Treatment of experimental ureteral strictures by endourological ureterotomy and implantation of stents in the porcine animal model

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Abstract

The objective of this study is to evaluate the dilation of the ureter using endoureterotomy and an expanding-sheath double pigtail ureteral stent in the treatment of experimentally induced ureteral strictures in the porcine animal model. This is a new treatment in the ureteral strictures resolution in Veterinary Urology, although it is not a common affection, it usually appears as a consequence of ureteritis and in the iatrogenic female genital surgery. The experimental study is design in three phases: induction of experimental stricture, diagnosis and treatment of the stricture and follow-up. We have used 10 healthy Large White female pigs. The internal ureteral diameter was measured prior to laparoscopic ligature stricture induction using retrograde ureteropyelography (RUPG). Experimental stricture was diagnosed 4 weeks after intervention, using RUPG and ultrasound, and treated by endoureterotomy and subsequent placement of a double pigtail ureteral stent, which was removed 6 weeks later. The study finished 4 weeks later with measurement of ureteral diameters using RPUG and ultrasound evaluation. Except in one case, all ureters displayed permanent dilation of the strictured area for 10 weeks after treatment (6 weeks with ureteral stent and 4 more weeks without stent). Finally, this technique proved to be effective in cases of short-length and short-living ureteral strictures, and represents a viable alternative to conventional surgery in animals.

Keywords: Pig; Urology; Stent; Ureterotomy; Stricture; Minimally invasive surgery

1. Introduction

Balloon dilation was first used by Gruntzig and Kumpe in 1979 for the treatment of coronary artery obstructions, and has subsequently been successfully applied in other areas, including urology and digestive-tract surgery. The recent development of small-caliber endoscopes has enabled retrograde cystoscopic access to the upper urinary tract, thus facilitating the evaluation of the whole urinary system and enabling the application of minimally invasive treatments to intraluminal lesions without the need of a laparotomy (Grasso and Bagley, 1994), thereby enhancing the well-being of animal patients.

The present treatment of ureteral strictures in veterinary surgery are by the traditional ureteroureterotomy, by transperitoneal or retroperitoneal approaches, and by ureteroneocistotomy. Although a relatively uncommon problem, ureteral stricture can occur as a complication of renal transplantation in dogs (Crowell et al., 1987) and cats (Aronson, 2002; Mishina et al., 1996), as
well as, as a consequence of ureteritis (Crawford and Turk, 1984; Polzin and Jeraj, 1980), or due to iatrogenic reasons, for instance in female genital surgery (Okkens et al., 1981).

The objective of this study therefore was to evaluate the application and efficacy of minimally invasive techniques in the correction of ureteral obstruction using an animal model, with particular reference to dilation by balloon rupture technique of the stricture, application and duration of stenting and type and caliber of the ureteral stent necessary.

A ureteric stent is a specially designed hollow tube, made of a flexible plastic material that is placed in the ureter. The stents are designed to stay in the urinary system by having both the ends coiled. The top end coils in the kidney and the lower end coils inside the bladder to prevent its displacement. The stents are flexible enough to withstand various body movements.

In this study, the partial obstruction model developed by Figenshau et al. (1994) was used. This model creates an obstruction at the ureteropelvic junction. The model has also been used by Nakada et al. (1996) to create a secondary proximal ureteral stricture.

2. Materials and methods

The experimental protocol was approved by the Minimally Invasive Surgery Centre’s Ethical Committee for Animal Research. The research study was carried out following the guidelines of the “Guide for the Care and Use of Laboratory Animals” (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, USA).

Ten healthy Large White females pigs, weighing 36.46 ± 3.19 kg were fasted for 12 h. Following intramuscular administration of 0.04 mg/kg atropine, 0.1 mg/kg diazepam and 10 mg/kg ketamine, anesthesia was induced with 2–3 mg/kg propofol intravenously and maintained with 2.5% isoflurane administered in oxygen using intermittent positive pressure ventilation (IPPV). Post-operative pain was controlled administering 1 mg/kg Ketorolac. The animals were kept in an Intensive Care Unit for observation and then returned to normal housing 24 h after the procedure.

All of the pigs underwent the same three-phase procedure, which was as follows.

2.1. Phase I: Experimental partial obstruction of the upper urinary tract

Ultrasonography (US) (Leopard 2001, type 8555, B&K Medical®) was used to determine the sonographic status of the urinary tract prior to starting the study. In the initial phase, the entire ureter and renal pelvis were examined endoscopically with nine French (Fr) actively deflectable flexible ureteroscope (Richard Wolf®). Endoscopic access to the urinary system was performed without previous dilatation of the ureteral orifice. The use of a small diameter flexible ureteroscope allowed the procedure to be performed without causing damage to the ureter. After examination, a centimeter-graduated straight catheter with radio-opaque markers (5 Fr, 80 cm, Cook®) was passed over a 0.035 in. hydrophilic radiofocus guidewire (Terumo®) and 7 ml of iodinated contrast medium (Urografin 76%; Schering®) diluted 1:3 in saline, were injected into the catheter for Retrograde ureteropyelography (RUPG) and for the measurement of the internal diameter of the ureter using digital C-arm fluoroscopy (BV-300 Philips®). The catheter was placed at the precise point at which the stricture was to be induced, that is, 5–6 cm caudally to the ureteropelvic junction (Fig. 1). Absence of vesicoureteral reflux was also confirmed at all stages by cystography up to maximum voiding pressure.

Following data collection, a partial ureteral laparoscopic obstruction was created. First, each animal was placed in sternal recumbency. When the bladder probe was inserted the animal was shifted to dorsal recumbency. The abdominal area was completely shaved and prepared for aseptic surgery.

Pneumoperitoneum was induced by the insertion of a modified Veress needle at a subxyphoid level, lateral to the abdominal midline, and at a 45° angle in order to avoid the falciform ligament and the cranial epigastric vessels. This is the point of greatest distance between the abdominal wall and the intra-abdominal structures (Usón et al., 2000). The needle was then connected to an automatic CO2 insufflation pump, at an initial flow-rate of 1 L/min in order to avoid sudden abdominal disten-
sion. Otherwise rapid distension would cause severe abdominal pain during recovery. Pneumoperitoneum was established at a pressure of 12–14 mmHg. The complete laparoscopy equipment set-up consisted of insufflation pump, monitor, camera source, light source (Karl Storz®) and videotape recorder.

This laparoscopy system required three trocars (2 × 10 and 1 × 5 mm): one for the laparoscope, one for the dissection forceps and the third for the laparoscopic scissors and needleholder. The first trocar for the laparoscope was placed at the umbilicus, and the other two trocars were placed in order to triangulate with the first one. The pig was placed in lateral recumbency to allow medial displacement of the intra-abdominal viscera. Laparoscopic examination of the abdominal cavity was performed using the clock-face reference system (Soria et al., 1998), with the diaphragm at 12.00 and the bladder at 6.00 h.

Following fluoroscopic identification of the exact site of the intended stricture, laparoscopic dissection of the ureter was begun. A 360° window dissection was created around the ureter, freeing 2 cm of its length, and the ureter was ligated with 2–0 catgut. Before the ligature, and to avoid complete obstruction, an intraureteral catheter was placed. Ligation was performed by manual laparoscopic knotting (Usón et al., 1999) using the dissector and the laparoscopic needleholder (Fig. 2).

Ligation of the ureter was checked by injection of diluted iodinated contrast through the intraureteral catheter and then the catheter withdrawn. The gas in the pneumoperitoneum was then removed, the three port sites were sutured and the animal was hospitalized.

2.2. Phase II: Diagnosis and treatment

The second phase started 4 weeks after ligation, this interval being deemed sufficient for suture degradation and stricture formation (Boothe, 1996). Dilatation of the renal collecting system was diagnosed by ultrasound and RUPG. Following radiographic and US diagnosis of the obstruction of the proximal ureter, ureteral and stricture diameter were measured as before by RUPG (Fig. 3).

The radiomarked catheter used to diagnose stricture was removed, and a stiff Roadrunner guidewire (0.035 in. Cook®) was inserted, over which a hydrophilic Cobra catheter (5 Fr, 0.035 in. and 65 cm, Terumo®) was advanced until the tip lay above the upper end of the stricture, in the renal pelvis. The Roadrunner guidewire was replaced by an Amplatz guidewire (0.035 in. and 4 m, Boston Scientific®) which provided greater ureteral rigidity. Afterwards the Cobra catheter was substituted by a dilating-balloon catheter (5Fr, 0.035 in., 80 cm, with balloon of 12 × 40 mm maximum inflation pressure 8–10 atm, Cordis®), positioned straddling the center of the stricture with 0.5 cm on either side. The balloon was then slowly dilated by a syringe connected to a manometer (Cook®). Stricture was initially evident as a notch on the dilating balloon, which gradually disappeared as dilation progressed (Fig. 4). The balloon was deflated and the area examined for presence or absence of extravasation of contrast medium from the ureteral lumen into the retroperitoneal space. If no extravasation was seen, the procedure was repeated (Fig. 5).

The objective of this technique was to rupture all the ureter layers and produce a complete ureterotomy by a

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Fig. 2. Experimental laparoscopic ureteral stricture induction by ligature with catgut. A radiomarked catheter is placed inside the ureter. Phase I: Laparoscopic view.
dilatation ballon (endoureterotomy). In this way, the serosal and muscular layers which would contribute to the post-treatment recurrency of the ureteral stricture are broken, and thereby we cause new healing with a larger ureteral lumen.

Following withdrawal of the dilating balloon, a 14/7 Fr, 22-cm temporary double pigtail endoureterotomy ureteral stent C-Flex® (Cook®) was placed in position. The stent was advanced over the Amplatz guidewire until the proximal tip reached the renal pelvis. The guidewire was then withdrawn and the pigtail tip at the renal pelvis end was spread. Afterwards, the distal pigtail in the bladder was deployed, fixing the stent firmly in the ureter (Fig. 6).

All the animals were administered prophylactic Sulfadoxin-Trimetroprim. During the three study phases microbiological studies of urine were performed and serum urea an creatinine levels were measured.

After 6 weeks, under cystoscopic guidance, a Dormia basket (Richard Wolf®) was used to trap the distal tip and pull out the stent. The procedure was carried out under general anaesthesia.

2.3. Phase III: Follow-up

Four weeks after stent removal the diameter of the treated area was measured by RUPG (Fig. 7). The renal
status was assessed by ultrasound and the presence of vesicoureteral reflux was also studied.

Results of ureteral diameter measurements over the three phases underwent statistical analysis using ANOVA with a post hoc Tukey test using a STATISTICA software package (Version 4.0, StaSoft, Tulsa, USA). Test for significance were carried out at the 0.05 level.

3. Results

All animals were monitored using US throughout the three study phases. At the start of the study, all animals displayed disease-free urinary systems. Laparoscopic stricture creation did not result in complications arising from the laparoscopic technique or approach used. Four weeks after ureteral stricture induction, dilation of the renal collecting system in all animals, was confirmed by US and RUPG. Eight of the 10 animals showed dilation of the renal pelvis. The other two developed a mild hydroureteronephrosis. The healthy contralateral kidneys showed no evidence of impairment. All strictures were less than 1 cm in length, and were dilated using the endoballoon dilation technique. Dilation was repeated in two animals due to initial absence of extravasation.

Results were assessed 4 weeks after removal of the ureteral stent. US and RUPG displayed dilation of the renal collecting system in two animals, hydroureteronephrosis in one, and in the other experimental animals, findings were normal. Permanent dilation of ureteral strictures was recorded in all except one pig, which displayed recurrent stricture of the ureteral lumen. Although all ureters prior to stricture induction were straight, afterwards they had a sigmoid appearance with between 3 and 5 bends. The results of statistical analyses of ureteral diameter in the three phases are shown in the table (Table 1).

At necropsy, the stent-containing ureter was thicker than its contralateral counterpart. Treated ureters displayed periureteral fibrosis at the endoureterotomy site, with fibrous bands attaching the ureter to the retroperitoneum, thus impeding normal movement. Fibrosis (the length of one ureteral segment affected by periureteral fibrosis) was considered mild in nine cases (<1 cm) and severe in one case, where it spread from the endoureterotomy site to the entire parietal and visceral surface of the kidney. In two animals degraded suture residue was present at the treated site, but did not impede the passage of contrast medium. No adhesions were observed between viscera and the treated area in the peritoneal cavity.

Results of urinalysis were normal for all except one pig, which had Proteus spp. isolated at stent removal. Antibiotic treatment was commenced at this stage and a follow-up culture displayed no evidence of infection. No statistically significant difference was recorded for serum urea and creatinine values between the different phases of the study.

All ureteral stents were inspected after being withdrawn. There was no evidence of stent breakage, blockage or migration. Vesicoureteral reflux tests were negative for all animals. None of the experimental animals were adversely affected by the experimental procedure.

4. Discussion

This animal model of a partial laparoscopic obstruction of the urinary tract successfully created a permanent and authentic ureteral stricture. Moreover, statistically significant differences were recorded for

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<th>Table 1</th>
<th>Ureteral diameter mean ANOVA, with a post hoc (Tukey test)</th>
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<td>(Mean ± standard deviation)</td>
<td>Ureteral diameter mean Phase 1 (4.68 ± 0.71 mm)</td>
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<tr>
<td>Ureteral diameter mean Phase 1</td>
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<tr>
<td>Ureteral diameter mean Phase 2</td>
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<td>Ureteral diameter mean Phase 3</td>
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* Significance statistical differences (p < 0.05).
mean internal ureteral diameter before and after stricture induction. This model enabled the assessment of the three factors that most affect the outcome of the ureteral stenosis treatment (Cormio, 1995): duration, length and location. In our study the duration was 4 weeks, the length was 1 cm or less and the location was the proximal ureter. Beckmann et al. (1989) found in humans that 86% of strictures standing of less than 12 months duration responded successfully to treatment, compared with 65% of older strictures. Kramolowsky et al. (1989) reported that short strictures respond better to endoscopic manipulation in humans, and that endoscopic treatment is contraindicated in strictures longer than 1–2 cm. In the present study, all strictures were less than 1 cm. In humans strictures in the ureteropelvic junction (UPJ) and the terminal ureter have a better prognosis than those in intermediate locations Smith, 1988. In the present model, strictures were only a few centimeters from the UPJ, and yielded good results.

The present study used a new endoscopic retrograde technique to treatment the ureteral stricture, thus avoiding both conventional transperitoneal or retroperitoneal surgery, as well as, anterograde percutaneous nephrostomy. The retrograde approach is the only one that avoids any incision in the skin of the patient, thus enabling a shorter and more satisfactory postoperative recovery and reducing the characteristic pain and complications of more aggressive approaches.

The balloon rupture technique was chosen because a number of studies have shown that other techniques based on simple dilation fail to address ureteral strictures successfully. Ravery et al. (1998) reported a success rate of 52% in the treatment of the ureteral stricture, and that the cause of the stricture persistence was the ureterotomy caused by the short duration dilation did not involve all the ureter muscle layers. The use of the endoballoon rupture technique enabled the control of the internal incision, obtaining a complete disruption of all ureteral layers, which healed around the implanted splint, thus avoiding recurrence of strictures due to scarring fibrosis. The study results demonstrate the value of this technique: no significant differences were recorded between the mean ureteral diameter before the stricture and after the treatment, while the diameters at stricture diagnosis displayed statistically significant differences with the pre and postoperative measurements. It can therefore be concluded that minimally invasive surgery successfully restored the internal diameter of the ureter during a 10-week follow-up period. Similar results are reported by Nakada et al. (1996), who used this technique to treat secondary ureteral strictures in a porcine model. The sole requirement of this technique is that the balloon must cross the stricture.

The decision on of both stent duration and what caliber of stent to use remains controversial (Schemeller and Leitl, 1992). Maximum tolerable stent duration is determined by the designed materials. The stent must be implanted just long enough to provide a scaffold for the tissue regeneration and to ensure urine drainage, but at the same time stent duration may be limited by certain potential adverse effects; increased intrapelvic pressure, urothelial erosion, risk of obstruction due to calculi or to mineral encrustation on the stent, bacterial infection, stent fracture or migration, perforation of the ureter, dysuria (Wollin et al., 1998). The optimal stent size also remains to be determined. Small-caliber stents (<7 Fr) have the advantage of not prompting ureteral compression, preventing a potential ischemia, and allowing the urine drainage both through the internal channel and around the stent. Disadvantages may include high incidence of recurrent ureteral strictures, since scarring fibrosis is more evident. On the other hand, large-caliber stents (>9 Fr) wholly occlude the pig ureteral lumen. Although they serve as a perfect scaffold for scarring, ischemia may result due to excessive compression of the ureter (Hwang et al., 1996). In this case urine drainage takes place only through the internal channel.

In the present study, the stent was left in place for 6 weeks, since the muscular layer of the ureter takes approximately 6 weeks to heal, and adverse effects are reported to be minimal over this time frame (Elgammal et al., 1990). The stent is left indwelling to ensure satisfactory scarring around it, and so avoid stricture recurrence. The exact mechanism of ureteral healing following balloon rupture dilation remains unclear. It may be by muscle fiber growth in the incised area or by the regeneration of pluripotential fibroblasts in the scarred area. Studies by Elgammal et al. (1990) suggest that both actions may be involved.

The size and design of the stent used in this study allowed satisfactory healing of the incised area, thanks to the expanding sheath deployed at the endoureterotomy site. At the same time, the adverse effects on urine drainage from the renal pelvis to the bladder were minimized with no problems of vesicoureteral reflux due to dilation of the ureterovesical junction or damage to the intramural ureter.

Stent properties appeared unaffected on withdrawal. The only complication which might be related to the stent was the detection of Proteus spp. at urinalysis in one pig. Infection is one of the most common side effects of stent implantation (Tunney et al., 1996), since stents are foreign bodies which may hinder urine drainage.

Only one animal failed to display satisfactory post-treatment progress (final internal diameter 1.6 mm) due to treatment induced retroperitoneal fibrosis with fibrous bands which almost completely impeded the passage of urine, leading to extrinsic ureteral stenosis. This periureteral fibrosis is caused by the excessive leakage of urine and iodinated contrast medium at the endoureterotomy site, and their deposition in the retroperitoneal space adjacent to the incision site. This
prompted an irritant reaction with subsequent fibrosis and adherences to the ureter, as reported by Nakada et al. (1996).

To avoid these complications, endoureterotomy should be more controlled, with minimum balloon pressure to ensure that ureteral rupture is complete, but only involves the stricture itself. The success of the operation can be confirmed by the observation of the extravasation of contrast medium into the retroperitoneal space, which should be minimal.

A further aim of this study was to determine whether the use of the new flexible ureteroscope would allow the examination of the upper urinary tract, obviating the necessary dilation of the ureteral orifice and the intramural ureter and its attendant adverse effects (Cormio, 1995). Thirty complete ureterorenoscopies were performed in this study. The reduced size, maneuverability and flexibility of the endoscope allowed direct cathe-terisation of the ureteral orifice. This method is thus recommended for such examinations, avoiding the troublesome and costly dilation of the ureteral orifice.

A controlled endoureterotomy with balloon rupture, followed by 6 weeks double pigtail endoureterotomy stent implantation proved to be effective in treating short-length and short lasting ureteral strictures, affording a viable alternative to conventional surgery in animals.

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References


