

# Prophylactic urethral stenting with Memokath® 028SW in prostate cancer patients undergoing prostate <sup>125</sup>I seed implants: phase I/II study

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## Abstract

**Purpose:** To study the feasibility/toxicity of urethral stenting with the Memokath® 028SW stent in patients undergoing prostate implant (PI) for prostate adenocarcinoma.

**Material and methods:** An Investigational Device Exemption from the Food and Drug Administration (FDA) and institutional review board (IRB) approval were obtained. Twenty patients enrolled. Baseline American Urological Association (AUA) score was obtained prior to PI. Follow-up information was obtained with weekly phone calls for the first 12 weeks and biweekly calls for the next 12 weeks to assess toxicity and AUA score. Removal of the stent was planned at six months after PI, or earlier due to excessive toxicity/patient request.

**Results:** Median age was 66.5 years. The median prostate volume was 39 cc (range: 10-90). The median baseline AUA score was 7.5 (range: 1-21). Three patients required intermittent self-catheterization (ISC) within 3 days after PI. No patients required ISC beyond day 3 after PI. The median duration of ISC was 1 day (range: 1-2). AUA scores returned to baseline values 6 weeks after PI. The week 6 AUA score was 10 (range: 4-16). Seven patients (35%) underwent early removal because of patient preference. The reasons were: incontinence ( $n = 3$ ), discomfort ( $n = 2$ ), hematuria ( $n = 1$ ), and obstructive symptoms ( $n = 1$ ). The median time of stent removal in these patients was 13.9 weeks (range: 0.9-21.4). Thirteen patients (65%) had ISC and/or urinary catheterization post stent removal. Median time for ISC use was 10 days (range: 1-90).

**Conclusions:** Urethral stenting with Memokath® in patients undergoing PI was feasible, but resulted in relatively high rate of urinary incontinence and discomfort. Given the adverse effects experienced by patients of this study, further studies should focus only on patients with highest risk of urinary obstruction from PI or those with obstruction needing ISC.

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**Key words:** urethral stent, prostate brachytherapy, prostate cancer, urethral obstruction.

## Purpose

Image-guided transperineal permanent prostate brachytherapy (PI) is an accepted curative treatment option for patients with early stage prostate cancer. Multiple reports have demonstrated its efficacy and shown it to be superior to antecedent trans-abdominal techniques [1, 2]. In addition, the efficacy of PI has been shown to be similar to radical retropubic prostatectomy (RRP) and external beam radiotherapy (EBRT) [2]. These positive results, however, are gained at the expense of toxicity. The most notable toxicity is associated with the urinary system. The most severe side effect of PI is urinary retention requiring intermittent self-catheterization (ISC). The reported rate of severe urinary retention following PI is approximately 10% [3-7]. Most of these patients can be managed with the use of ISC and

$\alpha$ -blockers for a few weeks. Although this is generally a temporary phenomenon, a small percentage will eventually require surgical intervention to permit urinary flow. This is a major concern for patients undergoing PI, but should not be a reason to avoid this form of curative treatment. Alpha<sub>1</sub>-blockers have been FDA-approved for use in patients with benign prostate hyperplasia (BPH) who have obstructive symptoms [8]. Tamsulosin is an antagonist of alpha<sub>1A</sub>-adrenoceptors in the prostate and has been used with success in reducing urinary symptoms from BPH [9-14]. The use of tamsulosin in prostate brachytherapy to reduce urinary symptoms has been studied prospectively. This involved a trial of 118 patients randomized to tamsulosin or placebo. There was no difference in the urinary retention rate. However, there was a significant difference in the American Urological Association (AUA) score in favor

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of tamsulosin at week 5. While it did reduce the irritative symptoms, it did not reduce obstructive symptoms [15].

Given that the reduction in smooth muscle tone is not sufficient in reducing the obstructive symptoms from prostate brachytherapy, other means are necessary to keep the urethra patent. The use of implantable stents has been successful in BPH patients. The Memokath<sup>®</sup> device has been shown to decrease the International Prostate Symptom Score from a mean of 20.3 to 8.2 in the first three months after stent placement in patients with bladder outlet obstruction unable to undergo a transurethral resection of the prostate (TURP). Few patients experienced side-effects, with pain in 3%, hematuria in 3%, incontinence in 6%, and infection in 6% of patients being reported [16]. A multicenter randomized trial with a control arm assessed the use of this device in patients with recurrent urethral strictures.

Given that few patients have experienced side effects with the Memokath<sup>®</sup> urethral stent in bladder outlet obstruction, we wished to assess the toxicity associated with this stent in a post-brachytherapy setting. In addition, we wanted to assess its efficacy when used prophylactically in reducing bladder outlet obstruction following prostate brachytherapy and its impact on the AUA score.

## Material and methods

An Investigational Device Exemption (IDE) for the use of the Memokath<sup>®</sup> 028SW urethral stent was obtained through the Food and Drug Administration (FDA). The study was approved through the Cleveland Clinic Institutional Review Board as a Phase I/II study of 20 patients. All patients with prostate cancer who were eligible for prostate brachytherapy and older than 50 years of age were considered for enrollment in the phase I/II study. Exclusion criteria included: 1) presence of any other urologic implant, including stents, penile prosthesis, or artificial sphincter, 2) history of a TURP procedure, 3) presence of urethral diverticuli, 4) inability to participate in study activities due to physical or mental limitations, 5) inability or unwillingness to return for all the required follow-up visits, 6) presence of urethral strictures, 7) presence of bladder calculi or tumors; prostatic urethra < 2.5 cm or > 6.5 cm.

### Prostate brachytherapy

All patients received PI according to the American Brachytherapy Society guidelines for treatment and post-implant dosimetric analysis [17, 18]. The only isotope used was <sup>125</sup>I. Approximately 85% of each implant contained RAPID Strand<sup>™</sup> stranded seeds. Some patients received three months of tamsulosin 0.4 mg b.i.d. (or a similar alpha-blocker) as usually prescribed post-brachytherapy.

### Stent placement procedure

All patients in the study received the Memokath<sup>®</sup> urethral stent shortly following PI while the patient was still under anesthesia. The stent was placed according to guidelines set forth by the stents manufacturer, Engineers and Doctors A/S, Copenhagen, Denmark<sup>®</sup>. After the patient

was prepped and draped, a cystoscopy was performed to assess the prostatic urethral length from bladder neck to proximal limitation of external urethral sphincter, the absence of urethral strictures in all parts of the anterior and posterior urethra, and the absence of bladder stones or bladder neoplasia. The appropriate length of the stent used was determined by the length of the prostate. The stent was placed under the guidance of cystoscopy. Warm water (53-58°C) was instilled to expand the stent into place.

### Assessments

A baseline AUA score for each patient was obtained prior to PI. An AUA score was obtained weekly for the initial 12 weeks after PI, then biweekly for the following 12 weeks or until removal of the stent. At each assessment, patients were asked about symptoms and toxicity, which were then graded. Urinary flow rate (UFR) and post-void residual (PVR) was obtained in the office at week 2 and month 3 as a part of follow-up.

### Toxicity assessment

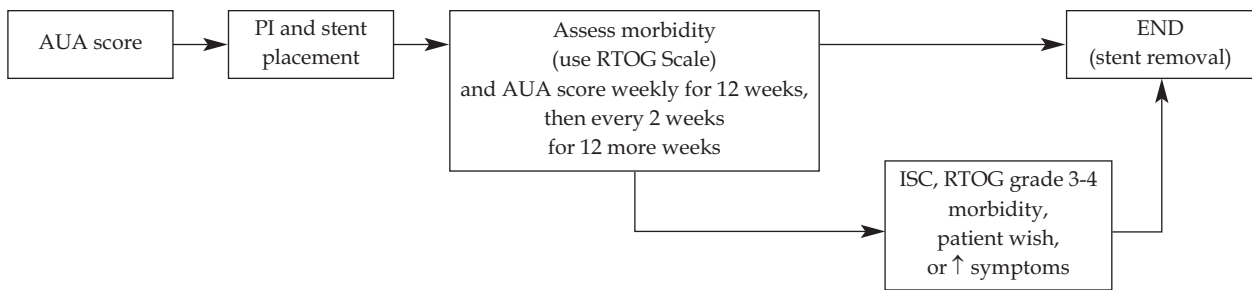
The Radiation Therapy Oncology Group (RTOG) Morbidity Scale was used to determine toxicity/safety of the Memokath<sup>®</sup> 028SW stent after PI. The AUA score was used to assess severity of urinary symptoms as a secondary endpoint. Patients were taken off the study if they needed repeated ISC, had intolerable urinary symptoms, developed a grade 3 or 4 toxicity that was the result of the stent, or wished to discontinue the participation in the trial. Their adverse events were recorded and the device was removed per protocol.

### Removal

Patients were to retain the stent for a total of 24 weeks or until they were taken off the study due to toxicity or patient choice. Stent removal was performed in the outpatient setting via cystoscopy. The study design is summarized in Fig. 1.

## Results

A total of 20 patients were enrolled in the study. Median age of the patients was 66.5 years (range: 51-72). The biopsy Gleason score was 6 in 13 patients (65%), 7 in 6 patients (30%), and 9 in 1 patient (5%). Stage was T1c in 15 patients (75%) and T2a in 5 patients (25%). Median initial prostatic specific antigen (iPSA) was 5.55 (range: 1.3-18.1). Only 1 patient was treated with androgen deprivation (duration 6 months). The median prostate volume was 39 cc (range: 10-90) and the median urethral length was 4.55 cm (range: 2.8-6.9). The median baseline AUA score was 7.5 (range: 1-21). One (5%) had androgen deprivation prior to PI. Two patients required ISC within 24 hours, and 1 patient required ISC 2 to 3 days after PI. No patient required ISC beyond day 3 after PI. The median duration of ISC was 1 day (range: 1-2). AUA scores returned to baseline values 6 weeks after PI (Fig. 2). UFR and PVF were obtained with the stent in place. At week 2, 18 out of 20 patients underwent testing. One patient had the stent removal before the



AUA - American Urological Association, PI -  $^{125}\text{I}$  prostate brachytherapy, ISC - intermittent self-catheterization, RTOG - Radiation Therapy Oncology Group

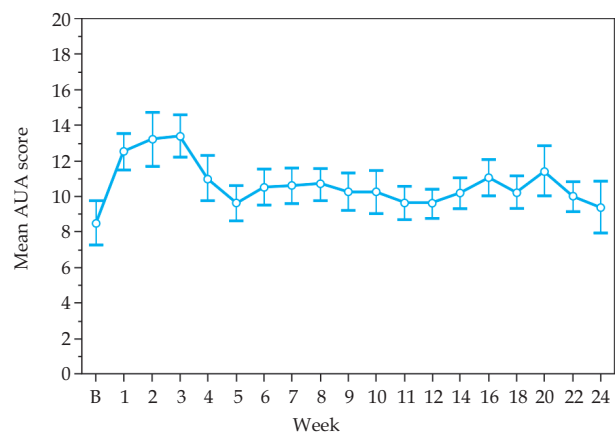
**Fig. 1.** Study schema. Primary endpoint: To evaluate the feasibility of urethral stenting with Memokath® for patients with prostate adenocarcinoma after prostate implantation. Secondary endpoint: To evaluate the ability of urethral stenting with Memokath® to reduce the peak AUA symptom score and to reduce the need for ISC after PI

week 2 visit and the second patient did not come for his week 2 follow up visit. Two weeks after PI, the median UFR was 4.2 mL/sec (range: 1.1-14) and the median PVR was 19.5 cc (range: 0-537). At 3 months, 11 patients underwent UFR and 12 patients underwent PVR. Of the patients that did not undergo testing at month 3, 6 patients already had their stent removed, 2 patients refused, and in 1 case, the UFR machine malfunctioned. The median UFR was 4.2 mL/sec (range: 1.6-12.2) and the median PVR was 31.2 cc (range: 0-148) at 3 months after PI. Fifteen patients (75%) developed urinary spasms or leakage following stent placement. The use of alpha blockers was noted to be associated with this side effect so their use was curtailed. The bladder spasms were resolved successfully by using a bladder antispasmodic medication such as trospium, darifenacin, or oxybutynin. Five patients (25%) had urinary burning relieved with the use of phenazopyridine. Two patients (10%) developed rectal spasm relieved by a short course of belladonna and opium suppositories.

Seven patients (35%) underwent early stent removal because of patient preference. The reasons for early stent removal were: incontinence (3 patients), discomfort (2 patients), hematuria (1 patient), and obstructive symptoms (1 patient). The median time of stent removal in these patients was 13.9 weeks (range: 0.9-21.4). Thirteen patients (65%) required ISC and/or urinary catheterization post removal. Median time for ISC was 10 days (range: 1-90). Patients undergoing early removal of the stent had a higher incidence of requiring ISC use following stent removal versus patients for whom the stent was removed 6 months after PI (85.7% vs. 53.85%). No long-term toxicity was noted. The study was completed without meeting stopping criteria.

## Discussion

Urethral stents have been used with some success in patients with post-brachytherapy bladder outlet obstruction. Five patients, who could not tolerate alpha-blockers or clean intermittent catheterization, received UroLume® urethral stents following one or more episodes of urinary retention [19]. All patients were able to void immediately after stent placement. No patient developed incontinence after the stent placement. The main complaints following



**Fig. 2.** Median AUA score by week (AUA score  $\pm$  1 SE) by week for patients on Memokath phase I study)

UroLume® stent placement were urethral bleeding, referred pain at the head of the penis, and dysuria. These symptoms required stent removal in 2 out of the 5 patients. In another study, 5 patients received Spannerurethral stents following significant urinary symptoms after prostate brachytherapy [20]. All patients were able to void spontaneously with no post-void residual volume of urine. Flow rates increased and the International Prostate Symptom Score decreased from a mean of 25.2 to 10 ( $p = 0.03$ ). However, 2 patients experienced pain, which required removal of the stent.

This present study was a Phase I/II study on the use of the Memokath® urethral stent in prostate brachytherapy. The first goal of this study was to assess the safety of this device and the second goal was to determine efficacy. Overall, the stent was safe in this group of patients. At the start of the study, all patients were placed on tamsulosin. However, it was noted that many of these patients developed urinary leakage with routine tamsulosin use. Use of tamsulosin was then discontinued and resulted in a reduction of urinary leakage. A majority of patients (75%) developed urinary leakage and spasms following stent placement which was well controlled after starting a bladder antispasmodic. Urinary irritation developed in 25% of the patients and was effectively controlled with phenazopyridine. Two patients had limited rectal spasms that were



relieved with belladonna and opium suppositories. Most patients tolerated the stent well with the use of medication, however, 35% of the patients ultimately requested early removal of the stent secondary to incontinence, discomfort, hematuria, or obstructive symptoms. No patient required repeated ISC following stent placement, which would have resulted in removal from the study. There were no RTOG grade 3 or 4 toxicities. There were no notable long-term toxicities. As such, the study did not meet early stopping criteria and was able to be completed as per the protocol. One concern at the start of the study was migration of the Memokath® stent into the bladder, especially for patients with small prostate glands. No migration was noted while the stent was in place and on cystoscopy at the time of removal. In regards to efficacy, no patient required repeated ISC and the stent was effective in preventing urinary obstruction. The UFR at week 2 and month 3 was stable at 4.2 ml/sec, and patients were able to urinate on their own. The AUA scores follow a similar profile when compared to the results of our previous trial with tamsulosin [15] (Fig. 3). Given that the baseline AUA score in these patients is higher than in the previous study, this suggests there may be a benefit in regards to obstruction with the prophylactic use of a urethral stent at the time of PI, especially in patients with a high baseline AUA and a high likelihood of developing obstruction.

Upon removal of the stent, 65% of patients experienced urinary obstruction requiring ISC. This elevated rate of ISC was speculated to be the result of removing the stent too early after PI, rather than an effect of the stent. The rate of urinary obstruction between patients who underwent early removal and those who underwent removal at 6 months differed by more than 30%. The number of patients in this study, however, is too small to make definitive conclusions.

## Conclusions

While the Memokath® stent was safe and did have some benefit in preventing urinary obstruction post PI, there were certain patient issues relating to discomfort and incontinence resulting in early removal. There is a high rate of ISC use following stent removal which may be due to early removal. Patients with this urethral stent should be encouraged to keep it in as long as possible. Given the high rate of adverse effects with only 65% of the patients able to complete this study, and a low risk of urinary obstruction from PI, this device should only be considered in patients who are at a very risk for ISC such as patients with a very high baseline AUA score, or those who developed urinary obstruction post PI and have difficulty performing ISC. Other risk factors include large prostate volume and prostate length of greater than 5 cm which has been shown to be an important predictor for ISC [21]. Prophylactic use in all patients is not advised. Further studies are needed to determine the optimal role of the Memokath® stent.

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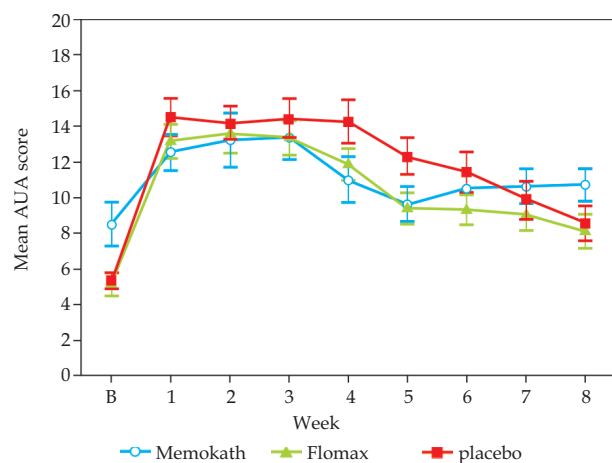


Fig. 3. AUA score in comparison to previous studies (AUA score  $\pm$  1 SE) by week for patients on Memokath, Flomax, or placebo)

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