procedure for surgical correction of stress urinary incontinence (SUI) was introduced in 1995 by Ulmsten and Petros [1]. The large randomized clinical trial (RCT) performed by Ward and Hilton showed that success rates were as good as Burch colposuspension, but that morbidity and cost were in favour of the retropubic sling [2,3]. Over time, the evolution in mid-urethral sling surgery has been to reduce surgical risk without compromising the high cure rate. The transobturator approach was developed to reduce intra-operative complications such as bladder perforation, which had been reported as high as 9% during retropubic sling placement [2]. However, the risk of persistent post-operative complications such as groin pain may be higher following transobturator procedures [4,5]. In a meta-analysis comparing both surgical approaches, efficacy rates were found to be similar, but in the most severe cases of incontinence the retropubic approach was associated with a higher cure rate and fewer re-

interventions [6]. Single incision mid-urethral slings (SIMS), popularly called mini-slings, were developed to further reduce risks and maintain high efficacy. The first SIMS, TVT-Secur, was associated with post-operative pain significantly lower than transobturator slings; however, the device was also found to have a high failure rate [7]. Poor efficacy damaged the reputation of SIMS, and to add further confusion the published outcomes with respect to other SIMS have been somewhat inconsistent. For instance, a randomized clinical trial (RCT) comparing Adjust (SIMS) to Align (standard transobturator) found more pain in the SIMS group [8], whereas a similar RCT performed by another research group showed the opposite [9]. Nevertheless, in more recent studies comparing SIMS to full-length transobturator slings, current SIMS are found to be non-inferior in cure and superior in post-operative pain and recovery with shorter operating time [10,11].

Altis™ SIS (Coloplast, Minneapolis) is a single incision sling with several unique design characteristics including low mesh elasticity, bi-directional intraoperative adjustability (post-deployment of anchor), and an anchoring mechanism that fully penetrates the obturator membrane. Prior to U.S. commercialization, a single-arm multi-center investigational device exemption (IDE) study was performed that followed patients through 24-months post implant [12,13]. The results of the IDE study found high efficacy with a good safety profile. Subsequently, Altis was cleared to market by U.S. Food & Drug Administration (FDA) in 2012. However, beginning in 2012, FDA ordered manufacturers to perform postmarket studies (522 studies) to address specific safety and effectiveness questions related to the use of single incision slings for treatment of SUI [14]. Following FDA's 522 postmarket order for Altis, a prospective trial was initiated to compare the safety and efficacy of Altis to retropubic and/or transobturator slings for the treatment of SUI (Altis 522 Study). In this paper we provide descriptive data from the Altis 522 study through 24-months of follow-up.

2. Materials and Methods

The design of the Altis 522 Study has been described previously [15]. In brief, the aim of the study was to compare the safety and efficacy of Altis to mid-urethral retropubic and/or transobturator slings in adult female patients through 36-months. The primary efficacy measure is 24-hour pad weight and secondary objective efficacy measures include dryness (defined as pad weight ≤ 4.0 grams) and negative cough stress test (CST). Collected subjective outcome measures include Patient Global Impression of Improvement (PGI-I), Urinary Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7). The primary safety measure is the rate of device- and/or procedure-related serious adverse events. Secondary safety measures include comparative assessments of relevant device- and/or procedure-related adverse events including observed rates of organ perforation, bleeding (including hemorrhage and hematoma), mesh exposure in the vagina, mesh erosion into the bladder, pelvic/urogenital pain, infection, de novo dyspareunia, urinary retention, recurrent incontinence, other urinary problems, neuromuscular problems, and revision/re-operation. Efficacy and safety assessments occur at 6, 12, 18, 24, and 36 months.

The study was conducted at 23 hospitals in the United States and Canada with all study sites receiving institutional review board/ethics committee approval. Prior to study initiation all participating surgeon investigators were experienced in performing mid-urethral sling surgery for SUI. The Altis 522 study is a non-randomized study with selection of the surgical intervention based on surgeon expertise and shared decision making with the patient. Eligible patients were required to have predominant SUI; additionally, patients were required to have failed two conservative incontinence therapies prior to enrollment. Exclusion criteria included pelvic organ prolapse Stage 2 or more as determined by the Pelvic Organ Prolapse Quantification System (POP-Q), prior SUI surgery, indication for concomitant surgical procedures (e.g., no concomitant surgery was allowed at the time of the implant procedure), active skin/urogenital infection, incontinence due to neurogenic causes, history of radiation or brachytherapy to treat pelvic cancer or post void residual (PVR) above 100cc on ≥ 2 occasions. Women planning future pregnancy were also excluded.

The study sample size was calculated to assess non-inferiority of the primary efficacy and safety endpoints at 80% power with a type-I error rate of 0.05 for each primary endpoint analysis. The final sample size was determined to be the maximum requirement for the primary efficacy and safety endpoints. Prior to accounting for loss to follow-up, the minimum sample size was determined to be 328. In this 24-month report endpoint results are summarized descriptively (e.g., via counts and percentages). To minimize potential bias, no statistical testing is performed, and no p-values are provided as all patients have not completed the study through the final 36-month follow-up visit.

3. Results

A total of 184 patients were implanted in the Altis-arm and 171 in the Comparator-arm. A description of patient baseline characteristics was previously published [15]. In summary, patients in the Altis-arm were older and more likely to be post-menopausal. Symptom severity and history of prior pelvic surgery were comparable between study arms. Mixed urinary incontinence (MUI) and current smokers were more common in the Comparator-arm and more patients in the Altis-arm had a diagnosis of intrinsic sphincter deficiency (ISD). The Comparator-arm was divided evenly between retropubic (49.7%) and transobturator (50.3%) slings. In both study arms, surgical procedures were most often performed in outpatient or ambulatory settings. Altis SIS surgical procedures were more often performed under local anesthesia.

Objective and subjective efficacy measures are presented in Table 1. At 24-months, efficacy outcomes appear similar between arms with high objective and subjective results observed.

Table 1. Efficacy measures at 24-month post-implant procedure

Efficacy (24-months)[1]	Altis-arm	Comparator-arm
Pad Weight Success (≥50% reduction)	125 (89.3%)	89 (88.1%)
Dry (≤4gm Pad Weight)	109 (74.7%)	51 (49.5%)
Negative CST	132 (90.4%)	87 (93.5%)
PGI-I ("Very much better" or "Much better")	134 (91.2%)	95 (91.3%)

UDI-6 score (SD)	9.1 (15.2)	10.0 (14.2)
IIQ-7 score (SD)	5.0 (14.7)	7.5 (15.8)

[1] Percentage or SD as indicated

No new serious procedure- and/or device-related adverse events were reported in either study arm since the previous 12-month publication. As such, through the first 24-months after implant surgery, two subjects in the Altis-arm and three subjects in the Comparator-arm experienced a serious device- and/or procedure- related adverse event (Table 2). Specifically, in the Altis-arm one patient experienced incomplete bladder emptying after surgery and a cystocele was diagnosed which worsened over approximately 70-days post-procedure. The event became an SAE following cystocele correction by anterior colporrhaphy, after which the patient could adequately empty her bladder. One patient experienced pelvic/urogenital pain two days post-procedure. The sling appeared to be functioning with no reported incontinence events and a pelvic exam was negative; however, the patient requested explantation of the sling after which the pain resolved. In the Comparator-arm, one patient had delayed wound healing with exposed mesh at the incisional site at 210 days post-procedure. This patient was found to have severe diabetes and abnormally high blood sugar. The sling was excised per patient request, after which the vaginal incision slowly healed. Within the retropubic sling comparator subgroup, one bladder perforation and one readmission to the hospital occurred. The retropubic sling bladder perforation was discovered and corrected at time of surgery. The readmission to the hospital occurred two days post-procedure due to shortness of breath and chest pain. Cardiac enzymes and ECG were found to be normal, and the patient was discharged the following day. In addition, there were no new surgical revisions observed within either treatment arm between the 12- to 24-month follow-up visits. Consequently, through 24-months post implant the revision/re-surgery rate remains lower in the Altis arm.

Table 2. Safety-related events through 24-month post-implant procedure

Event Type	Altis-arm	Comparator-arm
Serious procedure and/or device related adverse events		
Urinary retention/obstruction	1 (0.5%)	0
Pelvic/urogenital pain (groin)	1 (0.5%)	0
Delayed wound healing	0	1 (0.6%)
Perforation, bladder	0	1 (0.6%)
Chest pain/shortness of breath	0	1 (0.6%)
Revision Surgery		
Any revision/explant	2 (1.1%)	8 (4.7%)

As described below in Table 3, there do not appear to be any considerable differences in relevant device- and/or procedure-related non-serious adverse events between arms.

Table 3. Relevant non-serious device- and/or procedure-related adverse events through 24-months

Adverse Event Type	Altis-arm	Comparator-arm
Organ perforation	0 (0%)	0 (0%)
Bleeding	0 (0%)	0 (0%)
Mesh exposure	0 (0%)	0 (0%)
Pelvic/Urogenital (groin) pain	4 (2.2%)	3 (1.8%)
Infection	0 (0%)	1 (0.6%)
Dyspareunia, de novo	3 (1.6%)	2 (1.2%)
Urinary retention/obstruction	4 (2.2%)	3 (1.8%)
Recurrent incontinence	2 (1.1%)	7 (4.1%)
Other Urinary problems		
Voiding dysfunction	1 (0.5%)	0 (0%)
Urgency worsening	0 (0%)	2 (1.2%)
Dysuria	1 (0.5%)	1 (0.6%)
Neuromuscular problems	0 (0.0%)	0 (0%)

4. Discussion

Safety and efficacy data collected through 24-months find that the performance of Altis appears comparable to full-length retropubic and transobturator slings. Retropubic, transobturator, and single-incision surgical approaches were associated with excellent efficacy, high patient satisfaction, and a good safety profile. The Altis procedure was most often performed under local anesthesia without compromising results as compared to full-length mid-urethral slings through 24-months. Further, the low number of patients with urinary retention suggest that Altis may be an option for surgeons choosing to perform prophylactic midurethral sling in patients undergoing prolapse surgery. The non-randomized design of the study has the limitation of confounders; however, the advantage of our real-world design enhances the external validity of our results. Although characterized similarly, commercially available SIMS devices possess differences in mesh characteristics, dissection technique, predictability of placement, adjustability, and reliability of fixation. Specifically, Altis differs from other SIMS in the following aspects:

a) Insertion technique: The helical-type introducer used for Altis implantation is designed to facilitate a consistent surgical trajectory whereas a needle-type introducer may lead to more variability in placement. The small radius of the Altis introducer limits excessive horizontal movement ensuring proper fixation of the anchor at the obturator membrane and decreasing risk of injury to vasculature and nerves. In addition, during Altis implantation the surgeon must position the patient properly and keep the introducer in the correct direction at the start of rotation until the anchor has penetrated the obturator membrane. This ultimately results in a reproducible surgical trajectory supporting consistent placement.

b) Mesh characteristics: As a Type 1 mesh the pore size of Altis supports tissue integration. Altis mesh is the thinnest and lightest weight incontinence mesh available, yet it is the least likely to elongate under a load when compared to other mesh designs. Higher elongation may lead to more deformation during mechanical loading resulting in less urethral support. Mesh with lower elongation may be more equally distributed over the mid-urethra when subjected to increases in intra-abdominal force.

c) Fixation technique: Altis anchors are associated with a low insertion force and high pull-out force [12]. Altis anchors are designed in such a way that the sling, once anchored, can be adjusted bi-directionally allowing precise sling tensioning. Anchor sizes differ between SIMS, theoretically the smallest anchor that withholds the intra-abdominal forces being preferred as larger volume may create more fibrosis.

The optimized combination of Altis design features is unique and although head-to-head comparisons between SIMS have not been realized, it is important to understand the theoretical concepts behind each design. With a variety of treatment choices available to surgeons the benefit of SIMS from a patient perspective should be considered. Overall, as a surgical approach, SIMS have demonstrated shorter operating time, less post-operative pain and faster recovery, and apart from TVT-Secur, the efficacy of SIMS has been found to be non-inferior to conventional mid-urethral slings [10,16,17]. A recent preference study [18] found that patients consider the potential of faster recovery to be highly relevant leading to the belief that SIMS may fit well within the concept of value-based healthcare. Moving towards less invasive surgery is also relevant when considering that an ageing population is likely to result in increasing numbers of women requesting surgical correction of SUI [19].

5. Conclusions

These 24 months data show comparable efficacy and safety of Altis SIS and standard mid-urethral retropubic- and transobturator mid-urethral slings. Longer-term data are required to confirm the sustainability of surgical outcomes. We feel that the unique design characteristics of Altis help to facilitate favorable surgical outcomes.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and all 23 participating sites obtained Institutional Review Board approval. The first IRB approval was Western Institutional Review Board (Protocol Code: SU020 and date of approval: 20 October 2014).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: This study is registered with ClinicalTrials.gov, identifier: NCT02348112. Data sharing is not applicable to this article as the study is on-going and no data were statistically tested.

Conflicts of Interest: JHH is a consultant for Coloplast and Medtronic; KJ, RM, MP have no conflicts of interest.

The study is conducted under a 522 Post-market Surveillance order by FDA, as such, the study design was created by Coloplast Corp and approved by FDA. Data were collected by the participating study sites with data monitoring procedures performed by the sponsor throughout the study according to applicable regulations and standards. Data are compiled by a third-party statistician with the authors and sponsor participating in interpretation of data and manuscript writing. As a post-market surveillance study, the sponsor supports the decision to publish results to provide the medical community currently available data.

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