Endo-urology

Application of Paclitaxel-Eluting Metal Mesh Stents within the Pig Ureter: An Experimental Study

Evangelos N. Liatsikos,*, Dimitrios Karnabatidis, George C. Kagadis, Kostantinos Rokkas, Costas Constantinides, Nikolaos Christeas, Nikolaos Flaris, Theodore Voudoukis, Chrisoula D. Scopa, Petros Perimenis, Kriton S. Filos, George C. Nikiforidis, Jens-Uwe Stolzenburg, Dimitrios Siablis

aDepartment of Urology, University of Patras, School of Medicine, Patras, Greece
bDepartment of Radiology, University of Patras, School of Medicine, Patras, Greece
cDepartment of Medical Physics, University of Patras, School of Medicine, Patras, Greece
dFirst Department of Urology, University of Athens Medical School, 'Laikon' General Hospital, Athens, Greece
eDepartment of Anesthesiology and Critical Care Medicine, University of Patras, School of Medicine, Patras, Greece
fDepartment of Pathology, University of Patras, School of Medicine, Patras, Greece
gDepartment of Urology, University of Leipzig, Germany

Abstract

Objective: The purpose of the present study is to compare the standard bare metal stents (BMS) with the Paclitaxel-Drug Eluting Stent (DES) in the ureter of a pig model.

Materials and methods: We report on an experimental study with ten female pigs weighing between 25 and 30 kg. The stents were randomly placed in either the right or left ureter in each of 10 study animals, for a total of 20 stented ureters. Ten ureters were stented with an R-Stent (Orbus Medical Technologies, Hoevelaken Netherlands), and ten with a Paclitaxel-Eluting Coronary Stent (Boston Scientific, Natick, MA, USA). Patency was measured by radiograph of the nephrostomy tract, intravenous urography and virtual endoscopy at 24 hours and 21 days after the initial procedure, respectively.

Results: Free flow of urine through the stents into the bladder was documented in all stented ureters 24 hours after stent insertion by radiograph of the nephrostomy tract. At the 21 day follow-up examination, 5 R-Stents were found to be completely occluded and two partially stenosed, whereas no occluded stent was detected in the Paclitaxel-DES group. Pathology examination of the stents at 21 days follow-up showed that the obstructed R-Stents generated severe inflammation with metaplasia of the urothelium. The Paclitaxel-Eluting MS generated a mild inflammatory response within the ureteral lumen at the site of the stent, without hindering ureteral patency. R-stents proved to develop more hyperplasia compared to the Paclitaxel-Eluting MS.

Conclusions: Paclitaxel-DES, when compared with the standard R-Stent BMS, generated less inflammation and/or hyperplasia of the surrounding tissues, thus maintaining ureteral patency. Long-term animal trials are required to further validate our results.

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* Corresponding author. Department of Urology, University of Patras Medical School, Rio, Patras, 26 500 Greece. Tel. +1130 2610 999386; Fax: +1130 2610 999381. E-mail address: Liatsikos@yahoo.com (E.N. Liatsikos).
1. Introduction

Despite developments in endoscopic urology, the treatment of extrinsic ureteral obstruction can create a great dilemma to the urologist. The methods currently used are transvesical as well as antegrade placement of double pigtail stents, percutaneous nephrostomy and/or transluminal balloon dilation of the ureter.

The previous successful use of standard bare metal stents (BMS) in the vascular system and the biliary tree, has led several investigators to propose their use for other applications such as the treatment of benign prostatic hyperplasia, urethral strictures, and detrusor sphincter dyssynergia. BMS have also been used in the treatment of malignant and benign ureteral obstructions by others and us with encouraging results, however urothelial hyperplasia through the stent mesh results in luminal occlusion in a significant number of cases [1–6].

The ideal permanent stent for ureteral use has not been yet found. Metal mesh stents covered or coated with various biocompatible materials, have recently been introduced in vascular intervention for the treatment of both aneurysmal and/or occlusive peripheral arterial diseases. The principle of covered stents to reduce tissue in-growth initially appeared promising but failed to demonstrate its efficacy when used in the ureter due to a high rate of migration [7–9]. Drug Eluting Stents (DES) have been shown to minimize the restenosis rate after stenting the coronary vessels due to a reduction of both inflammation and smooth muscle proliferation [10,11]. The purpose of the present study was to compare the standard BMS with the Paclitaxel-DES in the ureter of a pig model to test the concept that similar tissue effects will also reduce luminal occlusion in the stented ureter.

2. Materials and methods

We report on an experimental study with ten female pigs weighing between 25 and 30 kg. The protocol was approved by the Institutional Animal Care Committee of our institution. All animals were allowed a minimum of 72 hours to recover from the stress of transportation before the first procedure, and food was withheld for 12 hours prior to anesthesia.

All interventions were performed in a standard operating room equipped with a C-arm fluoroscope with the animals under general anesthesia with a combination of ketamine (20 mg/kg of body weight) and xylazine (2 mg/kg of body weight). Thereafter, anesthesia was maintained with inhaled isofluorothane (3–4%). Postoperative analgesia was guaranteed with intramuscular administration of morphine sulfate (0.1 mg/kg body weight) as necessary. Prophylactic perioperative and postoperative antibiotics were administered to all animals.

Balloon expanded metal stents were randomly placed in either the right or left ureter at the level of the ureteropelvic junction in each of 10 study animals, for a total of 20 stented ureters. Ten ureters were stented with a 4 × 18 mm R-Stent (Orbus Medical Technologies, Hoevelaken Netherlands), and ten with a 4 × 32 mm TAXUS™ Express™ Paclitaxel-Eluting MS (Boston Scientific, Natick, MA, USA) which is currently indicated for use in stenting coronary arteries. Both categories of stents were coronary balloon expandable stents and thus their diameters were the same. Their length was different and not their diameter.

The TAXUS™ device consists of a stainless steel stent coated with paclitaxel in a polymer carrier and premounted on a balloon catheter. The TAXUS™ stent uses Translute Polymer, a proprietary polymer carrier technology, to control drug release. The durable Translute Polymer protects the drug and maintains coating integrity during preparation, delivery, and stent expansion. The polymer controls the release of paclitaxel, and allows for a desired drug release and distribution [12–14]. The R-Stent is a stainless steel balloon expandable vascular prosthesis, which is supplied mounted on a low profile dilation catheter and has two radiopaque marker bands that delimit the working length of the balloon.

The technique of stent insertion has been previously described [5]. Briefly, percutaneous nephrostomy was performed under ultrasonographic guidance and the collecting system was visualized after injection of contrast material through the nephrostomy sheath. Stents were positioned and balloon inflated to maximum diameter. When the deployment of the stent was finalized, the nephrostomy tube was capped.

Fig. 1 – Radiograph of the nephrostomy tract at 24 hours documenting ureteral patency of the TAXUS stent (right) and the R-Stent (left). The white arrowheads show the proximal and distal ends of the stents.
Patency of the ureteral lumen was evaluated by radiograph of the nephrostomy tract, intravenous urography and virtual endoscopy at 24 hours and 21 days after the initial procedure, respectively. In addition, conventional ureteroscopy of the stented ureters was then undertaken in vivo at 21 days. Following this, euthanasia and harvesting of the ureters took place, and the specimens were sent for pathology examination. Pathology examination was blinded and performed by the same pathologist minimizing possible bias.

3. Results

All stents were positioned successfully, and the postoperative course was uneventful. All animals survived the entire follow up period of 3 weeks without complications.

Free flow of urine through the stents into the bladder was documented in all stented ureters 24 hours after stent insertion by radiograph of the nephrostomy tract (Fig. 1). At the 21 day follow-up examination, 5 R-Stents were found to be completely occluded and two partially stenosed, whereas no occluded stent was detected in the Paclitaxel-DES group (Figs. 2 and 3). Two Paclitaxel-DES stents migrated distally within the ureter and were thus partially stenosed jeopardizing ureteral patency, due to the limitation of the small size of the coronary stent used in the ureter. Thus, 7 stents in the R-group and 2 stents in the P-group were at least partially stenotic, and when applying Chi Square, the two groups differed significantly ($p = 0.0246$).

Ureteroscopic evaluation revealed extensive polypoid hyperplastic response in the occluded R-Stents, while the lumen of the Paclitaxel-DES showed homogeneous epithelial lining ascertaining

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Fig. 2 – Intravenous urography at 21 days depicts sufficient patency of the right ureter (TAXUS stent, (a)) as well as the left ureter (R-Stent, (b)). In (b), an opacification pattern around the distal stent tip (trumpet-like configuration) is seen. This is certainly nonobstructive, and is probably due to the overdistension of the ureter and the resulting constriction of the muscular fibers of the adjacent ureteral segment. The white arrowheads show the proximal and distal ends of the stents.
patency. No stone formation or intraluminal encrustation occurred in any stent.

Mural inflammation was graded by using parameters as previously reported by Nakada et al. (normal: grade 0–worst effect: grade 3) [15]. Pathology examination of the stents at 21 days follow-up showed that the obstructed R-Stents generated severe inflammation (total grade 20) with metaplasia of the urothelium. The sections of the remaining unobstructed R-Stents revealed the presence of a polypoid reaction adherent to the internal surface of the devices (Fig. 4a and b). The Paclitaxel-Eluting MS generated a mild inflammatory response (total grade 6) within the ureteral lumen at the site of the stent, without hindering ureteral patency (Fig. 5a and b).

In order to check patency and inflammation differences between the ureters treated with R-Stents and/or Paclitaxel Stents (P-Stents) we applied the Wilcoxon signed-rank test. Two new variables called “Δ = difference in severity” and “E = difference in inflammation” were calculated for every pig taking as values the difference in hyperplasia formation severity (Δ) and the difference in inflammation formation (E) (R-group score minus P-group score). Hyperplasia formation severity according to the radiologists measurements (intravenous urography and virtual endoscopy) was clustered as ‘0 = patent’ when the stent had no stenosis or a stenosis <50%, as ‘1 = stenosed’ when the stent had a stenosis >50% and as ‘2 = occluded’ when the stent was completely occluded. Inflammation formation according to the pathologists measurements was clustered as described earlier. These measurements are depicted in Table 1. All statistical tests were two-sided and the threshold of statistical significance was set at 5% (α = 0.05). The SPSS v.11 statistical software package was employed for all data analysis and statistical calculations. Calculated median of the variable Δ (median = 1) proved to differ significantly (p = 0.0156) from zero. Calculated median of the variable E (median = 1.5) proved also to differ significantly (p = 0.0117) from zero. These findings support that R-Stents developed more hyperplasia and more inflammation compared to the TAXUS stents.

4. Discussion

The concept of BMS insertion is not new. They are used routinely in the cardiovascular and biliary systems, and they also have been used for various applications in the urinary tract [1–6]. Milroy et al. first reported experience with BMS in the treatment of urethral strictures [2]. Since then others have used them for the treatment of benign prostatic hyperplasia, detrusor-sphincter dyssynergia, and/or ureteral obstruction [1–6].
In previous reports we have showed our encouraging experience with the use of BMS in the treatment of malignant ureteral obstruction, and in the treatment of anastomotic strictures developed after ureteroileal diversion [5]. Nevertheless, there is a concurrence among investigators that urothelial hyperplasia of the stent lumen has been the principal drawback with placement of BMS in the ureter [3,4,6,16]. Thijssen et al. showed in an experimental study that the grade of urothelial hyperplasia protruding through the stent mesh (a) and microscopic histopathology (b) of an R-Stent with extensive inflammation (hematoxylin & eosin stain, magnification ×40).

Fig. 4 – Gross pathology showing urothelial hyperplasia protruding through the stent mesh (a) and microscopic histopathology (b) of an R-Stent with extensive inflammation (hematoxylin & eosin stain, magnification ×40).

Fig. 5 – Macroscopic image displaying constricted polypoid hyperplasia of the urothelium (a) and microscopic images of a TAXUS stent (b) with a mild inflammatory response (hematoxylin & eosin stain, magnification ×40).
reaction is proportionally dependent on the extent of the ureteral overstretching and resulting urothelial trauma [16].

Drug eluting stents (or DES) have been widely used in interventional cardiology in an attempt to decrease the restenosis rate after angioplasty and stenting [10,11]. Based on the existing vascular experience we embarked upon their use within the ureter.

Paclitaxel is an anticancer agent that promotes the polymerization of tubulin and inhibits the disassembly of microtubules, thus causing the death of the cell by interrupting the ordinary microtubule dynamics required for normal cell division. In addition it induces the expression of the gene for tumor necrosis factor $\alpha$. These properties of the drug led to the assumption that it could inhibit neointimal hyperplasia, and thus it was used in a plethora of trials that have shown a reduction in restenosis in human coronary arteries [10–12].

Song et al. applied paclitaxel for intravesical instillations in an animal model and documented its powerful antiproliferative effect upon the bladder urothelium [17]. In a recent report, Shin et al. have reported the use of paclitaxel-eluting polyurethane covered stents in a canine urethral model. They showed that there was a strong reduction of stent related tissue hyperplasia, and thus it was used in a plethora of trials that have shown a reduction in restenosis in human coronary arteries [10–12].

In the present study we assumed that Paclitaxel-Eluting MS would minimize urothelial hyperplasia and/or ingrowth of tissue in the ureteral lumen along the length of the treated segment thereby improving patency as compared to the conventional MS. We thus compared the standard MS with the Paclitaxel-Eluting MS in the ureter of a pig model. The results of the present study revealed that indeed the Paclitaxel-Eluting MS offered the advantage of minimal urothelial hyperplasia and/or limited intraluminal tissue growth. The difference in length of the two-stent groups could be considered a limitation of our study. Even though there are commercially available 32 mm R-Stents, they were unavailable to us. Nevertheless, the main purpose of this pilot experimental study was to depict the effect of the stent on the ureteral wall and show if it caused less “reaction” than the conventional stents.

In conclusion, Paclitaxel-Eluting metal mesh stent, when compared with the standard R-Stent, generated less inflammation and/or hyperplasia of the surrounding tissues, thus maintaining ureteral patency. To our knowledge this is the first report in the literature applying drug eluting metal mesh stents within the ureter of an animal model. Nevertheless, long-term animal and human trials are deemed necessary to further validate our results including optimizing dose and duration of drug delivery.

Acknowledgment

We would like to thank Boston Scientific Corporation (Natick, MA, USA) for the invaluable help provided and the supply of the TAXUS™ Express²™ Stents.

References


Table 1 – Patency and inflammation correlation between the ureters treated with R-Stents and/or Paclitaxel (P) Stents

<table>
<thead>
<tr>
<th>Pig 1</th>
<th>R-Stent patency</th>
<th>R-Stent inflammation</th>
<th>P-Stent patency</th>
<th>P-Stent inflammation</th>
<th>$\Delta = \text{difference in severity (R-group score minus P-group score)}$</th>
<th>$E = \text{difference in inflammation (R-group score minus P-group score)}$</th>
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<tr>
<td>Pig 2</td>
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<td>0</td>
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<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
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<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>–1</td>
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<tr>
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<td>3</td>
<td>0</td>
<td>0</td>
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<td>3</td>
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Range of the score 0 to 2 0 to 3 0 to 1 0 to 2 0 to 2 (–1) to 3


