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Prospects in the Development of Urological Stents

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Abstract: The impetuous growth of the minimally invasive technologies in the medicine during the last year sled to the fact that the modern surgery is very difficult to imagine without drainage devices. The spectrum of the diseases, where the stents could be applied, is widening. Nevertheless, the objective unresolved problems are linked to the stenting, which serve as the force for the development and modernization of the stents, accompanying delivery and removal systems, for the search of new methods of stenting and new materials, which could optimize their usage. This review outlines the main tendencies in the development and optimization of the urological stents. The materials used for the production of the stents are presented with the description of the main advantages and disadvantages in case of polymeric and metallic stents. The biodegradable materials are reviewed as for the modern evidence level. The publications to the construction and the fixation of the stents are also presented. The main complications are outlined: migration, obstruction, bacterial contamination and other. The main research directions are selected in the areas of antibacterial, ant proliferative and antiadgesive coverage, the modern publications are presented. Drawing a conclusion, the implementation of the urological stents led to their wide acceptance, decreased the operation-related traumatisms and the probability of the complications, in selected areas had dramatically changed the tactics of the treatment. Nevertheless, the disadvantages are also there, which warrant the development of constructively new devices and the search of new materials and covering agents.

Keywords: ureteral stent implant, bio inertness, biofilm, biodegradable materials, medical coverage.

The rapid growth of minimally invasive technologies in medicine in recent years has led to the fact that it is difficult to imagine modern surgery without draining interventions using stents. The range of diseases and pathological conditions for which these approaches are used, as well as treatment strategies, is expanding. Objectively, there are a number of unresolved problems associated with stenting. All this encourages the development and improvement of the stents themselves, delivery and removal systems, the search for effective ways to install and control the functioning of the stent, the development of materials that meet certain needs. The number of research papers and patents registered over the past five years in the Russian-language databases E-library and FIPS and the English-language databases PubMed and Web of Science amounted to 36,000, which indicates the demand for these studies and the unresolved nature of this problem.

MATERIALS FOR MANUFACTURING STENTS

For the manufacture of modern urological stents, metals and polymers are used. 3 times superior to similar indicators of polymer stents.

Polymeric materials are more bioinert than metals, stents made of polymers are one to two orders of magnitude cheaper than metal ones. The negative sides identified during their use can be called a greater likelihood of bacterial colonization and salt adhesion, a high risk of migration, and the development of irritative symptoms. Among the polymeric materials, silicone and polyurethane are the most widely used. The first one has the best bioinertness, its disadvantages include thermal lability with loss of rigidity and a large coefficient of surface friction, which increases the risk of migration, on the one hand, and causes difficulties in installation, on the other. The rigidity of polyurethane can be excessive, therefore, all manufacturers of polymer stents are conducting research on the creation of combined materials that have not only thermal stability, but also good handling properties. This has led to a variety of original proprietary materials: Siliteck, C-Flex, Percuflex, Tecoflex, etc.

For metal stents, materials such as steel and alloyed alloys of titanium, chromium and cobalt are most often used. Titanium alloys have the best indicators of bioinertness, which is due to the protective effect of a rapidly forming oxide film. Titanium nickelide (nitinol) can generally be called an ideal material for the manufacture of self-expanding stents due to the effect of martensitic transformation. The disadvantages of nitinol include the toxicity of nickel, which is part of the alloy, and its ability to diffuse and accumulate in parenchymal organs. To isolate nickel from tissues, attempts were made to create a protective layer of titanium on the implant surface. Experimental in vitro and in vivo studies have shown that a 20 nm nanolayer of titanium, formed by ion and electron beam methods, increases the corrosion resistance and bioinertness of implants compared to nitinol.

Another option for solving this problem is the use of molybdenum and zirconium as alloying materials. In the literature, these titanium alloys appear as β-metastable titanium alloys, the advantage of the latter is also the elastic modulus that varies over a wide range, determined by the conditions of heat treatment, and such properties as the shape memory effect and superelasticity.

The idea of removing the material after the stent has completed its function is not new, but it is not always convenient in the implementation of the model of temporary removable stents. Another way to achieve the result is the use of hydrolysable or so-called biodegradable materials.

Among the materials most in demand for these purposes, one should note hydrolysable polymers in the form of isolated stereoisomers of polyglycalide and polylactide or their combinations, in particular, they are used together, for example, in a ratio of 1:4.

Among the studied biodegradable materials, there are metal alloys, in particular, magnesium, manganese and iron. Depending on the composition, the rate of biodegradation can vary from hours to weeks and, although experimental studies to date are focused on their use in endovascular surgery, the use of biodegradable stents made of such materials in the future may also prove useful in urinary surgery. Foreign literature provides in vitro studies confirming the possibility of using these alloys as ureteral stents. The experimental model shows the best bactericidal properties against Escherichia coli, a lower tendency to salt adhesion and the ability to biodegrade in the urinary environment. Experimental studies by Y. Chen et al. showed the absence of cytotoxicity in relation to in vitro culture of mouse epithelial cells and in vivo models when implanted in the liver and kidneys of laboratory mice, as well as the ability of alloys to biodegrade in the urine medium.

FIXATION SYSTEMS

When using polymer stents, it is difficult to find an alternative to the "pig tail" ("pig tail"), the advantages in the controllability of fixation are undeniable, the disadvantages include the need for a cavity during its positioning.

A completely opposite picture exists in relation to metal and braided polymer stents, where each manufacturer modifies the fixing devices. Although they can also be reduced to two main techniques: cone-shaped extensions at the ends of the stent and spike-like or hook-shaped protrusions along the outer surface. To overcome such a disadvantage of polymer-coated metal stents as migration, many manufacturers perform a proximal fixation system without a polymer coating,

which made it possible to reduce the frequency of migration for these types of stents by a factor of three.

DESIGN FEATURES OF STENTS

The expediency of choosing a stent design is discussed in the literature. So, over the past four years, the medical portal PubMed.com published the results of at least 20 randomized experimental and clinical studies on the comparative use of polyurethane and metal stents, the results of which are ambiguous and emphasize the advantages and disadvantages of each of these devices.

In urology, the use of polyurethane stents without an internal lumen in the form of a trefoil or cross was considered, which, according to single-center studies, had an advantage in the throughput of the stent. This model did not have further clinical use due to obstruction by mucosal granulations. In urological practice, a stent of a similar design is used, which is installed after remote shock wave lithotripsy.

When using uncoated metal stents, there is a high probability of obstruction of the lumen by neoplastic or granulation tissue, which in the first 6 months can reach 51.2%. Polymer coatings made of Teflon, polyurethane and silicone increase the safety of the drainage function of the stent by more than 2 times, in addition, these polymers can be used to create nipple valves and prevent reflux. But, as experimental and clinical studies show, they also increase the risk of bacterial colonization and salt adhesion to the polymer surface with the formation of biofilms and violations of the integrity of coatings (especially Teflon) according to electron microscopy.

Segmental drainage of the ureter in urology with a jj-stent helps to avoid irritative symptoms (stent symptoms), reflux and thus hydrodynamic damage to the kidney, anastomotic failure and the risk of ascending infection. In addition, a larger diameter/length ratio reduces the likelihood of saline adhesion and stent obstruction. As laboratory studies show, a 10 mm stent length is not accompanied by the formation of a saline film during 6 weeks of perfusion, while 100% of 60 mm stents have a continuous layer of urinary salts, which increases from the periphery to the middle of the stent. Similar data in terms of better drainage function compared to jj-stents of larger diameter were obtained during experimental and clinical testing of a segmental Micro-StentTM (Percutaneous Systems Inc.) on a model of acute upper urinary tract obstruction caused by ureterolithiasis.

In order to reduce irritative symptoms in the production of internal ureteral jjstents, materials of different stiffness are also used. By making the cystic curl from a softer material, it is possible to reduce the severity of irritative symptoms (Sof-Curl/ACMI and Polaris/Microvasive Urology–Boston Scientific). For the same purpose, the authors make the size of the cystic curl smaller or replace the latter with a thin loop, behind which traction occurs. The use of such a loop also reduces the risk of developing vesicoureteral reflux.

To increase the internal lumen and increase the elasticity of the vesical end of the stent, Boston Scientific Corporation proposed a spiral jj-stent Percuflex HelicalTM Ureteral Stent, the spiral of which is made of a polymer tape. Manufacturers report an improvement in urine flow through the stent and a decrease in irritative symptoms.

The far from new idea of using magnetic inserts in a stent to remove it without cystoscopy is experiencing a surge in popularity in the works of W.N. Taylor and I.T. McDougall. The authors, using a magnet at the end of a small diameter catheter, removed 29 out of 30 installed stents with a steel ball at the vesical end of the stent. They associate the reason for the only failure with a large average share in benign prostatic hyperplasia.

The installation of two parallel drains increases the efficiency of drainage; for this purpose, an attempt was made to create a double-lumen ipsilateral stent, which was studied during stenting of the porcine ureter in comparison with one and two parallel installed jj-stents. The authors established statistically significant advantages of the proposed stent model in providing both intraluminal and extraluminal urine flow.

The idea of creating a completely metal jj-stent was implemented in the spiral model Resonance stent by Cook (Ireland). To ensure controlled removal of metal stents, manufacturers offer materials with the effect of martensitic transformation (nitinol). By cooling the lumen of such a stent with a saline solution at a temperature of 10°C, the diameter of the stent is reduced (restoration of the delivery form), which allows it to be removed. This technical solution was implemented in Memokath stents from Engineers & Doctors A/S (Denmark). Another solution to this problem is the use of woven, including polymer-coated stents, the weaving of which allows, when pulled by the loop, to assemble the stent into a delivery state, which has found its application in the UVENTA stent from Taewoong Medical (Korea).

The idea of using metal stents as an active electrode during radiofrequency ablation has received positive experimental results and, according to the authors, may qualify for clinical implementation.

ANTI-ADHESIVE BIODEGRADABLE COATINGS AND STENTS

The use of biodegradable coatings or so-called hydrogels has the following goals: reducing the friction coefficient, which facilitates the installation of the stent; "Washing off" from the stent with a degradable layer of biofilms and struvite, which reduces the risk of stent obstruction and infectious complications. Manufacturers have increased the period of guaranteed operation of the drainage from 1 to 12 months.

The idea of self-removal is implemented in biodegradable stents, the effectiveness of which has been studied for the treatment of benign obstruction of the ureter, choledochus, esophagus and trachea, as well as for occlusive lesions of the arteries. Morphological studies after the installation of such stents on experimental models showed a lower severity of leukocyte infiltration and sclerotic changes in the wall of the drained organ. The commercial production of the biodegradable ureteral stent UripreneTM degradable ureteral stent (Poly-Med Inc.), recommended for installation after endopyelotomy, has been implemented.

An interesting approach has been implemented in a biodegradable coating of linear polymers of hydroxy derivatives of alkanoic acids (polyhydroxyalkanoates) of bacterial origin obtained by biosynthetic means using the strain Cupriavidus eutrophus VKPM V-10646. An experimental study of endobiliary stents made of polyhydroxyalkanoates showed their advantages over silicone ones in terms of the absence of adhesion of salts and less inflammatory infiltration and sclerotic changes in the choledochus at a drainage time of up to 100 days. In experimental studies in vitro, in addition to the hydrolytic destruction of polymers, the presence of natural bacterial biodegradants from among the bacteria of the genera Variovorax, Stenotrophomonas, Acinetobacter, Pseudomonas, Bacillus and Xanthomonas and micromycetes - Penicillium, Paecilomyces, Acremonium, Verticillium and Zygosporium was revealed. These properties of the material must be taken into account under conditions of bacterial contamination in terms of the rate of loss of stent strength, on the other hand, bacterial biodegradation will reduce the likelihood of biofilm formation, struvite obstruction of stents and infectious complications.

The ability to resist the adhesion of urinary salts was noted for a coating based on molybdenum disulfide nanoparticles. On the basis of scanning electron microscopy, X-ray photoelectron spectroscopy, and X-ray powder diffraction, the authors report not only a decrease in salt adhesion, but also the ability of nanocoating self-organization in the presence of defects. The latter is associated with the fullerene-like properties of the nanocoating.

ANTI-PROLIFERATING COATINGS

Steroids, targeted drugs (sirolimus, paclitaxel, zotarolimus, everolimus, biolimus A9, tacrolimus, pimecrolimus), cytostatics, non-steroidal anti-inflammatory drugs, anti-inflammatory drugs are used as antiproliferative agents with a dosed release of a drug (Drug eluting stents). Such approaches have often been used in the development of methods for the prevention of restenosis after endovascular stenting. In various studies, positive results have been obtained, reducing the frequency of restenoses by 11.8-15.4%, with virtually no effect on the occurrence of acute thrombosis. There are experimental single-center clinical studies on the use of antiproliferative coatings in the treatment of

benign narrowing of the ureter and urethra, in which encouraging results have been obtained. The effectiveness of the use of radioactive coatings (essentially brachytherapy) of tumor strictures of the ureter in the literature is evaluated in different ways: a number of studies have shown an increase in overall survival with this approach, some authors did not receive benefits when using stents with radioactive coatings.

An experimental study of stents with a slow release of paclitaxel (zotarolimus) was carried out on experimental models of the urethra of dogs, the ureter of a pig and a rabbit during stenting for 4-8 weeks. Metal stents were implanted in the urethra, polyurethane and coated metal stents were implanted in the ureters, the groups were randomized according to the presence of 0.4% paclitaxel coating. Conducted ultrasound, x-ray, helical computer and optical coherence tomographic and morphological studies confirmed the best drainage properties of stents protected by paclitaxel and less hypertrophic changes in the urothelium compared with the control group.

With the use of non-steroidal anti-inflammatory drugs, the possibility of combating irritative symptoms (stent symptoms) that occurs after the installation of an internal ureteral jj stent is also associated. B. Chew et al. used ketorolac as a drug coating on a model of a stented porcine ureter and studied the distribution of the drug. A total of 92 Yorkshire pigs after transurethral stenting of the ureter were randomized into 5 observation groups. Three groups of drug-coated stents with ketorolac at a concentration of 15%, 13% and 7% and two groups without coating, one of which received the drug orally at average therapeutic doses. The resorption of most of the drug did not depend on its concentration in the coating and was completed by 30 days. The content of the drug in the ureters and bladder of the animals of the experimental groups was dose-dependent and exceeded that in the group with oral administration of the drug. In addition, in the latter group, higher concentrations of ketorolac in plasma, liver and kidneys were noted, as well as an ulcerogenic effect. The authors make a conclusion about the safety and effectiveness of using the coating in the treatment of stent symptoms in patients.

ANTIBACTERIAL COATINGS

Bacterial contamination of drains, including urinary stents, occurs within a few hours after implantation, which contributes to the development of struvite lithiasis, stent obstruction and the manifestation of infectious complications. The idea of creating a coating capable of programmed release of an antibacterial agent is not new and consists in providing a bactericidal concentration for 4-8 weeks after implantation. The main problem is to maintain the bactericidal concentration of the released antibacterial agent. Almost all antiseptic and antibacterial agents have been tested as antibacterial agents. Moreover, in experimental in vitro and in vivo studies, the authors note a fairly good effect, accompanied by elimination or a decrease in the adhesion of the pathogen, but clinical trials did not give such good results. A breakthrough in the development of antibacterial coatings can be called the creation of the American medical system IngibiZone coating based on rifampin and minocycline, which passed all phases of testing, proving a reduction in the risk of wound infection, including in patients with diabetes mellitus, and was approved by the FDA US Food and Drug Administration (FDA) as a coating for falloprostheses and artificial bladder sphincter. However, there are also skeptical results of multicenter studies that have not shown benefits when using implants with IngibiZone.

The use of silver as an antibacterial agent also has mixed results, possibly due to the content, structural distribution, and degradability of the latter in coatings. Experimental data on the antiproliferative effect of a nanostructured coating based on silver and carbon for endovascular stents have been obtained.

An attempt to use stents with a radioactive coating did not prevent the colonization of stents by microorganisms, which was accompanied by a greater frequency of obstruction in comparison with uncoated plastic stents.

REDUCING THE RISK OF MICROORGANISMS COLONIZING THE STENT

As experimental and clinical studies show, the effectiveness of antimicrobial therapy with formed biofilms is close to zero, therefore, most of the research is aimed at inhibiting the adhesion of microorganisms on the stent surface.

To prevent bacterial adhesion in the experimental model in vitro in the urinary environment in the presence of Proteus mirabilis, an alternating electric field was applied to the electrodes mounted in the catheter. Control electron-microscopic and bacteriological studies recorded a five-fold decrease in the formation of biofilms on the catheter surface compared with control. The authors claim that the clinical implementation of this model will not cause technical problems.

Bioinert and anti-adhesive properties of heparin coatings were studied both in laboratory and experimental models of urinary stents. In vitro studies in the presence of Escherichia coli on the basis of electron microscopy and bacteriological studies have established a decrease in adhesion of both the microorganism and the formation of salt deposits when using a heparin coating.

BIOINERT COATINGS

If you do not consider the possibilities of tissue engineering with coating of the ureter frame or urethral plate with autologous cells, then the state of complete bioinertness or biocompatibility of the implant is practically unattainable. The contribution of the first to surgical implantology today is “nanoscale”, and in the future it will not replace the implants used, including stents, so the development of bioinert coatings and materials is an urgent problem.

Taking into account the fact that the list of materials used for the manufacture of stents is rather narrow, modern research attaches great importance to the change in surface properties with coatings. With a few exceptions (biodegradable materials of bacterial origin), materials and coatings used in medicine do not have a stereometric molecular structure and, accordingly, cannot possess antigenic properties. Implementation of immune responses to the implant in the body is triggered by a non-specific part of the immune system. The process of recognition of "friend or foe" is mediated by the monocyte-macrophage system, and intercellular (lymphocytic, epithelial and fibroblast) interactions are provided by the secretion of cytokines. used antibacterial drugs. With regard to stents, the presence of exudate containing a large amount of protein contributes to lithogenesis and stent obstruction. Thus, with the concept of bioinertness, not only a local inflammatory reaction is closely intertwined, but also the likelihood of infectious complications and obstruction of the stent by salts.

The bioinertness of a material or coating is determined by their ability to biodegrade, as well as the toxicity of the substances formed. With regard to metals, one should understand corrosion with developing metallosis in the surrounding tissues. With regard to polymeric materials, they are more often faced with hydrolysis, the resulting monomeric compounds may have a toxic effect.

The bioinertness of silicone has long been known and surpasses that of polyurethane and styrenes, but the former has slightly pronounced thermoplastic properties, which is associated with a higher frequency of migration of silicone stents, and also silicone has a higher coefficient of surface friction, which makes it difficult to install such walls. Manufacturers of silicone stents use coatings that reduce the coefficient of surface friction, while polyurethane stents use coatings that are more bioinert.

The bioinertness of titanium is due to the oxide film that forms on its surface. The mechanical properties of titanium (brittleness, lack of shape memory effect) limit its use as a stent material. It seems promising to use titanium-containing alloys, which are devoid of the disadvantages of pure titanium and their use provides longer drainage periods. Of titanium alloys, nitinol (titanium nickelide) is more often used, the latter has the ability to martensitic transformation, i.e. to the "shape memory" effect. Unfortunately, the presence of nickel has a toxic effect on the tissues of the body.

CONCLUSION

The use of internal stents to maintain the lumen of the hollow organ has become widespread in various branches of surgery and urology. This reduced the trauma of surgical interventions, the

likelihood of developing postoperative complications, and in some cases changed the tactics of managing patients. However, along with the positive, there are also negative aspects of the use of internal drainage. The objective shortcomings of internal drainages push both to the development of new design options and to the search for materials and coatings that minimize the described disadvantages of stents and satisfy the specific surgical situation. In the future, in this regard, the creation of bioinert, antibacterial, antiadhesive and antiproliferative coatings and biodegradable stents is being considered. Moreover, the development of other complications directly depends on the indicators of bioinertness of the stent material.

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