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International Journal of Antimicrobial Agents 19 (2002) 507–510

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.isochem.org

Heparin coating reduces encrustation of ureteral stents: a preliminary report

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Abstract

The present study evaluated the inhibition of ureteral stent encrustation by heparin coating. In contrast to uncoated polyurethane stents, heparin coated ureteral stents did not show any organic (biofilms) or anorganic (crystals) deposits after being in situ for up to 6 weeks and effectively inhibited the encrustation process. © 2002 Published by Elsevier Science B.V. and International Society of Chemotherapy.

Keywords: Heparin; Ureteral stent; Encrustation

1. Introduction

With the introduction of improved biocompatible materials such as polyurethane and silicon, ureteral stenting for de-obstruction of the urinary passage has become a routine procedure in urology. Whereas in the majority of stone patients an indwelling stent is used temporarily until the obstructing calculus is removed, stenting may also be a permanent solution for urinary drainage in patients suffering from benign or malignant ureteral obstruction. Especially in this latter group of patients, stent encrustation is a major problem that is mostly met by exchange of the indwelling stent at regular intervals of 6–12 weeks. However, the stent may get obstructed as a consequence of encrustation. The patient's pain and the possibility of septic complications make this an emergency.

The initial step for encrustation of any urinary drainage device (catheters, stents, nephrostomy tubes) is thought to be bacterial colonization [1–4]. Several investigators have demonstrated a 70% bacterial colonization rate of temporary and a 100% colonization rate of permanent ureteral stents that is not reduced by prophylactic antibiotics [1,4]. The presence of bacterial biofilms on stent surfaces in combination with urine pH elevation and electrolyte composition is responsible for crystal formation and consequently, stent encrustation [5].

Thus, modifications of the implant surface have been developed that interfere with the adhesion of bacteria or anorganic molecules [6]. Heparin with its antithrombogenicity and its strong electronegativity that repels cellular organisms is an excellent candidate for an antiadhesive stent coating. Research on the modification of catheter surfaces with heparin has been carried out over the last 30 years especially in the field of vascular protheses. In 1987, Ruggieri et al. showed a 90% reduction of bacterial adhesion on heparin-coated urinary catheter surfaces [7]. Hildebrandt demonstrated a reduction of stent encrustation by heparin-coating in an experimental setting [8]. However, no controlled studies on heparin-coated ureteral stents have previously been performed.

The recent development of a heparin-coated ureteral stent initiated a pilot study that evaluated the encrustation status in comparison with uncoated polyurethane stents.

2. Patients and methods

In a patented procedure, the interior and external surfaces of commercially available polyurethane ureteral stents and silicone nephrostomy tubes were coated with a spacer to which heparin was bound in a covalent

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0924-8579/02/$ - see front matter © 2002 Published by Elsevier Science B.V. and International Society of Chemotherapy.
PII: S0924-8579(02)00097-3

manner. Twenty heparin-coated and 20 uncoated stents were inserted into obstructed ureters in a prospective randomized study under sterile conditions and left indwelling for periods between 2 and 6 weeks. Stents were removed, under sterile conditions, sealed in sterile covers and sent for electron-microscopic evaluation. Nephrostomy tubes were used in two patients with permanent bilateral external urinary drainage that suffered from frequent catheter obstruction by encrustations resulting in repeated emergency visits. In these patients, a heparin-coated and an uncoated nephrostomy tube were used simultaneously for either side so that direct comparison of the encrustation was possible.

3. Results

Electron microscopy showed a significant difference between heparin-coated and uncoated ureteral stents. Only 2 weeks after insertion, two kinds of deposits could be detected on the surfaces of uncoated stents: (1) amorphous anorganic deposits consisting of mineralized crystals (Fig. 1); and (2) bacterial biofilms (Fig. 2). Heparin-coated stents were unaffected by encrustations after 6 weeks of indwelling time (Figs. 3 and 4) but all uncoated stents showed varying degrees and forms of deposits. This difference is marked in Fig. 2 and Fig. 4 that are from the same patient who had an uncoated and a heparin-coated indwelling stent simultaneously on either side for 4 weeks. In contrast to the luminal biofilm in the native polyurethane stent, the heparinized stent surface is absolutely free of deposits. Within the limited observation period of this pilot study, none of the uncoated stents became totally obstructed.

The heparinized nephrostomy tubes stayed patent for the whole 6–8 weeks indwelling periods (Fig. 5), whereas uncoated tubes became obstructed within 2–3 weeks (Fig. 6). The two patients concerned refused further drainage with uncoated nephrostomy tubes, and no emergency visits for nephrostomy obstruction were necessary for the following 6-month period of follow up.

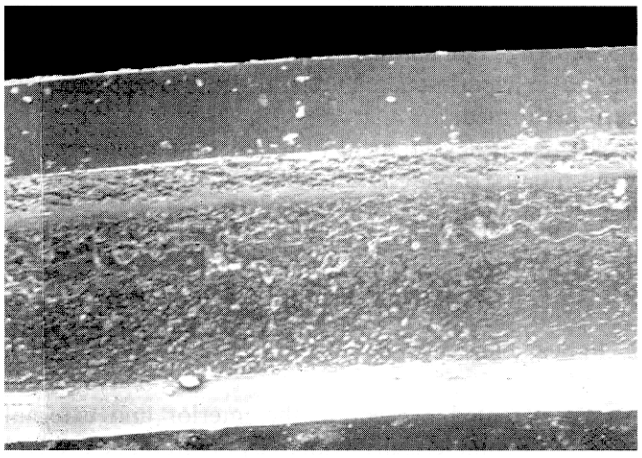

Fig. 1. The inner surface of an uncoated stent with anorganic deposits (indwelling time 2 weeks; magnification × 43).

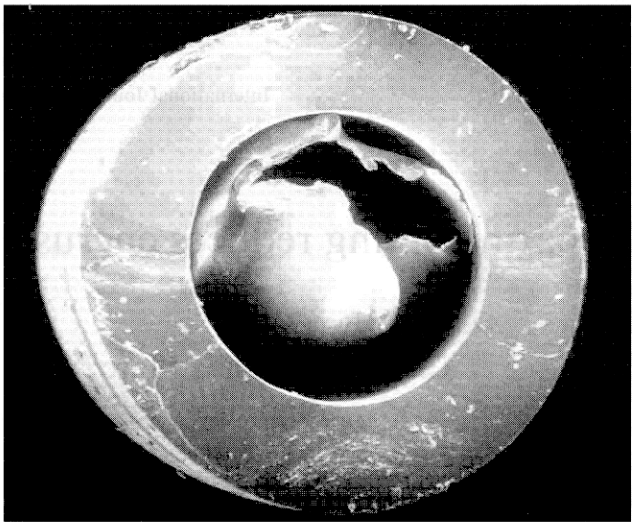

Fig. 2. Biofilm inside the lumen of an uncoated ureteral stent, dissolved from the inner surface as an effect of fixation and dissection for electron microscopy (indwelling period 4 weeks; magnification × 35).

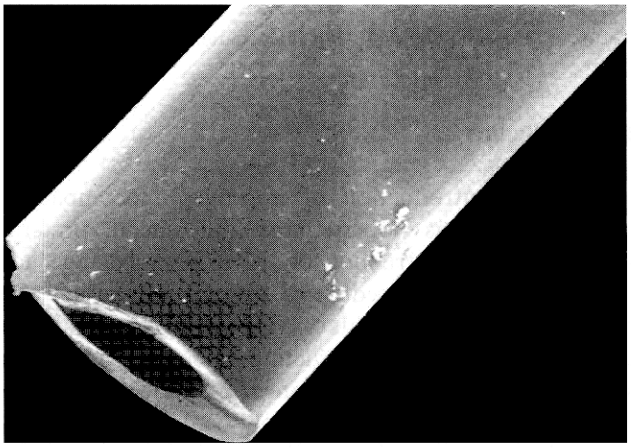

Fig. 3. External surface of a heparin-coated stent without deposits (indwelling time 2 weeks; magnification × 32).

4. Discussion

Infection, encrustation and blockage of long-term indwelling catheters, ureteral stents and nephrostomy tubes are significant medical and health-economic problems. Because of these problems, about 50% of patients with permanent urinary drainage devices present as emergency cases during their course of disease and produce costs of up to 1.5 billion US $ per year in Western Europe and a similar amount in North America [5,9]. Thus, effective strategies for the prevention of

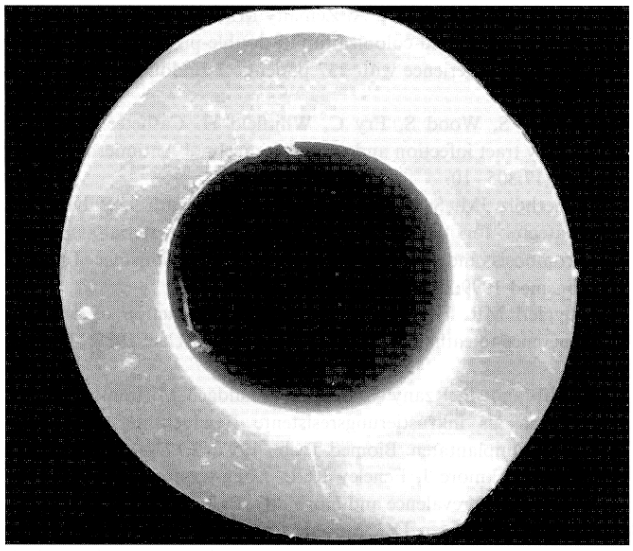

Fig. 4. Lumen of a heparin-coated stent without any deposits (indwelling period 4 weeks, same patient as Fig. 2; magnification × 35).

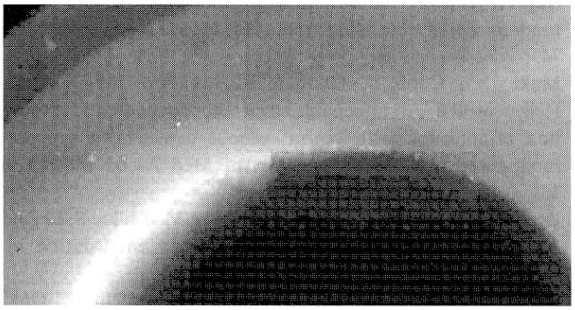

Fig. 5. Heparin-coated nephrostomy tube (indwelling time 6 weeks; magnification × 40).

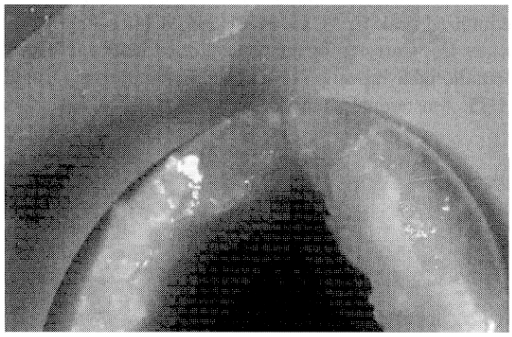

Fig. 6. Uncoated nephrostomy tube (indwelling time 2 weeks; magnification × 40).

catheter-associated infections are necessary to interrupt the process of biofilm formation and encrustation, that runs as follows: protein absorption to biomaterials—formation of biofilms with urease-producing bacteria and consecutive elevation of urinary pH—attraction of calcium and magnesium ions and formation of crystals.

The prevention of bacterial adherence to biomaterial surfaces is an extremely difficult task to achieve, since a high number of adhesion mechanisms via various molecules exist such as specific receptors, proteins, glycoproteins and lipopolysaccharides, that may even vary between different species of bacteria. In addition, the direct adhesion of human blood proteins (albumin, fibrinogen, fibrinonectin) to catheter surfaces coats the modified anti-adhesive structures such as heparin and that may again facilitate bacterial adhesion.

The complexity of the adhesion mechanisms is the reason why none of the anti-adherence strategies investigated hitherto proved to be optimal. Silver coatings show antibacterial activity in vitro, but failed to be effective in multiple clinical trials [10]. Antibiotic impregnation of medical devices effectively reduced bacterial colonization in several clinical investigations [11]. However, the ideal antibiotic for impregnation is still to be defined. Such a substance should be stable (no degradation in vivo), with an antibacterial spectrum as broad as possible, with a minimal risk of toxicity and allergic reactions and a low rate of resistance in long-term use [12]. Hydrogel coatings lower adhesion rates by a reduction of surface energy, but showed a higher degree of in vitro encrustation compared with other biomaterials [13].

The present pilot study confirms the results of several in vitro investigations that postulated the inhibition of biomaterial encrustation by heparin coating. In a clinical setting, we were able to show that heparin-coated ureteral stents stayed free of deposits over the indwelling times up to 6 weeks, whereas organic biofilms or anorganic crystals were observed on uncoated polyurethane stents as soon as 2 weeks after insertion.

Three different ways for surface heparinization of medical devices have been described [6]. Whereas physically adsorbed heparin is released quickly within hours after insertion and effective only during this limited period of time (only useful for interventional devices), and heparin incorporated into polymers may not be released to a sufficient degree to prevent adhesion of molecules and cells, covalent heparin bonding seems to be the procedure of choice, if stability is guaranteed for a longer period of time [14]. The reduction of thrombogenicity and bacterial colonization using covalent heparin bonding has been demonstrated in a clinical pilot study on venous catheters [15]. The present study extends these findings to catheters in the urinary tract.

A new substance recently used for coating of urological drainage devices is phosphorylcholin. Phosphorylcholin coatings seem to show a similar ability to heparin in the prevention of encrustation of medical devices [16]. Clinical and cost comparison of both regimens are needed to evaluate the advantages of either material.

As a continuation of the this pilot study, the indwelling times of heparin-coated ureteral stents have been extended to 3 and 6 months, and bacteriological evaluation of stent biofilms is added to the protocol. A biomaterial coating that effectively reduces bacterial colonization and encrustation rates would be an important tool in the reduction of morbidity and costs in long-term or permanent urinary drainage patients. Heparin coating should also be applied to transurethral catheters, the most frequently used urinary drainage device, which also causes the majority of problems from encrustation. Heparin coating is a relatively inexpensive procedure and may become the strategy of choice for the solution of the encrustation problem.

5. Conclusions

The pilot study has shown that heparin-coated stents stay free of organic or anorganic deposits for indwelling periods of up to 6 weeks. The continuation of controlled studies that evaluate extended indwelling times, bacterial colonization and, finally, compare heparin-coating to other current anti-adhesive strategies is necessary to define the role of heparin-coated urinary drainage devices for the future. At present, the insertion of heparin-coated stents is recommended for long-term urinary drainage and for cases of recurrent stent or catheter blockage.

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