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Original Article

Preliminary assessment of the effectiveness of an anti-reflux ureteral stent with a novel device in a swine model

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Abstract: We aimed to determine the effectiveness of drainage potency and anti-reflux properties of a novel anti-reflux ureteral stent in pigs. Six pigs were randomly divided into two groups (group A and group B), and the ureters were bilaterally inserted with conventional stents and novel anti-reflux ureteral stents in the pig's ureters. Meanwhile, ureters without a stent placement were set as the control group (group C). For the detection of drainage potency and anti-reflux property, saline was injected into the bladder until the intravesical pressure reached 30 and 50 cm. The results suggested that the difference in drainage potency of group A and B was not statistically significant ($P>0.05$), however they were superior to that of group C ($P<0.05$). None of the conventional stents in group A prevented vesicoureteral reflux (VUR) (0%, 0/6), whereas the anti-reflux stents in group B displayed anti-reflux properties (100%, 6/6). The average ureteropelvic pressures in groups A, B, and C were 16.67±1.63 mmHg, 8.17±0.75 mmHg, and 7.08±0.90 mmHg, respectively; with significant differences among them ($P<0.05$). Collectively, the novel anti-reflux stent effectively prevented VUR compared with conventional stents without clear urinary obstruction in the animal.

Keywords: Anti-reflux, ureteral stent, vesicoureteral reflux

Introduction

Ureteral stents are widely used to facilitate urinary drainage under obstructed ureteral conditions and secure ureteral patency after urological procedures or surgery [1-3]. Double pigtail ureteral stents, which are also known as Double-J stents (DJ stents) [4, 5], have become one of the most commonly used therapeutic instruments in urology. The usage of DJ stents has greatly promoted the development of minimally invasive urology surgery.

During the use of DJ stents, we aimed to relieve upper urinary tract obstruction, keep urinary tract drainage unobstructed, prevent urinary tract infection (UTI), promote healing after urinary tract injury, prevent and cure ureteral stricture caused by various reasons [6]. Despite the benefit and wide usage of ureteral stents, several side effects such as dysuria, bladder irritation, and flank pain limited the usage of DJ stents [7]. According to the long-term sequelae caused by vesicoureteral reflux (VUR), VUR is considered to be the most prominent side effect [8]. In this study, we aimed to assess the effect of our novel anti-reflux ureteral stent, which would effectively prevent reflux and have little reduction of drainage patency.

Materials and methods

Animal study

Six female Bama miniature pigs (25-31 kg) were purchased from Dongguan Songshanhu Pearl Experimental Animal Science and Technology Co., Ltd. Six pigs were randomly divided into two groups and the ureters were bilaterally were inserted with a common DJ tube used in group A, or new anti-reflux DJ tube used in group B. All data was collected before inserting the two stents as group C. Under ureteroscopy, the common DJ stent was inserted in group A,

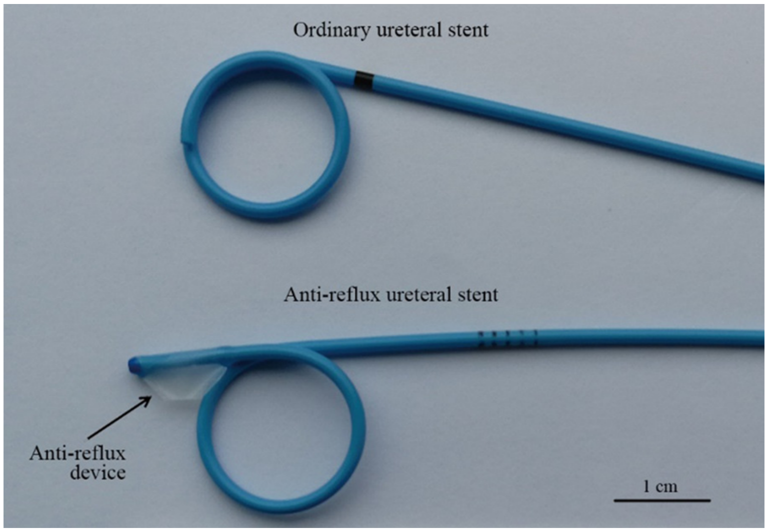

Figure 1. Photo images of the ordinary ureteral stent (up) and our new designed anti-reflux ureteral stent (below).

and the anti-reflux DJ stent was placed by a retrograde method over a guidewire previously passed through the ureter. After going through the vaginal vestibule, the ureteroscope, aided by the monitoring system, gained access to the urethra right above in the vaginal vestibule, and gradually is inserted inside the bladder along the urethral canal to search for the opening of ureters on both sides. Guided by the monitoring system, a straight guide wire is placed by the ureteroscope into the inspected opening of the ureter, and then the ureteroscope exits from the body. After inserting the guide wire into the stents, the assistant inserts the guide wire into the top pipe, and the ureteroscope again goes into the bladder along the urethral canal, pushing the corresponding stents into the ureter with help of the top tube guided by the monitoring system until the catheter goes into the renal pelvis at one end, and the bladder at the other end. After confirming the stent is placed at the right position, we remove the ureteroscope from the body. What is different from a conventional stents is that before inserting the guide wire into the anti-reflux stents, it's necessary to use the hard end of the guide wire to pierce through the rubber plug at one end of the stents. The position of the stent was assessed by X-ray. A Foley catheter was inserted into the bladder and secured with a suture. A renal pelvic fistula was placed in the renal pelvis via nephrostomy to monitor the pressure.

Measurement of renal pelvis pressure

For measurement of renal pelvis pressure, the sensor is connected to the pressure monitor. Saline was injected through the renal pelvic fistula and the pelvis pressure (mmHg) was recorded in the pressure monitor as experimental data of the group C when the experimental animals spontaneously urinate.

Ureteral drainage patency and anti-reflux property

The average drainage speed (ml/min) of physiological saline injected under 30 cm and 50 cm pressure was measured. The bladder was filled with saline (adding methylene blue) until the animal urinated. When the experimental animal's spontaneous urination was without any blue liquid in the renal pelvis the fistula tube was marked as "no VUR" or "effective", which indicated that the ureteral stent tube had anti-reflux effect, or on the contrary, it was marked as "invalid".

After connecting to the pressure monitor, the sensor and the renal penal are placed at the same height. Then the saline is continuously injected into the bladder. When the experimental animals automatically urinate, the injection of fluid into the bladder was stopped and the value of the renal pelvis pressure was recorded (mmHg).

Statistical analysis

The SPSS program (IBM, version 22.0) was used for statistical analysis. T test was used to compare the drainage rate and renal pelvis pressure in the two samples. The Fisher's Exact Test was used to assess the effectiveness between the groups. A probability $P<0.05$ was considered statistically significant.

Results

Novel anti-reflux ureteral stent

Figure 1 shows the new anti-reflux ureteral stent, and the anti-reflux device at the flow-out

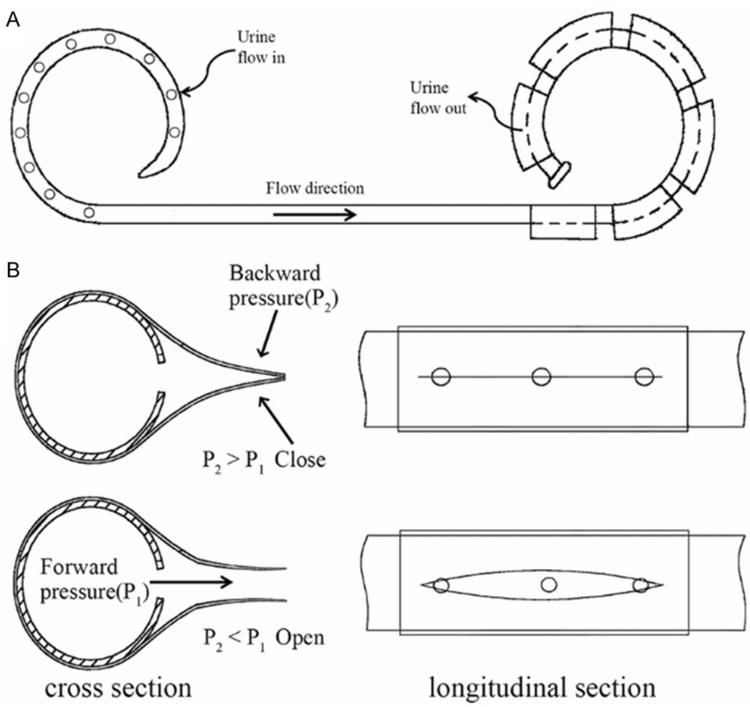

Figure 2. Schematic diagram of the new designed anti-reflux ureteral stent (A) and the structure of the anti-reflux device (B).

Table 1. The average drainage speed of three group on different pressure

Group	Cases (n)	Speed (ml/min)	
		30 cm H_2O	50 cm H_2O
A	6	7.47±0.45	10.72±0.87
B	6	7.08±0.23	10.01±0.75
C	12	4.54±0.28	6.45±0.64
p value	A and B	0.089	0.16
p value	A and C	<0.001	<0.001
p value	B and C	<0.001	<0.001

end of the stent. In detail, the stent contains a urine flow-in end placed in the pelvis, a hollow catheter placed in the ureter, and a urine flow-out end in the bladder with at least one elastic thin silicone membrane acting as a one-way valve (**Figure 2A**). In short, the stent is a conventional DJ stent with elastic thin silicone membrane valve. The valve consisted of two lip-like membranes and an inner cavity. The inner cavity had the function of both a fluidic channel and a space for shape change of the elastic membrane under pressure. The valve material possesses the important characteristics of flexibility, deformability, compactness, and good life span, which allowed the valve to function effectively with large deformation. The operation principle of the valve is shown in **Figure 2B**. When the forward pressure (P1) was greater than the backward pressure (P2), the pressure difference caused the valve to open, which might enable urine to flow in an anterograde direction from the renal pelvis to the urinary bladder. When P2 was greater than P1 (filled bladder state), the valve was closed, so that retrograde urine flow might be prevented.

Ureteral drainage patency of common stent and anti-reflux stent

All experimental animals' surgeries were successfully completed. We evaluated the average drainage speed of the three groups by injecting normal saline through the renal pelvis fistula to maintain two different pressures (**Table 1**; **Figure 3**). The difference of average drainage velocity between group A and C was statistically significant ($P<0.05$). There was significant difference between the group B and C in the average drainage velocity ($P<0.05$). On the contrary, there was no significant difference between the group A and B ($P>0.05$). These data indicated that the two stents had no difference and performed much better than that without a stent in drainage patency.

Anti-reflux property of common stent and anti-reflux stent

No upper urinary tract reflux was found in the VUR examinations at baseline. However, the anti-reflux stent inserted in the urinary tract of group B effectively prevented VUR compared with conventional stents without obviously urinary obstruction in the animals. A statistically significant difference was observed in VUR findings between groups A and B ($P=0.002$) (**Table 2**). What's more, to compare renal pelvic pressure during spontaneous urination, the pressure with anti-reflux stent was much lower than that of common stent ($P<0.001$) (**Table 3**), and

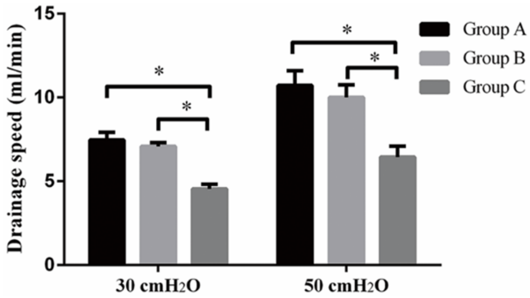

Figure 3. Average drainage speed with different stent or without stent under 30 or 50 cm (*, $P<0.05$, *t*-test).

Table 2. The effect of anti-reflux property between two stents

Group	Positive (n)	Negative (n)	Total (n)	Effective rate (%)
A	0	6	6	0
B	6	0	6	100

Table 3. Comparison of renal pelvic pressure during Spontaneous urination

Group	Cases (n)	Pressure (mmHg)
A	6	16.67±1.63
B	6	8.17±0.75
C	12	7.08±0.90
p value	Group A and B	<0.001
p value	Group B and C	0.022

these results suggested that the anti-reflux stent had effective anti-reflux property.

Discussion

After nearly 40 years of development, the Ureteral stent has become one of the most widely used therapeutic instruments in urology. Its purpose is to relieve upper urinary tract obstruction, maintain upper urinary tract patency, prevent UTI and promote urinary tract injury healing, prevent ureteral strictures caused by various reasons [6, 9]. The most basic function of DJ tubes with good drainage patency (from the kidney to the urinary bladder drainage function), is to reduce hydronephrosis and protect renal. Usage of anti-reflux ureteral stents has long been reported, but not universally accepted by clinicians, the most important reason is that drainage functions are worse than ordinary ureteral stent tubes [10, 11]. A previous study by Soria *et al* designed an anti-reflux ureteral stent that dilates the upper urinary tract without affecting the ureterovesical junction and consequently reduces morbidity associated with DJ ureteral stents [11]. In the present study, an anti-reflux ureteral stent with a novel device was designed. Further anti-reflux performance testing indicated that anti-reflux effect of anti-reflux DJ tube was significantly better than that of the ordinary DJ tube ($P<0.05$) [11]. On the other hand, when we continuously injected saline into the bladder untill spontaneously urination, the pelvis pressure difference of group A and B was statistically significant ($P<0.05$), and pelvic pressure difference of group B and C was also statistically significant ($P<0.05$). Remarkably, the anti-reflux DJ tube was significantly better than the ordinary DJ tube in anti-reflux property. However, increasing pelvic pressure could also be seen when the experimental animals urinary tract was inserted with an anti-reflux ureter stent, compared with being stent-free.

Ureteral reflux can produce long-term sequelae, vesicoureteral reflux can cause urinary tract infections, bladder pain, repeated fever and other clinical symptoms, have the possibility of causing pyelonephritis, and other diseases. When the bladder is filling or contracting, bladder pressure exceeds the pressure within the ureter, but the urine does not flow back into the ureter, mainly because the ureteral bladder valve prevents urine reflux [12]. The proposed anti-reflux ureteral stent was designed and fabricated to potentially reduce side effects such as flank pain and urinary tract infection that occur because of the retrograde urine flow caused by the conventional DJ stent. Several groups have previously developed anti-reflux ureteral stents to solve these problems [13, 14]. Yamaguchi [14] designed an anti-reflux ureteral stent by adding a thin silicon sleeve at its distal end, which acted as an anti-reflux valve in 1992. Later in 2012, Ritter [13] designed a different type of anti-reflex ureteral stent with a long, thin, and uncurled distal end. The distal end of this stent acted as an anti-reflux valve. In 2015, Park [15] designed an anti-reflex ureteral stent combined with 7F Double-J (DJ) stent and a polymeric flap valve and fabricated using a 3D printer, which effectively prevented backward flow while minimizing reduction in forward flow *in vitro*. These newly designed stents, however, are not yet widely used clinically.

For practical use of the anti-reflex ureteral stents clinically, maintaining the original form of the ureteral stent is thought to be important [15]. If the newly designed anti-reflex ureteral stents have any changes in size, such as being larger or longer in any part, it may have side effects such as difficulties in stent insertion, more severe stent-related symptoms, and mucosal injuries of the lower urinary tract [16, 17]. Our newly designed anti-reflux stent had no changes in size, so it would avoid additional stent-related symptoms. The anti-reflux device was made of more than one lip-like valve by elastic thin silicone membrane which was more easily manufactured than others, such as *Chang-Ju Park's* valve made by 3D printer [15]. The membrane valve was made of silicone, which is a rubber-like material that has high elasticity, and therefore the stent has a high potential to return to its initial shape.

In the bladder trigone, a ureter with a certain angle of inclination is needed to go into the bladder. When inserting a common DJ tube, the ureter orifice at the upper and lower lip cannot be closed. When the bladder fills or during urination, the bladder pressure increases, and the urine will flow from the higher pressure of the bladder up to the lower pressure of the renal pelvis. There for an anti-reflux ureteral stent with the elastic thin silicone membrane acting as a one-way valve is needed. When the bladder pressure increases, the valve is compressed and closed, which can effectively prevent the urine flow going back to the renal pelvis. Despite the increased intra-pelvic pressure after the anti-reflux ureteral stent placement, no anti-reflux ureteral stent tubing was found to allow methylene blue fluid come back from the bladder during anti-reflux testing. We speculate that when the experimental animals urinate, the pressure measured inside the pelvis comes from the conduction of abdominal pressure, in addition to urinary reflux. Of course, the anti-reflux ureteral stent may still have mild VUR, only because the reflux is minimal and urine in the bladder does not flow back to the renal pelvis.

Although the pressure in the renal pelvis was higher than that in the non-stent area when the animal had the anti-reflux ureteral stent independently, it did not flow back to the renal pelvis. Due to the existence of the stent tube, the anatomy of the junction has many changes, including forced ureteral wall segment expansion, which may cause ureteral congestion and edema, and decreased compliance. The ureteral upper lip is pulled by the end of the double J tube causing a gap between the stent tube and the ureter, lacking the ureter Oral lip protection, where the bladder ureter junction is still expanding [18]. When the experimental animals urinate, the bladder pressure increases, the bladder fluid will enter the ureter from the gap between the ureter and stent junction, resulting in renal pelvis pressure greater than the stent-free state. The average renal pelvis pressure placed the anti-reflux ureteral stent was 8.17±0.75 mmHg, slightly higher than the 7.08±0.90 mmHg without stent, but significantly lower than the 16.67±1.63 mmHg placed the common ureteral stent, so we think although the placement of anti-reflux ureteral stent may still have mild VUR, but compared with ordinary ureteral stent, anti-reflux effect was significantly better than the latter.

Due to the smaller inner diameter of the DJ tube, it is mainly the peritubular drainage after indwelling the stent tube, rather than drainage through the lumen that is flowing [19]. At present, it has not been reported whether the VUR caused by ureteral stent is mainly refluxed from the tube or from the outside space of the tube. This anti-reflux stent tube is designed for the reflux through lumen. When the experimental animal urinates, the renal pelvic fistula tube has no liquid outflow that was applied to the anti-retrograde stent, and the average renal pelvis pressure was 8.17±0.75 mmHg. According to VUR grading standards, the VUR grade was grade I, considering the fluid back was in the lower ureter only. In the conventional ureteral stent group, the renal pelvic fistula tube was visible for blue liquid outflow, and the average renal pelvis pressure was 16.67±1.63 mmHg. The VUR grade was grade II. Average pelvis pressure was statistically significant different between the two groups ($P<0.05$). Therefore, we hypothesized that the VUR with a DJ tube applied was mainly through the lumen of the stent.

Collectively, our data suggested that the average drainage velocity of ureteral stent and anti-reflux ureteral stent under different pressures had no significant difference ($P>0.05$), but the drainage velocity of both stent tubes is greater than that without stent and the difference was statistically significant ($P<0.05$). These data indicated that the drainage patency performance of our novel anti-reflux ureteral stent tube was the same as the clinically used DJ tube. With the most basic and remarkable drainage function, the anti-reflux stent is worth further and extensive study. The anti-reflux ureteral stent is expected to benefit patients who need long-term placement of ureteral stents. These patients may probably suffer from repeated VUR in the presence of a conventional DJ stent. The proposed stent may also reduce the negative effects, such as micturition-caused flank pain and acute pyelonephritis from transient VUR compared with those with conventional DJ stents inserted. This animal experimental study confirmed that this anti-reflux ureteral stent has better anti-reflux performance than the traditional ureteral stent and also has the same effect as the ordinary ureteral stent in drainage patency. At the same time, we hypothesize that the VUR appearing in the DJ tube is mainly through the lumen reflux, but this still needs to be further confirmed by clinical trials. What's more, for clinical application, strict clinical studies should be conducted in the near future to assess the function and potential of the new designed stent.

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Disclosure of conflict of interest

None.

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