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A bioresorbable urethral stent

An experimental study

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Summary. The aim of the present study was to examine the suitability of biodegradable polymers as materials for a urethral stent. A new urethral stent made of biodegradable self-reinforced poly-L-lactide (SR-PLLA) was implanted in 16 male rabbits after urethrotomy. Seven stents of stainless steel served as controls. The dimensions of the two types of stents were identical: length 15 mm, diameter 8.2 mm. The mechanical construction was a helical spiral. The SR-PLLA spiral was sustained with three microspirals, and the whole device was coated with DL-lactide to achieve an active initial tissue reaction and better tissue penetration. The SR-PLLA stent showed more favourable implantation properties than the steel one. Within 6 months all PLLA stents had implanted, and the tissue reaction around the stent material was minimal. The helical spiral of stainless steel induced a remarkable inflammatory reaction due to poor implantation properties. We suggest that biodegradable SR-PLLA is a promising material for a urethral stent to prevent re-stenosis of urethral strictures.

Key words: Biodegradable material – Experimental study – Urethral stent – Urethral stricture

The therapy of urethral strictures has changed dramatically during the last two decades. Optical urethrotomy and pediculated, vascularized island skin-flap procedures are now the most frequently used therapeutic techniques. Intermittent dilatations are partly substituted by intermittent catheterization done by the patient himself [5]. None of these methods has, however, totally prevented re-stenosis of the stricture. There is still a need to find more effective therapeutic techniques. One of the latest techniques is to make a dilatation or urethrotomy and thereafter to insert a self-expanding metallic stent into the strictured area of the urethra to keep the lumen open [4]. The results have been promising, though long-term follow-up over 3 years is not yet available [1].

Biodegradable materials have certain advantages: the organ preserves its normal function after resorption of the device, and the biocompatibility properties are relatively good. It is possible to make different types of construction out of modern high-strength bioresorbable materials – even self-expanding models. The bioresorption time can be affected by the choice of basic molecule, the degree of its polymerization, and by the coating material used for the device. The biodegradable materials are metabolized to water and carbon dioxide inside normal tissue. The normal elasticity of the urethral wall is therefore restored after total degradation of the device.

Materials and methods

Urethral stent

Poly-L-lactide (PLLA) was chosen as the material for the stent, as it has the longest biodegradation time of the basic molecules available. The initially high molecular weight of PLLA (660000) was used to extend further the time of biodegradation. The material was self-reinforced with the mechanical deformation technique to increase its modulus, initial strength, and retention in vivo [11]. The self-reinforced poly-L-lactide (SR-PLLA) stent was coated with DL-lactide (molecular weight 100000) to achieve tissue penetration by inducing a local inflammatory reaction. DL-Lactide consists of the two stereoisomers, laevo-lactide and dextro-lactide. It is degraded therefore rapidly, in approximately 6 weeks. The mechanical construction of the stent was a simple helical spiral made of 0.7 mm wire. The helical shape was sustained by three SR-PLLA microspirals fixed with the coating material (DL-lactide) on the outer surface of the main spiral. The length of the stent was 15 mm and the outer diameter 8.2 mm. Helical spiral stents made of 0.5 mm stainless steel wire with the same dimensions were used as controls (Fig. 1). The stents were gamma-ray sterilized.

Animals

A total of 23 male rabbits with a mean weight of 3.0 kg (range 2.4–3.3 kg) were used as experimental animals. Male rabbits were chosen

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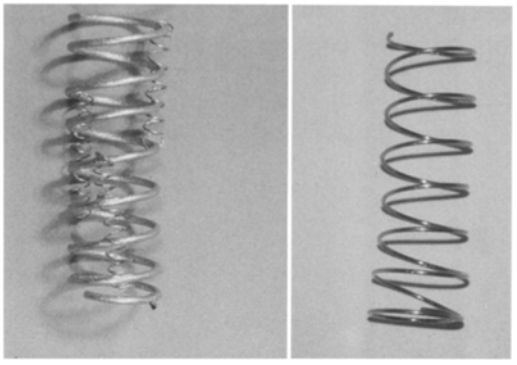

Fig. 1. *Left,* Urethral stent of biodegradable SR-PLLA; three microspirals support the main spiral. *Right,* Stainless steel spiral stent

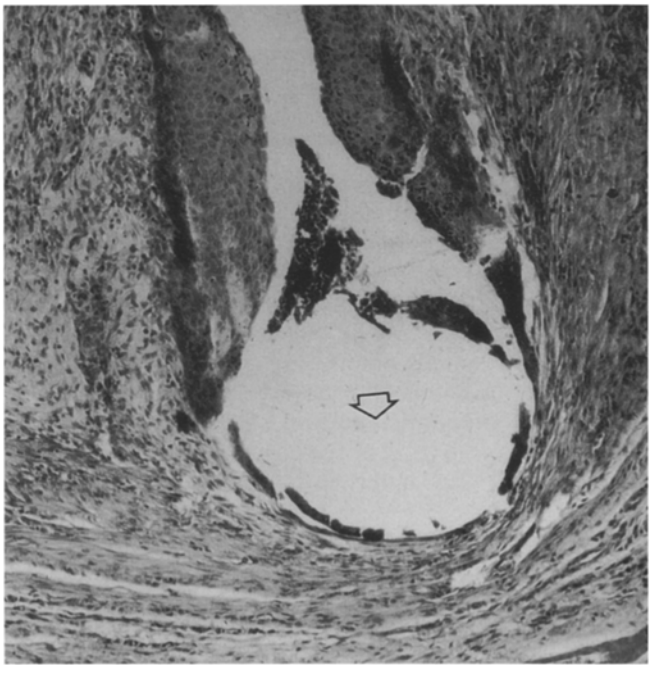

Fig. 2. Typical groove *(arrow)* in the urethral wall 3 months after implantation of a SR-PLLA stent

because of the large calibre of the urethra. There were 8 rabbits in the PLLA group and 7 in the stainless steel group. In addition, 8 rabbits were used in the pilot studies to test the implantation and fixation methods and to establish the period of bioabsorption of SR-PLLA in the rabbit urethra.

Experimental procedure

The rabbits were anaesthetized with ketamine hydrochloride 20–27 mg/kg, intramuscularly and in part intravenously, plus pentobarbital (Mebunat) 2–4 mg/kg intravenously. The animals maintained their own breathing. The urethra was incised with a blind Otis urethrotomy instrument to 24 Ch at the 12 o'clock position. The spirals were fixed distally with two non-absorbable monofilament sutures. The fixation method was tested in the pilot studies. This was considered necessary, since the rabbit urethra is short and elastic. Urethroscopy was performed after 1, 3 and 6 months. The animals were killed after implantation periods of 1, 3, 6 and 12 months. The urethra and the corpora were excised completely. The excised tissue blocks were fixed, with spirals in situ, in 10% formalin. After fixation, pieces of tissue were selected for histological examination and the sections stained with haematoxylin and eosin (H & E). The spirals were removed before cutting the specimens since no reliable method was available for dissolving the SR-PLLA or steel spirals before histological examination. Macroscopic and histological examinations of the whole urethra were performed. The degree of macroscopic implantation, inflammatory changes and fibrosis were evaluated.

Results

In the urethroscopic evaluation the SR-PLLA spirals were seen to be well implanted into the urethra. After 1 month part of the spiral at the urethrotomy site was completely implanted, and after 3 months the remaining part also was mostly inside the urethral wall. A variable amount of fibrinous grey tissue was seen at the penetration site, but it was still possible to pass the lumen with the 15 Fr urethroscope. Thus the inner calibre of the lumen was more than 5 mm.

In the macroscopic dissection the same phenomenon as above was seen: penetration around the urethrotomy area was almost complete after 3 months. The remaining part of the stent had compressed grooves in the urethral wall and was visible without penetration into the tissue. We think that this phenomenon corresponds to the pseudopolypoid pattern of the epithelium also described with stainless steel stents. No inflammation, erosions or intraluminal calcification were seen. After 6 months the whole stent was covered by the epithelium and the lumen had remained open. The SR-PLLA had also started to lose its mechanical strength. After 12 months, particularly the part of the spiral at the site of urethrotomy, which first penetrated into the urethral wall, was macroscopically degraded. There was no pathological obstructing tissue reaction. The lumen of the urethra was intact.

During the first 3 months only a few erosions were seen histologically around the SR-PLLA stent and these were mainly located in the areas of the deep grooves made by the stent (Fig. 2). There were also foci of granulocytes inside the epithelium in these grooves. At all stages of the study a few mononuclear inflammatory cell infiltrates were observed in the subepithelial stromal tissue, especially in the grooves and corresponding mucosal folds. No epithelial erosions or foci of granulocytes were seen at 6 and 12 months. In the urethral wall microscopic islands of the stent material were observed (Fig. 3). Only a slight inflammatory reaction was seen around the implanted SR-PLLA at any stage of the study. The foreign body reaction was minimal. Instead of inflammation a few calcium deposits and bony metaplasia were seen around the stent material after 12 months. The amount of fibrosis was quite small at all stages of the study, and the lumen had kept its normal calibre after 12 months.

Our stainless steel stents had a mechanically relatively inflexible construction compared with the model used by Milroy et al. [4]. At the urethroscopic evaluation after

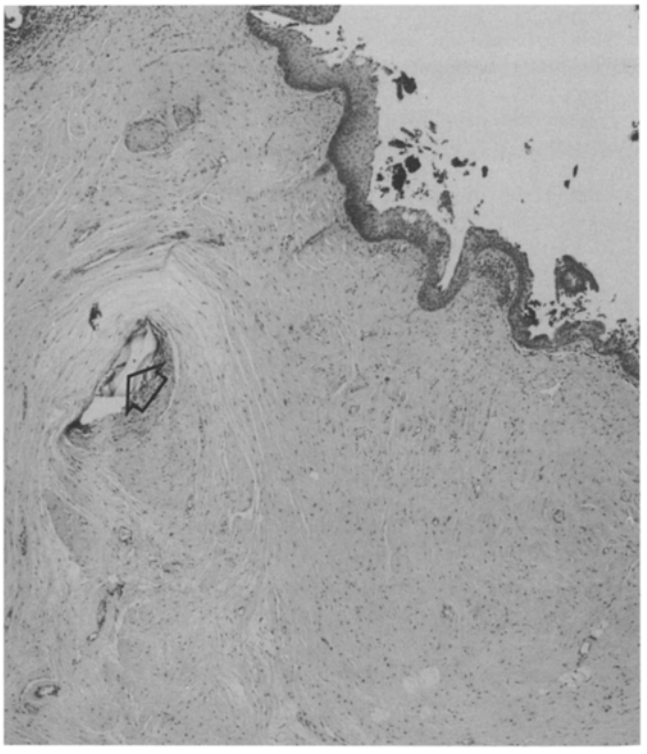

Fig. 3. Urethral wall 12 months after implantation of a SR-PLLA stent. A remnant of stent material is visible *(arrow)*; the epithelium is normal

1 month, only 30% of the surface of the spirals was implanted into the urethra, and the percentage did not increase after 3 months. According to the macroscopic evaluation of the tissue specimens, only 20% of the total surface of the stainless steel stents was inside the urethral wall. The remaining part had caused large erosions in the epithelium and, later, the stents were obstructed by calcified encrustation material. In these animals the urethral lumen was beside the device (via falsa). Histologically a strong inflammatory reaction was seen around the stent. There were severe erosive lesions, and the epithelium was damaged in large areas.

Discussion

The therapy of recurrent urethral strictures is a challenge to the urologist. Optical urethrotomy, popularized by Sachse in 1974 [10], is the most frequent modality of treatment. Recurrences thereafter are common occurring in up to 71% of cases [2, 6]. Ninety-four per cent of strictures reappear within 1 year [9]. Metallic stents for keeping the strictured part of the urethra open were first introduced by Milroy et al. [4] in 1988. The tissue penetration of the stent is dependent on the thickness of the material as well as on the radial force which the self-expanding construction exerts towards the urethral wall. Stainless steel is fully implanted into the human urethra in 4 months [1]. After approximately 6 months the epithelium is completely remodelled, smooth, and covers the device totally. These types of expanding stents have been developed by angiologists to be inserted after percutaneous transluminal angioplasty [8]. Devices made of titanium are also currently available.

The metallic material remains in the urethral wall, keeping the lumen permanently open after urination with a consequent uncontrolled afterdripping. Occasionally the stent can also induce local pain and discomfort [8]. Hypertrophic obstructing proliferation of the epithelium has also been reported, and the stent must then be removed by open surgery [1].

The present idea of using biodegradable SR-PLLA as the material for a urethral stent arose from the favourable results obtained with the same material in the fixation of bone fractures [7], as well as from the encouraging results with urethral stents made of stainless steel.

SR-PLLA was selected as the material because of its long strength retention time in vivo. It is known that inside bone an SR-PLLA rod 3 mm thick retains its strength for about 1 year and is absorbed in approximately 3 years [7, 11]. In our preliminary study a PLLA wire 1 mm thick was macroscopically eliminated during 14 months in the rabbit urethra. This may be due to the more rapid metabolism in the urethral wall as compared with that in bone. Naturally the different thicknesses of the devices also influences the rate of absorption. The effect of urine on SR-PLLA is unknown. A good mechanical strength of the device will last for more than 6 months. We think that this resolution time is long enough for overcoming the strong hyperplastic tissue reaction around the strictured area. It is, of course, an open question as to whether this period is long enough in vivo to solve the problem of recurrence of the urethral stricture. The period of biodegradation can be prolonged by increasing the molecular weight of the material. New polymers with longer absorption times can also be found.

The coating of the long-chained SR-PLLA with short-chained DL-lactide seems to influence the tissue penetration. DL-Lactide induces an active initial inflammatory reaction which subsides when the coating material is absorbed. L-Lactide has a better tissue tolerance than DL-lactide. In the present study when, after 3 months, the DL-lactide had biodegraded, the tissue reactions around the implanted steel and SR-PLLA stents were nearly equal. We believe that continuous hydrolysation on the surface of the biodegradable material when the stent has not yet implanted gives protection against encrustation and calcification. SR-PLLA induces a tissue reaction which, in this study, was not as intensive as to obstruct the lumen. After 3 months the tissue reaction was seen macroscopically to be gradually decreasing. It remains to be seen what will happen after 12 months in the urethral wall: whether the foreign body or bony metaplasia will increase or whether there will be any other late complications.

The poor results with the stainless steel spirals may be due to the inflexible construction of the stent and probably also to the experimental animals we used. The stent did not penetrate well enough into the urethral wall, and the lumen could later be filled by encrustation material. This phenomenon has been recognized with other kinds of foreign materials in the urinary tract. In future studies the

biodegradable stent, particularly the self-expanding model, should be compared with the tubular mesh stainless steel self-expanding wire stent, which has shown favourable results in clinical studies.

We believe that biodegradable SR-PLLA is a promising material for a urethral stent in the treatment of recurrent urethral strictures. The results of the present experimental study are encouraging. The material itself and the construction of the stent need further investigation before application in human urethral strictures.

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