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ORIGINAL PAPER

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Biocompatibility, encrustation and biodegradation of ofloxacine and silver nitrate coated poly-L-lactic acid stents in rabbit urethra

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Abstract The purpose of this study was to evaluate the biocompatibility, encrustation and biodegradation properties of silver nitrate and ofloxacine blended caprolactone-L-lactide copolymer coated self-reinforced poly-L-lactic acid (SR-PLLA) urospirals in situ in the male rabbit urethra. SR-PLLA urospirals coated with 10% by weight silver nitrate or 5% by weight ofloxacine blended copolymer or pure copolymer were inserted into the posterior urethra of 18 male rabbits. No prophylactic antibiotics were given. The animals were sacrificed 1 or 6 months after insertion. Urethral tissue reactions were histologically scored semiquantitavely and the appearence of the stents assessed using scanning electron microscopy. The biodegradation time of SR-PLLA stents was remarkably reduced by the caprolactone coating. Silver nitrate and ofloxacine blended copolymer coated urospirals caused less tissue reaction than urospirals with a pure copolymer coating. Silver nitrate coating effectively prevented biofilm formation and stent encrustation. Silver nitrate and ofloxacine blended copolymer coated SR-PLLA urospirals had good biocompatibility properties in rabbit urethra. In particular, coating with silver nitrate may provide possibilities of preventing bacterial adhesion to bioabsorbable stents.

Keywords Biocompatibility · Bioabsorbable · Urethral stent · Encrustation

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Introduction

Since Kulkarni et al. reported the manufacturing of bioabsorbable polylactic acid (PLA) sutures in 1966 [12], an intensive development has been going on in the application of bioabsorbable materials for surgical purposes. The development of bioabsorbable devices for urologic use started in the late 1980s. The materials used most often are high molecular weight polymers of polylactic (PLA) or polyglycolic acid (PGA). In an experimental study by Kemppainen et al. [11], self-reinforced poly-L-lactide spiral (SR-PLLA) stents had good tissue penetration and biocompatibility properties. Since then, SR-PGA spirals have been clinically used after visual laser ablation of the prostate [19, 24], transurethral microwave therapy [5] and free skin urethroplasty for recurrent bulbar urethral strictures [18]. SR-PLLA stents have been used clinically in the treatment of recurrent urethral strictures with optical urethrotomy [9] and combined with finasteride in the treatment of acute urinary retention [10].

Urological stents have several problems, such as migration, encrustation and infection [17, 28], which cause significant morbidity. Urinary tract infection occurred in 14–30% of patients with a SR-PGA stent after visual laser ablation of the prostate [19, 24] or after interstitial laser coagulation [2]). All of these patients also had a suprapubic catheter, which probably increased the

infection rate. This was less than the infection rate with metallic coil stents [1, 26]. The adherence of uropathogens to the uroepithelium or to the surface of prosthetic devices is the key event in the pathogenesis of urinary tract infection [4, 22]. Adherence can be prevented by immersion of the stent in a suitable antibiotic solution [3] or by coating the stent with antibiotic or antibacterial compounds [14, 15]. The prevention of bacterial adherence is of crucial importance because during insertion the stent is in contact with the distal urethra, which is colonized by bacteria.

The process by which crystalloids and colloids adhere to biomaterial surfaces is referred to as "encrustation" [2]. The encrustation process is complex and it can occur both in sterile and infected urine. Initially, urinary protein absorbs onto the biomaterial, and the formation of a conditioning film and a biofilm follows in infected urine. Urea-splitting bacteria like *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas* spp. and *Corynebacterium urealyticum*, adhere to the biofilm, multiply and cause an elevation in the urinary pH. Magnesium and calcium precipitate in the alkaline environment produced by urea hydrolysis, forming struvite encrustations [6, 27].

The exact mechanism of encrustation in sterile urine is not completely understood, but appears to depend on both urinary constituents and the properties of the biomaterial. Metabolic disorders such as hypercalciuria, hyperuricosuria or hyperoxaluria may accelerate the encrustation of devices, even in a sterile environment. [23] Stents made of bioabsorbable materials such as PGA and PLA are not prone to encrustation [11, 20].

The degradation of bioabsorbable polymers is the sum of many factors and is accelerated by the presence of residual monomers and oligomers in the polymer, the alkaline pH of the surroundings, the reduction of crystallinity and orientation, certain enzymes (e.g. pronase, proteinase-K and bromeline) and the sites of implantation, for example whether muscular movements and stresses impose a load on the implant [25]. In the study of Kemppainen et al. [11], the SR-PLLA stents had degraded and were voided from the anterior urethra of rabbits within 14 months.

The biocompatibility properties of ofloxacine or silver nitrate blended caprolactone-L-lactide coated SR-PLLA stents have been acceptably good in the rabbit muscle implantation test [16]. However, tissue reactions at urothelial surfaces may differ from those in muscle. The aim of this study was to investigate the in situ biocompatibility, encrustation and biodegradation of these stents in the rabbit urethra.

Materials and methods

The bioabsorbable SR-PLLA spiral stents were coated with ϵ-caprolactone/L-lactide copolymer. This coating is a semi-crystalline co-polymer of caprolactone (95 mol%) and L-lactide (5 mol%). The molecular weight of the polymer is 107,000 g/mol. The melting temperature is 52°C and glass transition temperature –60°C. The copolymer coating is rigid and hard below –60°C, but becomes elastic at normal body temperature, thus enabling a rapid dilatation of a pre-molded SR-PLLA spiral. The copolymer is miscible with a variety of compounds, making it possible to add new properties to it. Caprolactone/lactide polymers were manufactured according to the method developed at the Helsinki University of Technology [8].

The copolymer coating of the SR-PLLA stents was blended with 10% by weight of silver nitrate or 5% by weight of ofloxacine. Pure copolymer coating served as a control. SR-PLLA test material was manufactured by Bionx Implants (Tampere, Finland) and ofloxacine was obtained from Hoechst Marion Roussel (Romainville, France). The stents resembled the configuration of the original Fabian stent [7], with an outer diameter of 4 mm and length of 4 cm. The thicknesses of the SR-PLLA wire and the caprolactone-copolymer coating were 0.7 mm and 0.1 mm, respectively.

Eighteen New Zealand White male rabbits were used in the experiment. They had a mean weight of 2.9 kg (2.5–3.1 kg) at the beginning of the experiment and 3.6 kg (3.0–4.9 kg) at the end. They were divided into six groups (A–F), with three rabbits in each group. The animals were anesthetized with Domitor® 1 mg/ml (medetomidine hydrochloride) 0.3 ml/kg and Ketalar® 50 mg/ml (ketamine hydrochloride) 0.3 ml/kg intramuscularly. The prostatic spiral stents were implanted into the prostatic urethra along a guide wire by using a 14 Ch cystoscope. No antibiotic prophylaxis was given. Groups A and D received a stent with silver nitrate blended caprolactone-L-lactide coating, groups B and E with ofloxacine blended caprolactone-L-lactide coating and groups C and F with pure caprolactone-L-lactide coating. The stents were fixed into the urethral wall by a non-resorbable suture through the distal ring of the stent in order to prevent the migration of the stent. Groups A–C were killed after 1 month and groups D–F after 6 months by an overdose of Mebunat 60 mg/ml (sodium pentobarbital) intravenously.

Three urethral tissue blocks from each animal were excised and fixed in 10% formalin. The most distal block had not been in contact with the stent, and served as a control for the two proximal blocks. After paraffin embedding, routine 4-μm-thick sections were prepared and stained using the standard haematoxylin and eosin method. The histological analysis was performed by an experienced pathologist (M.L.). The histological parameters assessed and recorded included the presence of acute and chronic inflammatory cell reaction and tissue fibrosis. In addition, areas of erosion in the urethral epithelium were investigated. Scoring was semiquantitave.

The stents were removed, rinsed with saline, cut into three pieces and the pieces fixed in 2% glutaraldehyde. Thereafter the specimens were dehydrated in ethanol, dried in a critical point dryer and coated with a 200 Å thick gold layer in a Jeol Fine Coat Ion Sputter JFC-1100 (1.2 kV, 5–10 mA, 6 min). Scanning electron microscopic (SEM) analysis was performed for ten randomly selected areas per stent (DSM 962, Zeiss, Germany). The analyzed parameters were: loosening of coating and presence of crystals (magnification 100×), and the presence of bacteria, inflammatory cells and biofilm (magnification 2,000×). The relative areas of the parameters were estimated and the means were calculated.

Results

All of the stents were in situ and there were no macroscopic signs of biodegradation after 1 month. Tissue reactions in the urethral blocks after 1 month are shown in Table 1. Both silver nitrate and ofloxacine blended caprolactone-L-lactide coating caused less tissue reaction than pure copolymer coating. Only minimal erosions in the epithelium were seen in all test groups at the site in contact with the stent.

Tissue reactions in the urethral blocks after 6 months are shown in Table 2. Two rabbits had died of an unknown cause before the end of the 6 months follow-up.

Table 1. The severity of tissue reactions in urethral blocks after 1 month. The presence of lymphocytes and plasma cells reflects chronic inflammation, the presence of eosinophils indicates a foreign body reaction or an allergy and the presence of neutrophils indicates an acute inflammation. The "test" blocks were in contact with the stent, the "control" blocks were not. Each row presents one test animal. A = AgNO3 blended caprolactone-L-lactide copolymer coating; B = ofloxacine blended caprolactone-L-lactide copolymer coating; C = pure caprolactone-L-lactide; + = weak reaction; + + = moderate reaction; + + + = marked reaction

Coating	Lymphocytes		Plasma cells		Eosinophils		Fibrosis		Neutrophils		Epithelial erosion	
	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control
A												
1	+	(+)	+ +	–	+ +	–	(+)	–	–	–	–	–
2	+ +	(+)	+ +	–	+	–	+ +	–	–	–	–	–
3	–	–	–	–	–	–	+	–	–	–	+	–
B												
1	+	+	+ +	+	+ + +	–	+	–	+	–	+	–
2	+ +	+	+ +	+ +	–	+ +	–	+ +	–	+ +	–	–
3	+	+	+	–	+	–	+	–	–	–	–	–
C												
1	+	+	+	+ +	+ +	+	+ +	+ +	+	–	–	–
2	+	(+)	+ +	+	+ +	(+)	+ +	–	+	–	–	–
3	+ +	+	+	+ +	+ + +	–	+ +	+ +	+ +	+	+	–

Table 2. The severity of tissue reactions in urethral blocks after 6 months. The presence of lymphocytes and plasma cells reflects chronic inflammation, the presence of eosinophils indicates a foreign body reaction or an allergy and the presence of neutrophils indicates an acute inflammation. The "test" blocks were in contact to the stent, the "control" blocks were not. Each row presents one test animal. C1 and C3 had stent pieces left in the urethra. A = AgNO3 blended caprolactone-L-lactide copolymer coating; B = ofloxacine blended caprolactone-L-lactide copolymer coating; C = pure caprolactone-L-lactide; + = weak reaction; + + = moderate reaction; + + + = marked reaction

Coating	Lymphocytes		Plasma cells		Eosinophils		Fibrosis		Neutrophils		Epithelial erosion	
	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control
A												
1	+ +	+	+ +	+	+	+	+	+	–	–	–	–
2	–	–	–	–	–	–	(+)	–	–	–	–	–
3	+ +	+ +	+	–	+ +	+	–	+ +	+	–	–	–
B												
1	(+)	+	–	+	+	–	–	+	–	–	–	–
C												
1	+	+	+	+	–	–	+	–	–	–	–	–
2	+ +	+ + +	+	+	+ + +	+ +	+	+	+	–	–	–
3	+ +	+	–	–	+ +	–	+ +	–	+	–	–	–

The stents had degraded in the remaining seven rabbits and only two rabbits had stent pieces in their urethras. The rest of the animals had presumably voided the stent pieces between 1 and 6 months after insertion. In spite of this, the planned tissue samples were taken, and in analysis, the stents with silver nitrate or ofloxacine blended copolymer coating were shown to have caused less tissue reaction than the pure copolymer coating. Epithelial erosion was not seen in any animal.

Scanning electron microscopic analysis of the stents at 1 month after insertion is shown in Table 3. Silver nitrate blended caprolactone-L-lactide coating prevented biofilm formation and the accumulation of bacteria and inflammatory cells. Crystal formation was sparse on the silver nitrate coating (Fig. 1), whereas it was more marked on both ofloxacine (Fig. 2) and the pure caprolactone-L-lactide coating (Fig. 3).

The loosening of the ofloxacine coating was marked, which was obviously one factor causing the accumulation of inflammatory cells and bacteria on the stents. The two stents remaining 6 months after insertion both had pure caprolactone-L-lactide coating. The biofilm formation was extensive, there were masses of inflammatory cells and bacteria and also heavy encrustations were seen on the degraded stent pieces.

Table 3. Scanning electron microscopic analysis of stents at 1 month after insertion. Each row presents the relative percentage area of the parameter

Coating	Loosening of coating	Crystals	Bacteria	Inflammatory cells	Biofilm
$AgNO_3$					
Rabbit 1	0.2	0	0	0	0
Rabbit 2	3	0.05	1.25	0.13	3.75
Rabbit 3	16	0.25	3.3	0.3	23
Ofloxacine					
Rabbit 1	18.9	1.0	0	0.8	64.4
Rabbit 2	11.7	13.9	35	14.2	92
Rabbit 3	10	3.5	36	9.0	80
Pure caprolactone					
Rabbit 1	46	2.2	7.2	1.3	47
Rabbit 2	13	2.05	9.8	1.93	48.5
Rabbit 3	15	3.8	19.5	3.0	84

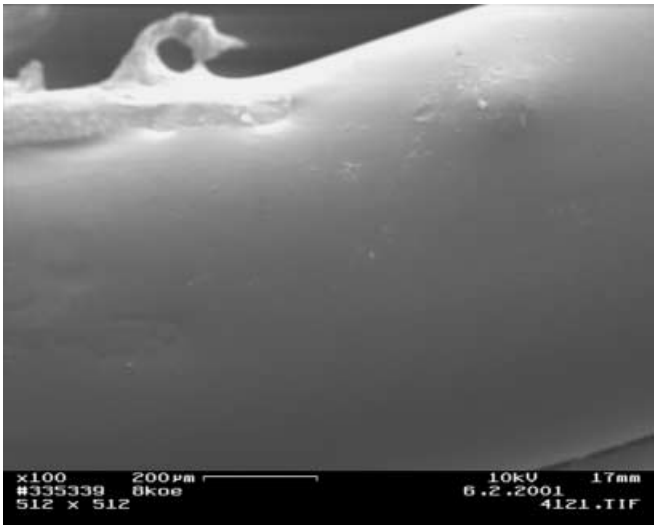

Fig. 1. Crystal formation is very sparse on silver nitrate blended coating and there are no signs of loosening of the coating. Magnification: 100×

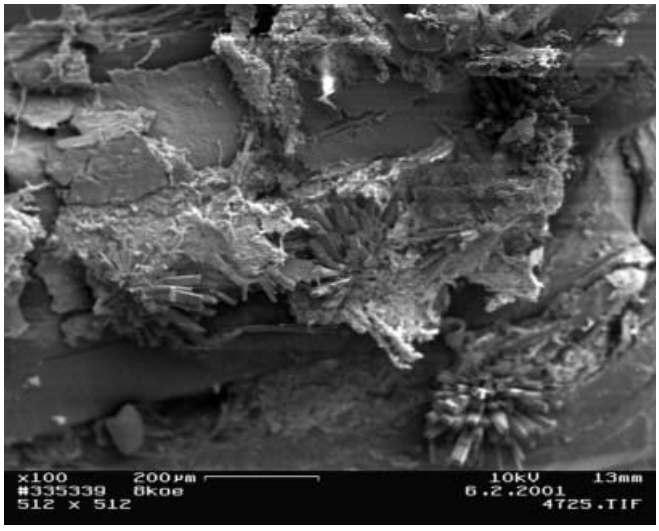

Fig. 3. Encrustation is marked on pure caprolactone-L-lactide coating. In this picture the loosening of the coating is also clearly visible. Magnification: 100×

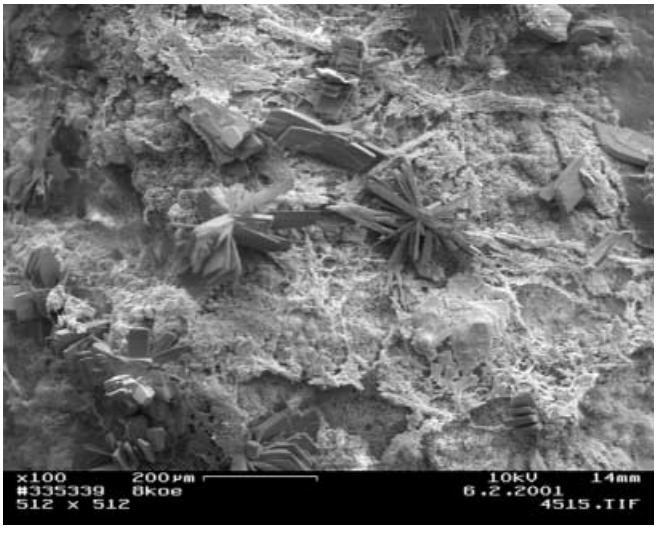

Fig. 2. Encrustation is marked on ofloxacine blended coating. Magnification: 100×

Discussion

In the study of Kemppainen et al. [11], the implantation of SR-PLLA stents into the urethral wall was achieved by coating the stent material with a layer of small molecule D-lactide. The stents were macroscopically eliminated in 14 months in vivo. No implantation was seen in our study, and the stents had degraded unexpectedly soon, although the wire diameter was 0.7 mm in both studies. Obviously the caprolactone coating itself reduced the stability of the SR-PLLA material in situ and led to a remarkable promotion of biodegradation. The degradation time was still shortened after blending the caprolactone coating with silver nitrate or ofloxacine. It is known that the degradation of bioabsorbable polymers may be accelerated by the presence of residual monomers and oligomers in the polymer and the small chain polymer coating of the core polymer [11, 25]. In addition, the activity of the pelvic floor muscles possibly had some effect on the biodegradation, since in this study the stents were positioned in the posterior urethra instead of the anterior urethra of the earlier study [11].

It has been assumed in earlier studies that because of continuous hydrolyzation, biodegradable stents are partly protected from becoming encrusted [11, 20]. The findings of this study showed that pure caprolactone-L-lactide coating did not prevent encrustation, as the stent pieces were heavily encrusted 6 months after insertion. The encrustation may be caused by the properties of the caprolactone coating itself. However, it seemed that the silver nitrate blended caprolactone coating prevented biofilm formation and bacterial adhesion on the stent surfaces, which may be important for the prevention of encrustations. This finding is in agreement with our earlier in vitro study [14], in which we demonstrated that the bacterial adherence preventing the effect of silver nitrate blended caprolactone coating lasts for at least 2 weeks incubation in artificial urine.

The loosening of the ofloxacine coating was associated with the accumulation of inflammatory cells and bacteria on the denuded areas of stents. The ofloxacine coating was also rough, which was caused by the selected blending method; ofloxacine was added to liquid caprolactone as a small particle powder.

The inflammatory cell reaction in the posterior urethra in contact with the stent was more pronounced than in the areas not in contact with the stent. This is possibly due to the irritating effect of the stent. However, this irritation is at least partly induced by the movements of the animal and muscular activity around the stent. On

the other hand, a chronic inflammatory cell reaction may partly be caused by the migration of silver nitrate into the urethral epithelium, although we did not discover any silver nitrate particles in histological analysis of the urethral wall in our study.

In the rabbit muscle implantation test the biocompatibility properties of silver nitrate and ofloxacine coatings upto 5% by weight were good [16]. In contrast to the rabbit muscle implantation test, the 10% by weight silver nitrate blended copolymer coating also showed good biocompatibility properties in this study. In an experimental study by Liedberg et al. [13], silver coated latex, teflon and silicone catheters had better biocompatibility properties than non-coated catheters in the urethra of a rat. In a cell culture test, silver coated silicone and non-coated silicone were not cytotoxic. Silver nitrate coated silicone, teflon and latex showed cytotoxicity. However, silver nitrate coating slightly reduced the toxicity of latex and teflon [13].

At 6 months, when the stents had degraded and been voided, the tissue inflammatory and fibrosis reactions at the test sites had subsided and were at the same level as the control samples.

There are some limitations to our study. The number of animals was limited, but three animals in each group made it possible to analyze tissue reactions which were very similar in all the rabbits having a stent with a certain coating. The histological analysis was performed from three urethral areas per animal, so there were nine tissue samples for each coating and time period. The small number of stents used for assessing the biomaterial surface was compensated by performing SEM analysis from ten randomly selected areas per stent piece. It is possible that the variability in the composition of the urine or the possible presence of infection could have influenced the outcome of the study. However, the animals were very similar in terms of weight and age, they were maintained in similar conditions and fed equally. Therefore, the composition of the urine was probably very similar in all of them. Prophylactic antibiotics were not used, as the aim was to study the characteristics of stents having antibacterial properties. In any case, the prophylactic antibiotics would hardly have been able to prevent bacterial adherence to stents during insertion through the distal urethra which is colonized by bacteria.

In conclusion, we suggest that coating SR-PLLA spiral stents with caprolactone-L-lactide accelerates the degradation rate of the stents. The biodegradation time is still shortened by blending the coating with silver nitrate or ofloxacine. All of the tested bioabsorbable polymers showed good biocompatibility in the urethra and, in particular, the silver nitrate blended caprolactone coating effectively prevented the encrustation of the polymer. The ofloxacine blending method has to be developed to achieve acceptable mechanical properties. However, further studies have to be done on the suitability of silver nitrate or ofloxacine blended caprolactone-L-lactide as a coating material for bioabsorbable spiral stents in humans.

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