Ten Steps to Strategic Planning for the Urinary Stents of the Future

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1 Introduction

To summarise all the knowledge in the current book and to allow its use both at clinical practise and its application in patients, as well as in the improvement of urinary stents, the simplest way is to build a decalogue that provides a global vision of the requirements for the improvement of these medical devices.

2 Understanding the Side Effects and Complications Related to Urinary Stents

An in-depth knowledge of the side effects, complications, their pathophysiology and, above all, the etiopathogenesis associated with urinary stents is essential on the way to reduce the effects on patients, as well as to improve urinary stents. This knowledge allows urologists to identify symptoms early, as well as to arrange therapeutic measures to alleviate these symptoms [1]. Mainly antimicrobials, alpha-blockers or antimuscarinics to reduce discomfort in the lower urinary tract and, of course, analgesics. Knowledge and research into the etiopathogenesis of each of the adverse effects allows researchers to focus their research [2]. The detection of the cause of each adverse effect allows the identification of whether it is caused by the stent design itself, by the biomaterial or by a weak coating; these three factors are responsible for the majority of adverse effects related to urinary stents. We

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differentiate between adverse effects, which we consider inherent to the urinary stents themselves, such as vesicoureteral reflux, biofilm formation, and complications which, although related to the stents, are due to a malfunction of these medical devices. Among these complications, migrations, perforation, etc. are the most important. Therefore, the first factor to take into account is always knowledge of the adverse effects and complications produced by stents [3].

3 Proper Indication for the Use of Urinary Stents

It is clear that the simplest way to reduce the harmful effects associated with urinary stents is to reduce their use. This is the first choice in the face of the high percentage of associated complications. Since it is impossible to avoid their use due to their evident beneficial effects on patients, it would be necessary to determine in which type of patients their use outweighs the adverse effects. Unfortunately, this is currently the case with the use of metallic stents both at the ureteral or urethral area, with very high complication rates; their use is reduced to a very small number of patients and in many cases exclusively as a palliative treatment.

According to the current scientific literature, the use of ureteral stents after endourological treatment of ureteral or renal lithiasis is approximately 80%. This is a very high percentage, which means that the population susceptible to stent-related problems is very high. Unfortunately, both European and American guidelines cannot define with great scientific evidence the indications for urinary stenting. Stenting is well indicated in complicated ureteroscopies, but the difference between a complicated URS and a non-complicated URS always remains the surgeon's decision. As a result, since there is no criteria for deciding when it is mandatory to place a stent and, above all, when it is not mandatory, the use of these devices is on the rise. Although it is true that a great advance in this aspect is that stenting times have been reduced in an attempt to reduce adverse effects [4]. These effects and complications have been shown to be significantly related to the stenting time, increasing adversely in prolonged stenting times, generally longer than 6 weeks [5].

So a decrease in their use or at least a shortening of the stenting time, without delays in the removal date, would be associated with a better quality of life for patients.

4 Biomaterials

Another of the cornerstones on which the improvement of current urinary stents is based is the research being carried out on biomaterials that allow their use in the urinary tract. As can be seen, this point is critical, as the weaknesses demonstrated by the polymers, metals or their alloys currently in use are one of the main reasons for encrustation, bacterial and even fungal contamination, and sometimes stent

fracture. The development of new biomaterials with better characteristics and suitable for the urinary environment will reduce these side effects. Certainly, the future of biomaterials to overcome the limitations they present in the urinary environment depends fundamentally on three factors. The first is to improve their mechanical properties in order to be effective in extrinsic strictures of malignant origin. Secondly, combining biomaterials in the same stent to combine the advantages of each, reducing their weaknesses. Finally, it is possible to coat the biomaterials so that they are not in contact with urine, so that only the coating is affected and the inner part keeps all its properties intact [6].

5 Coatings

This area of knowledge is probably where most resources are being allocated, as research into coatings that prevent or reduce biofilm formation is an issue that involves not only urinary stents, but virtually all implantable medical devices, catheters, prostheses, implants, catheters, etc. Thanks to coatings it is possible to isolate the rest of the biomaterials that make up the stent from the urine, as well as to combat the formation of biofilm that is associated with bacterial contamination as well as encrustation. Therefore, the search for new coatings is of great importance to improve the durability of urinary stents [7]. The aim of these coatings is to provide an "antibiotic free solution" to biofilm formation. To this end, a number of strategies have been developed, as described in the previous chapters. The use of agents with antimicrobial properties has been emphasised: metals such as Zn^{2+}, Ag^{1+}, CuO; superhydrophilic coatings, hydrogels [8]. Mainly in this section, AMPs, antimicrobial peptides, which are proteins with antimicrobial properties, stand out, especially CWR11, RK1 and RK2. Efforts are also being made to detect probiotics that compete against biofilm-forming bacteria and prevent their development. As well as agents with anti-adhesive properties that prevent bacterial adhesion to the stent surface by preventing the action of bacterial adhesins, thanks to bacteriocins [9].

6 New Designs

Another essential element in the improvement of stents and thus the decrease in the adverse effects associated with their use in the urinary tract is the development of new urinary stent designs. It is noteworthy that the design of pigtail ureteral stents has remained virtually unchanged over the last four decades, despite their obvious side effects. Many efforts have been made to reduce the effects related to the bladder pigtail, which is associated with dysuria and LUTS. Therefore modifications of this pigtail, reducing its size, changing its conformation, have been presented and evaluated in patient trials. Despite the decrease in patient discomfort, they have not demonstrated clear scientific evidence, and their use is currently not established in daily

clinical practice [10]. To prevent vesicoureteral reflux, stents with anti-reflux systems have also been designed, which have not shown a clear improvement over conventional ureteral stents [11]. However, the development of intraureteral stents, or stents with a small bladder tip to facilitate their removal, has shown scientific evidence regarding the improvement in the quality of life of patients, making them a very interesting option for the present and future for certain patients [12, 13]. Magnetic ureteral stents for removal without the need for cystoscopy have also shown less painful and faster removal [14].

A further design innovation that have proven to be very useful and that were unthinkable decades ago is the possibility of removing metallic, ureteral or urethral stents. This design improvement is extremely attractive and broadens the indications for these stents in the urinary tract [15]. As has been seen in recent years and is expected in the coming years, design variability will reduce the discomfort associated with current designs. The goal is to personalise stents for each patient. The availability of more stent designs will allow choice, which with current plastic stents is almost impossible at the moment.

7 Biodegradable Stents (BUS)

One of the premises for the development of urinary stents is that they should all be biodegradable. In order to achieve the requirements that defines an ideal stent. It is difficult to understand that in the twenty-first century a surgical procedure is necessary to remove a stent. Avoiding cystoscopic removal of stents, avoiding anesthesia in pediatrics patients and avoiding the "forgotten stent" are short-term goals [16]. The development of BUS has expanded in recent years because the most important limitations in its development have been overcome. Firstly, the control of degradation, making this rate controllable thanks to the selection of polymers and copolymers, natural–synthetic or metallic, and above all the use of combinations of different biomaterials with different degradation rates [17]. On the other hand, the control of degradation fragments is a key limitation, since this is a major drawback, in particular when this type of stent is placed at the ureteral lumen level. BUSs must degrade gradually and fragment into small pieces smaller than 2 mm to ease their evacuation. A strategy that has been described for this type of stent and that is related to its design is the ability to degrade from distal to proximal, so that, despite degradation, the stent continues to perform its function as an internal scaffold [18, 19]. One of the most important current challenges is the preservation of the mechanical properties of the BUS, regardless of the nature of the biomaterials that comprise it. Therefore, a balance between the rate of degradation and the maintenance of the mechanical properties of the stents is necessary, which is of great importance in ureteral stents, but is completely mandatory for segmental stents at the urethral

level, when used as an internal scaffold, cellularised or not, after treatment of urethral strictures.

8 Drug Eluting Stents (DES)

In an attempt to reduce lumen restenosis after vascular stenting, DESs were introduced. Neointimal hyperplasia resulted in in-stent reestenosis in 20–30% of cases after intervention with bare metallic stents. DES were developed not only to act as vascular scaffolds in the diseased coronary artery but also to reduce the relatively high rates of "in-stent reestenosis" and subsequent "target lesion revascularization" compared to its predecessor Bare Metallic stents. DESs have the potential of endoluminal release of pharmacological anti-proliferative substances and reduce the hyperplastic reaction by inhibiting the smooth muscle cell cycle and their proliferation. With the excellent background of vascular stents, applications in the urinary tract are a very encouraging field of development. The idea is to take advantage of the stent to add such an innovative and promising feature as local drug delivery. In this regard, local release of anti-inflammatory, analgesic, or even antiproliferative drugs to reduce urothelial hyperplasia related to urinary metallic stents, or chemotherapy in the upper urinary tract are some of the drugs that have been evaluated [20].

This delivery system would avoid systemic drugs side effects. Possibly reduce the total daily drug dose. As well as using drugs with a short half-life. An important factor is that this urinary delivery system avoids drug absorption, distribution and metabolism, as the urinary tract is a watertight system with low absorption capacity and the drugs are constantly eliminated through urination. A very important consideration is that with these delivery systems, there is the possibility of maintaining urine drug levels in the optimal therapeutic range [21, 22]. Compared to current bladder or pyeloureteral instillation systems, the improvement of patient satisfaction is to be expected.

9 Urine and Infection

The association between UTI and urinary stents, mainly ureteral stents, is one of the most common complications in patients. It should not be forgotten that the prevalence of bacterial colonisation of urinary stents is between 42 and 90%, leading to the development of bacteriuria and UTI [23]. One of the current problems, which needs urgent evaluation to allow for the improvement of stents, is related to the laboratory techniques used for the quantification or detection of urinary bacteria. Regarding the analysis of biofilm and bacteriuria associated with CDJs, despite a low sensitivity of 21–40% and a specificity of 46–64%, culture is the method of

choice for detecting bacterial colonisation of the stent and asymptomatic bacteriuria. The first by direct culture of stent fragments and the latter by culture of urine samples [3, 23, 24]. As a result, there is currently no consensus on the ideal microbiological technique to make a fast and, above all, consensual determination that allows for the standardisation of clinical and experimental studies.

It is evident that the aim with current stents is that they remain in place for as long as necessary, since the rates of colonisation and bacteriuria increase considerably with time [3, 23–25]. With regard to biofilm formation, an incidence of 34–66% is found when the stent remains in place for less than 2 months, compared to 75–100% when the stent remains in place for more than 3 months [23, 25]. The incidence of asymptomatic bacteriuria ranges from 7 to 33% in patients with less than 1 month of stenting, 21–50% between 1 and 3 months and when the stent remains in place for more than 3 months, the incidence can reach up to 54% [24, 25]. With regard to the bacterial strains that make up the biofilm and those present in the urine, a large discrepancy has been demonstrated between stent cultures and urine cultures, showing that there is no direct correlation between the bacteria that colonise the stents and those that cause UTI [25].

Unfortunately, the source of colonisation is unlikely to be eradicated, as contamination is mainly at the time of insertion, through skin bacteria or the urethral microflora itself. This could justify the fact that in some series a double incidence of colonisation is observed in women compared to men, given the short length of their urethra and the risk of contamination; as well as the highly frequent presence of Gram+ bacteria in the stents, bacteria commonly present in the distal urethra and vaginal flora.

This susceptibility of urinary stents to contamination, being aware that urine has its own microbiome, must be taken into account in both clinical and research settings. The development of new biomaterials and coatings with antimicrobial properties is therefore one of the milestones for the development of safe and more effective stents. Especially since antibiotic prophylaxis has not shown clear scientific evidence in reducing colonisation of urinary stents. Therefore, only with contamination prevention and strategies to reduce formation is it possible to make progress on this issue, as bacteria in a biofilm can usually survive the presence of antimicrobial agents at a concentration, 1000–1500 times higher than the concentration that kills planktonic cells of the same species.

10 Drugs to Change the Composition of Urine

One of the promising strategies that may reduce the side effects of urinary stents, mainly related to encrustation and possibly also bacterial contamination, is the possibility of changing the composition of the medium in which the stent is placed, which is the urine. The main efforts are being made to alter the composition by oral administration of compounds that modify the urinary pH. Modification of the urinary pH alone causes a very important change as it affects both microorganisms and

the precipitation capacity of compounds that are dissolved in the urine and which, due to their supersaturation, can precipitate and cause incrustation on the surface of urinary stents. In addition to pH modification, it is possible to administer crystallisation inhibitors that significantly reduce the risk of lithiasis formation or incrustation [26].

This strategy has begun to show encouraging results in clinical studies evaluating potassium sodium hydrogen citrate, or L-methionine and phytin, reducing the occurrence of stent encrustation. In addition, the synergistic ability of many compounds may allow combinations of these compounds to achieve better results in this area. It is clear that urinary stent fouling is multifactorial, but within these causes the composition of the urine is the main factor that triggers this phenomenon, along with the composition of the stent [27]. The availability of this tool and the fact that it is so easy to apply, usually orally, and safe, suggests that this is an important way to reduce the adverse effects of stents. Not only adverse effects, but also future designs with biodegradable materials that can be modulated in this sense or to activate drug release in DES.

11 Receptor-Based Stents and Tissue Engineering

Another future strategy for the development of urinary stents is, as with DES, to make more profit from the device in the urinary tract. This attempt to expand the benefits of stents is aimed on the one side at obtaining data from the urinary tract, and on the other at allowing the stents to be bio-coated and to facilitate tissue engineering applications.

The development of stents with nano pressure sensors, which can provide information on intrapyelic or intravesical pressure, or with other sensors capable of stimulating ureteral peristalsis. The miniaturisation of this type of sensors allows them to be incorporated into the surface of the stent and send wireless information of great interest.

The possibility of coating stents to promote tissue regeneration, or proper healing, is one of the future hopes of research. In particular, their use would be extremely useful as a scaffold after the treatment of complicated stenosis, mainly at the urethral level. Biocovered stents could reduce fibrosis and thus the formation of stricture scars. Biodegradable biocovered stents would allow their function as an internal scaffold and cellular vehicle to be followed by their controlled disintegration [7].

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