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REVIEW

Ureteral stent technology: Drug-eluting stents and stent coatings

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Abstract Ureteral stents are commonly used following urological procedures to maintain ureteral patency. However, alongside the benefits of the device, indwelling stents frequently cause significant patient discomfort (pain, urgency, frequency) and can become encrusted and infected. The importance of these sequelae is that they are not only bothersome to the patient but can lead to significant morbidity, urinary retention, ureteral damage, recurrent infections, pyelonephritis and sepsis. When these problems occur, stent removal or replacement alongside antibiotic, analgesic and/or other symptom-modifying therapies are essential to successfully treat the patient. In an attempt to prevent such morbidity, numerous approaches have been investigated over the past several decades to modify the stent itself, thereby affecting changes locally within the urinary tract without significant systemic therapy. These strategies include changes to device design, polymeric composition, drug-elution and surface coatings. Of these, drug-elution and surface coatings are the most studied and display the most promise for advancing ureteral stent use and efficacy. This article reviews these two strategies in detail to determine their clinical potential and guide future research in the area.

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1. Introduction

Ureteral stents are widely used in urology to maintain urinary flow from the kidney to the bladder in the presence of kidney stones and other obstructing lesions including strictures and extrinsic causes. While the vast majority of these devices are placed for a relatively short amount of time (1—2 weeks), a portion of patients will require more chronic (weeks to years) of ureteral stenting. For those requiring short-term stenting, pain and discomfort caused by the device are the most common symptoms, especially during activity and urination. This is typically managed using oral nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesic medications but can still result in patients presenting with moderate to severe urinary symptoms during the indwelling period. A small portion of patients may also develop stent-related infection and/or encrustation, but since the devices are only in for a short period of time, encrustation will typically be minor and infection can often be adequately dealt with using broad-spectrum antibiotics until device removal. Chronically-stented patients are more difficult to manage as they face all of the above sequelae on a continuous basis and often require new stents to be inserted immediately following the removal of any infected or encrusted device. This short turnaround time between stents enhances direct transfer of organisms from an infected device or urinary environment to the new one and once organisms securely adhere to the new device and form a biofilm, they are virtually impossible to eradicate. Even the use of high-dose antimicrobial agents alongside device replacement does not always prevent infection, as the same organism has often been cultured from the replacement stent even months later.

Question 1: Is there any other way to avoid urinary catheter-associated infection and other discomfort?

To date, no ureteral stent adequately addresses the issues of pain, discomfort, infection and encrustation associated with their use. However, numerous approaches have been employed in an attempt to do so, primarily the development of novel surface coatings and drug-elution strategies. This review focuses on these two areas of research to determine their potential in preventing stent-associated infections, encrustation and patient symptoms.

2. Stent coatings

Question 2: Surface coatings for ureteral stents typically target the prevention of infection and encrustation by inhibiting bacterial attachment and survival on the device, as well as resisting urinary crystal formation and adherence. Numerous strategies have been developed and tested, largely based upon the application of anti-adhesive (modifying surface charge, hydrophobicity and roughness) and antimicrobial (silver, antibiotics, detergents, others) compounds. What are their characteristics and what situations are they best suited for?

2.1. Heparin

Heparin is a highly-sulfated glycosaminoglycan widely used in medicine for a number of clinical indications, predominantly anticoagulation. Due to its relative safety, high negative charge and existing use as an anti-adhesive coating on blood-related tubing and devices, the molecule has been applied to urinary stents and tested for its ability to reduce biofilm formation and encrustation (Endo-Sof™, Radiance™, Cook Urological). In addition to the heparin coating, this stent possesses thermosensitive properties that allow more rigidity during placement followed by a softening once exposed to body temperature, promoting increased patient comfort. An initial study involving two patients with stents indwelling for 10 and 12 months showed no encrustation as well as no changes in the heparin layer, suggesting that it might be a useful tool for long-term urinary drainage [1]. However, a subsequent *in vitro* study by Lange et al. [2] failed to show any benefit for the heparin-coated device over controls in resisting bacterial adherence. Ultimately, further studies need to be conducted to determine whether stents with a heparin coating have true potential as long-term devices able to resist both encrustation and biofilm formation *in vivo*.

2.2. Diamond-like carbon coatings

Although the development and use of diamond-like carbon coatings (DLCs) for reduced friction and wear have been studied for decades, the first description of their application on urological devices was in 2004 by Dr. Norbert Laube's research group [3] at the University of Bonn, Germany. They applied a plasma-deposited, diamond-like amorphous carbon material to segments of both urethral catheters and ureteral stents and demonstrated preliminary efficacy in reducing encrustation and ease of insertion. Based upon its overall nanocrystalline structure, outer monomolecular layer of non-polar hydrogen atoms and thin film application, the coating is chemically inert, biocompatible, superlubricious and extremely durable. That initial work was followed by both *in vitro* and *in vivo* studies published in 2007 that demonstrated great promise in reducing patient symptoms, infections and encrustation [4,5]. The latter study involved 10 chronically-stented patients suffering from numerous underlying disorders and requiring frequent stent changes due largely to heavy encrustation. Several different types of uncoated, polyurethane Double J stents were coated and 26 devices placed for a total of almost 2500 days across this population. Overall, the results showed reduced encrustation, biofilm formation, patient symptoms and complications, and also increased physician ease in device handling, placement and removal. Unfortunately, no further studies investigating this coating strategy on urological devices have been published since. Future studies should target short-term patients to investigate whether significant decreases in infection rates can be achieved in this population.