Assessing the Safety and Efficacy of the ClearRing™ Implant for the Treatment of Benign Prostatic Hyperplasia in a Canine Model

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Key Words
Benign prostatic hyperplasia • Endoscopy • Surgical devices

Abstract

Background: Transurethral resection of the prostate is the most common procedure for the treatment of benign prostatic hyperplasia (BPH). Although effective, transurethral resection of the prostate can be associated with side effects including prolonged recovery, storage and voiding symptoms, risk of acute urinary retention. Objectives: In this study, we describe a new minimally invasive device for the treatment of lower urinary tract symptoms due to BPH, implanting a nitinol C shape ring in a circular incision in the prostatic tissue, surrounding the urethra, done by electrocutting blade over a dilatation balloon. Methods: Two groups of dogs (4/group) were implanted with the device under anesthesia. Clinical observation, body weight and weekly blood and urinary tests were performed throughout the study period to evaluate safety. Fluoroscopy and cystoscopy were used throughout the study period to evaluate implant condition and urethral dilatation. At the end of 3 weeks (Group I) or 3 months (Group II), the animals were sacrificed. The implantation site was examined macroscopically and histologically to evaluate urethral dilatation and tissue response. Results: The presence of the ClearRing™ implant in an animal’s prostate was associated with significant dilatation of the prostatic urethra. Fever, pain, behavior disturbances or gross hematuria, when occurred, resolved within 72 hours post procedure and no severe adverse events were observed. There was no evidence of prostatic hyperplasia associated to ring implantation. Partial epithelial coverage of the implant surface was observed without evidence of encrustation. Conclusion: The ClearRing™ implant seems a feasible minimally invasive procedure for relieving lower urinary track symptoms due to BPH.

Introduction

Transurethral resection of the prostate (TURP) is the most common invasive procedure for the treatment of benign prostatic hyperplasia (BPH). Although effective, TURP can be associated with side effects including prolonged recovery period, storage and voiding symptoms, risk of acute urinary retention, and routine catheterization. Retrograde ejaculation is the most common long-term complication of TURP and can occur in as many as 90% of cases. Moreover, urinary incontinence and erectile dysfunction are reported in 1–3% of the patients [1].
Less invasive treatments such as intraurethral stents for the treatment of BPH [2] were abandoned mainly due to obstruction, encrustation, infection, and migration [3]. Thermal ablative techniques are minimally invasive, however limited due to uncomfortable urinary symptoms during healing. Symptom relief does not occur immediately, and patients often need to have a catheter during the recovery period. More recently, the UroLift® device has been granted FDA approval for BPH treatment after showing long-term efficacy. The treatment consists of transurethral delivery of small implants to secure the prostatic lobes in a patent position [4].

The ClearRing™ system is designed to treat lower urinary tract symptoms (LUTS) due to BPH by expanding the urethra by positioning supporting C shape implants in the perimeter of the enlarged prostate tissue, thus avoiding any long-term contact with the urine. The implants are designed to prevent the prostate tissue from compressing the urethral lumen.

In this study the ClearRing™ system was evaluated on 8 beagle dogs.

**Materials and Methods**

Animal handling was performed according to guidelines of the National Institute of Health and the Association for Assessment and Accreditation of Laboratory Animal Care.

The study was performed after approval by “The Hungarian Board for Animal Experiments” and in compliance with “The European Animal Welfare Act” Approval No. I/1411/49/2/3/2012.

Eight male beagle dogs of 3–8 years old were used. Each dog was screened by ultrasonography to demonstrate a prostate gland > 30 mm long. ClearRing™ prototype implantation device included 2 main components: 1) An open nitinol ring shaped implant 2 mm wide, 25 mm diameter. 2) Delivery system, which included a shaft and a cutting blade over a dilation balloon (fig. 1). The device is 24 F in size and in its distal end incorporates a dilation balloon that inflate to 18 mm diameter at 2 atmosphere that, upon inflation within the urethra, expands the obstructed area and enables the pre-positioning of the implant in its designated
location while creating the passage intended upon deployment. A small electro-cutting blade, located on the top of the dilation balloon, enables the production of a circumferential incision in the tissue surrounding the prostatic urethra. The implanted ring expands into the incision.

**Design**

The study was divided into 2 consecutive phases. Phase I consisted of 4 animals which were treated using the ClearRing™ implant and were kept alive for a follow-up period of 3 weeks. Phase II consisted of 4 animals which were treated using the ClearRing™ implant and were kept alive for a follow-up period of 3 months post procedure.

**Surgical Procedure**

Anesthesia was induced by intramuscular injection of ketamine/xylazine (85/15 mg/kg), and maintained by inhalation (2.5% isofluran/97.5% dry air) until the completion of the operation and implantation procedures. Thereafter, the dog was awakened.

After induction of anesthesia, a lower abdominal laparotomy was performed and the bladder and the prostate were exposed. Before implantation fluoroscopic markers were placed at the prostate's proximal and distal edges. The rings were implanted into the animal’s prostate tissue using a dedicated delivery system (fig. 1), in an anterograde fashion through a small cystostomy. The positioning was controlled by fluoroscopy. Post implantation cystoscopy and fluoroscopy were used to evaluate implant condition and urethral dilatation. A Foley catheter was left at the end of the procedure.

In 1 animal the implant was removed using standard grasper under cystoscopy vision, 103 days post procedure, and the dog was kept for additional 3 months to assess the tissue behavior post implant removal.

**Follow-Up**

Clinical inspection was performed within the first day following operation (day 0) and recovery and thereafter on days 3, 7, 14, 21 and termination day. Cystoscopy visualization and fluoroscopy were recorded, per dog, on day 0 at the end of procedure, day 21 and on termination day to evaluate implant condition and urethra.

Supportive medications with non-steroidal anti-inflammatory drugs (NSAIDs) were used as needed. Catheter was removed 4 days after the operation.

**Histology**

Samples were fixed with 10% buffered formalin. The tissues included the urinary bladder and prostate in one full sample. Tissues were embedded in paraffin and sectioned. They were stained with hematoxilyn and eosin.

**Results**

**Clinical Data**

Most animals had no abnormal clinical signs. In 1 animal body temperature rose up to 39.3°C during the first 48 hours post procedure but subsided to 38.7°C after supportive medication of NSAID. From day 3 thereafter until day 23 (termination day) no abnormal clinical signs were recorded, body temperature and respiration rate were normal on days 3, 7, 14 and 23. No macroscopic signs of infection or inflammation were found on pathology at the end of the follow-up. In another animal hematuria, back arching, slow movement and tremors were recorded during the first 36 hours post procedure. Symptoms disappeared after supportive medication with NSAID; urine was almost clear with no hematuria. Clinical symptoms were mild with slight back arching. Full recovery symptom free was observed from day 4 until day 23 (termination day). Another 3 animals showed slight decreased appetite and reduced food uptake.

Transient hematuria was noted in most animals and resolved within 24–72 hours.

![Fig. 2. A Left, ring implant in the prostate. B Middle, contrast agent fills the bladder and the ring area in the prostate. C Right, 3 months post implant removal.](image-url)
The implants in 7 animals lead to significant dilatation of the lumen of the prostatic urethra (fig. 2). In 1 animal, due to a technical failure during procedure, incision wasn’t fully completed. Therefore the implant was not placed within a circumferential incision, and migrated down along the urethra. Despite its migration, no sign for obstruction, inflammation or contamination were recorded during follow-up period. In 1 animal the implant was removed and the animal was kept for additional 3 months post implant removal to evaluate chronic prostatic reshaping, and significant widening of the urethra was observed, 6 months post procedure (3 months post implant removal).

**Histology**

Cross section at the ring area showed dilated urethra into a large cystic space, partially lined by urothelial proliferation. The areas not covered by urothelium had a heavy infiltrate of neutrophils, dilated alveoli filled with neutrophils and heavy plasmacytic and lymphocytic infiltration. There was moderate interstitial fibrosis and fibrosis underlying the areas of regenerated epithelium. There was marked epithelial vacuolation and exocytosis. There was heavy lymphoplasmacytic infiltration of the prostate.

In area of penetration of the edge of the rings the space where the edge of the ring was lodged was lined by markedly urothelial proliferation, surrounded by a mild band of fibrosis and heavy lymphoplasmacytic infiltration with smaller numbers of eosinophils.

The ring was covered with epithelial cells in clusters and smaller numbers of neutrophils were present on the surface of the ring cover.

The ring area consisted of a saccular dilation of the urethra, which was, for most of its circumference, lined by epithelium (urethral regeneration). The epithelium was mostly hyperplastic with area of vacuolation and was infiltrated by leukocytes.

There was fibrosis and neovascularization in the submucosa and moderate to heavy lymphoplasmacytic inflammation. Neutrophilic inflammation was heavy in ulcerated areas or next to the areas of ring penetration.

The prostate surrounding the implant was extensively affected, with heavy interstitial mononuclear cell infiltration. Alveoli in the gland are either dilated or atrophic and many were filled with neutrophils and fewer macrophages.

In 2 animals, perforation of the edges beyond the prostate was observed. These edges were covered by urothelial proliferation, surrounded by a thin layer of fibrous tissue with heavy associated plasmacytic, lymphocyte and neutrophil or eosinophilic infiltration.

No mineral deposited on the ring surface was observed. The ring cover examined had small clusters of epithelial cells attached to its surface. There was no evidence of prostatic hyperplasia associated to ring implantation.

There was no significant difference between the 2 groups except for slightly more fibrosis after 3 months.
In the animal that was kept for additional 3 months post implant removal, the space created by the ring persisted and was entirely lined by urothelial proliferation even 3 months post implant removal. Fibrosis was slightly increased. Inflammation in the prostate and submucosa of the urethra was persistent, consisting mostly of eosinophils and plasma cells (fig. 3).

Discussion

In this work a new prostatic reshaping device was evaluated. Previous experiments with urethral stents in human were associated with obstruction, encrustation, infection, and migration [3]. We assumed that by inserting a scaffold into the prostate these complications would be avoided. Recently, the use of the UroLift® transurethral implant for the treatment of LUTS due to BPH demonstrated safety and efficacy in human trials [4]. Therefore, a ring that avoids contact with urine and at the same time provides a circumferential support to the prostatic urethra may have the potential of long-term efficacy. In this study we demonstrated that the implant was successfully positioned in 7 out of 8 dogs. In these 7 dogs a significant urethral dilatation was observed. All dogs urinated after catheter removal with no observed obstruction. No severe adverse events were observed. Fever, pain, behavior disturbances or gross hematuria, when occurred, resolved within 72 hours post procedure with supportive care only and did not reoccurred until the end of the follow-up. Laboratory examination showed no urinary tract infection or kidney failure. Histological evaluation of the implantation site at the prostatic urethra revealed secular dilatation covered mostly with hyperplastic epithelia. The exposed area showed heavy inflammation with neutrophils and lymphocytes and plasmocytes and initial fibrosis which was more significant in the chronic animals. Partial epithelial coverage of the implant surface was observed without evidence of encrustation.

Minor perforations that were observed on histology are related to the dog’s small prostate, and were not associated with apparent adverse event.

Results of this study demonstrate that the ClearRing™ device can establish a long lasting reshaping of the prostatic urethra. The implants in 7 animals led to a significant dilatation of the prostatic urethra, and therefore potentially improve LUTS due to BPH. The use of long-term implant in the prostate may be associated with risk of infection however, long-term safety of other small implants such as the UroLift® device [4], demonstrated that leaving a small implant in the prostate can be safe.

It is noted that after removal of the device the implant area is re-shaped, and remained dilated 3 months post implant removal (fig. 2A, fig. 3B).

Clinical Perspective

BPH affects 32–52% of men aged 51–60 years and 77–99% of men ≥ 81 years of age [5]. The most effective treatment TURP is associated with significant morbidity [1]. The proposed procedure may enable a less invasive procedure by implantation of a supporting ring without the need to remove the prostate. The UroLift® device is another approach to improve the symptoms of BPH by an implantable device [4]. However, the UroLift® support is based on 2–4 points in each longitudinal cross section at the prostatic urethra while the ClearRing™ device provide a circumferential 270° support at each longitudinal cross section potentially providing a more durable effect. However, long-term human trials will be needed to determine if there is a difference in efficacy between the 2 procedures. Another important aspect of the device is the removability of the ring 3 months post implantation. This was conducted in 1 animal using a standard grasper, and demonstrates the ability to conduct TURP in case needed after device implantation.

Conclusion

This study shows preliminary feasibility of the use of the ClearRing™ device for minimally invasive treatment of BPH. Further studies are needed to demonstrate the safety and efficacy of this approach.

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