

COMPLICATIONS OF ENDOSCOPIC TREATMENT WITH VANTRIS IN PRIMARY VESICoureTERAL REFLUX IN CHILDHOOD

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Abstract: Introduction: VUR constitutes 20% of the causes of chronic kidney disease in childhood Objective: to determine the complications of endoscopic treatment of primary VUR with the use of Vantris. Material and methods: A descriptive, retrospective study was carried out in 263 patients with a diagnosis of primary VUR who received endoscopic treatment with Vantris, at the Centro Habana Pediatric Hospital, between January 2011 and December 2020. Results: Female gender and females predominated. ages 5 to 9 years, the average age was 6.12 years. 52.47% of patients presented bilateral VUR. In total, 401 ureteral meatuses were injected, VUR grades III (34.16%) and IV (31.42%) predominated, 11.40% of the sample presented a complete double excretory system. Conclusions: The endoscopic treatment of VUR With the use of Vantris it is associated with few complications, the most frequent being minor. Late ureteral obstruction is the most serious complication.

Keywords: Vesicoureteral reflux, Endoscopic Treatment, Vantris

INTRODUCTION

Vesicoureteral reflux (VUR) is defined as the retrograde passage of urine from the bladder to the upper urinary tract. It is caused by a failure of the valve mechanism that normally exists at the level of the ureterovesical junction. This failure may be primary due to the existence of a congenital malformation of the trigonal area or secondary to other functional or anatomical anomalies of the lower urinary tract such as voiding dysfunctions. neurogenic or not, posterior urethral valves, ureteroceles, paraureteral diverticula, ureteral ectopia among others 1, 2,3.

The exact prevalence of VUR is unknown, it is considered that one third of patients treated for urinary tract infection(UTI) are carriers of VUR. UTI occurs in between 5 and 10% of all

children, in 20% of them the infection recurs, VUR is considered a predisposing factor for recurrence¹. In Cuba this condition has an incidence of 1% in healthy children and 30 to 50% in children with UTI⁴.

The association between VUR has been clearly established. As a consequence of the combination of hyperpressure on the kidney and urinary infection, pyelonephritic changes occur capable of causing kidney failure and hypertension; the kidney damage caused is known as scarring nephropathy. VUR constitutes 20% of the causes of chronic kidney disease in childhood^{1, 4, 5}.

The diagnosis of VUR is essentially made through imaging studies. Ultrasound of the urinary tract is the first-line study in children with recurrent UTI; Dilation of the excretory system is an ultrasonographic sign of VUR. These dilations are not always present, they vary depending on the degree of reflux and can be modified with bladder emptying. Ultrasonographic signs of VUR can be evident even from the prenatal stage. Radiological voiding urethrocytography is the method of choice for the definitive diagnosis of VUR, since it allows visualization of the anatomy of the urinary tract and establishes the degree of severity of VUR. Static radioisotope studies make it possible to determine the existence of renal scars and establish relative renal function, which makes it possible to evaluate the degree of renal damage associated with VUR^{5,6}.

Currently there are three therapeutic options for VUR. The goals of treatment in children with VUR are to prevent febrile urinary tract infections, as well as the subsequent kidney damage they cause, and to minimize the morbidity of treatment². These therapies include medical or conservative treatment that is essentially based on general measures. and antimicrobial chemoprophylaxis to maintain sterile urine, endoscopic treatment that consists of the injection of bulking substances

with the aim of coapting the refluxing ureteral meatus, and surgical treatment that includes different techniques to correct the anomaly of the ureterovesical junction and create a longer submucosal tunnel. Each of these therapeutic options has its specific indication and depends fundamentally on the age of the patient, the degree of reflux, bilaterality, kidney damage, etc.^{1,6}.

Since its introduction and popularization in the 1980s by Matouschek (1981) and O'Donnell-Puri (1986), endoscopic treatment has been gaining acceptance by urologists treating VUR in children. The advantages it offers, typical of a minimally invasive procedure, as well as the high cure rates achieved with its application have made it an alternative to open surgery. It consists of the injection of a bulging substance into the refluxing ureteral meatus that lasts over time, is not antigenic, teratogenic, carcinogenic, does not migrate, and is easy to acquire and apply^{6,7}.

The first technique used, described by O'Donnell and Puri, was called STING and consists of submeatal injection. Later, a modification called HIT (hydrodistention implantation technique) was described, which requires distension of the ureter through irrigation fluid⁸.

There have been several agents used for the endoscopic correction of VUR. These materials can be classified as particulate or degradable and autologous or non-autologous. The concern in particulate agents is migration and in degradable agents it is durability. Among the agents most used internationally are Deflux, Macroplastine and more recently Vantris. Bovine collagen was used, but in addition to presenting some allergy problems, it was found that its volume decreased to only 15% after two years, which is why it fell into disuse. The use of autologous substances such as fat and cartilage (chondrocyte) was also attempted with various results, none of them good enough^{8, 9, 10}.

Complications associated with endoscopic treatment of VUR develop in less than 10% of treated cases and appear even when the procedure has been performed by expert surgeons. The most reported in the international literature are febrile urinary infection, hematuria and transient hydronephrosis. These complications are mostly resolved with medical or conservative treatment and do not leave long-term sequelae. The most feared complication is persistent ureterovesical junction obstruction since it evolves with deterioration of renal function and in most cases requires ureteral reimplantation; it can affect 2% of patients 4, 8, 9, 10,11.

The present investigation was carried out with the objective of determining the complications of endoscopic treatment with Vantris for primary vesicoureteral reflux in childhood.

MATERIAL AND METHODS

A descriptive, retrospective study was carried out in 263 pediatric patients with a diagnosis of primary VUR who received endoscopic treatment with Vantris, at the Centro Habana Pediatric Hospital, between January 2011 and December 2020.

A review of the medical records was carried out and a database was created in Microsoft Excel. The data were processed using SPSS version 23.0.

The variables studied were: age, gender, conditions or anomalies associated with VUR, degree and laterality of reflux, injection technique, complications, severity of complications (Clavien Dindo Classification) and treatment of complications.

To summarize all variables, absolute and relative frequencies (percentages) were used; in addition, mean and range were determined for age.

Work methodology: patients with suspected VUR underwent the following studies for confirmation: ultrasound of the urinary tract, voiding retrograde urethrocytography and renal scintigraphy (DMSA). In those who confirmed the diagnosis of primary VUR with an indication for endoscopic treatment, the following were performed as part of the preoperative check-up: blood count, erythrocyte sedimentation rate, coagulogram, group and factor, nitrogen and urine culture. The patients were admitted on the same day of surgery and received perioperative prophylaxis with cefazolin at a rate of 40 mg/kg/dose. In all cases the bulking substance used was Vantris. No patient had a urethral catheter left and all procedures were outpatients. After treatment, they were evaluated in the outpatient clinic after one month and then every 3 months during the first year. In the second year, the follow-up in the clinic was every 6 months depending on the individual evolution. Follow-up was performed with urine culture and ultrasound of the urinary tract.

Antimicrobial prophylaxis was continued until three months after surgery. Evolutionary urethrocytography was only performed in patients who presented urinary infection or presence of dilation of the excretory system in the evolutionary ultrasounds.

RESULTS

The female gender predominated (57.79%) and the group of patients from 5 to 9 years old (42.20%), the average age was 6.12 years, with a range of 10 months to 18 years.

Age (years)	Gender					
	Female		Male		Total	
	Number	%	Number	%	Number	%
<5	62	23.57	45	17.11	107	40.68
5 - 9	57	21.67	54	20.53	111	42.20
10 - 14	32	12.16	11	4.18	43	16.34
15 - 18	1	0.38	1	0.38	2	0.76
Total	152	57.79	111	42.20	263	100

Table 1: Distribution according to age and gender.

Source: Clinical History

A total of 19.01% of the patients had some condition or anomaly associated with VUR, the complete double excretory system was the one that predominated, observed in 11.40% of the sample. Only 5.70% of cases presented scarring nephropathy. VUR grades III (34.16%) and IV (31.42%) predominated. 52.47% of patients presented bilateral VUR, the behavior of unilateral VUR on both sides was similar. In total, 401 ureteral meatuses were injected.

The most used injection technique was STING (71.10%). The HIT technique was used in patients with high-grade VUR.

Conditions associated with reflux	Number	%
Scarring nephropathy	15	5.70
Complete double excretory system	30	11.40
Horseshoe kidney	2	0.76
Renal ectopia	3	1.14
Reflux degree n=401		
Grade I	18	4.48
Grade II	104	25.93
Grade III	137	34.16
Grade IV	126	31.42
Grade V	16	3.99
Laterality		
Right	60	22.81
Left	65	24.71
Bilateral	138	52.47

Table 2. Distribution according to characteristics of VUR and associated conditions.

Source: Clinical History

A total of 10.26% of cases presented complications, urinary infection was the most frequent (6.46%) followed by late ureteral obstruction (2.28%). Most complications were resolved with medical treatment (77.77%). Of the six patients who presented late ureteral obstruction, in four of them the diagnosis was made one year after surgery and in two it was made after two years of treatment. Two patients underwent dilation of the ureteral meatus and catheter placement. JJ for 3 months, evolving favorably after its removal, the remaining four patients required surgical treatment (ureteral reimplantation), significant ureteral fibrosis being noted during surgery.

Regarding the severity of the complications according to the Clavien Dindo classification, minor complications (Grades I and II) predominated (77.77%), 14.81% of the patients presented Grade I complications that corresponded to the cases hematuria and transient hydronephrosis. 62.96% of the complications were Grade II, corresponding to cases that presented febrile urinary infection that required the use of parenteral antibiotics. Only 22.22% of the complications were Grade IIIB, which corresponded to cases of late ureteral obstruction that required endoscopic and/or surgical treatment with the use of general anesthesia.

DISCUSSION

Endoscopic treatment of VUR has revolutionized the management of this disease in recent decades. There is evidence on the association between febrile urinary infections in childhood, the formation of kidney scars and its evolution to chronic kidney damage (scarring nephropathy). Several authors consider endoscopic treatment a valid alternative to daily antimicrobial prophylaxis and surgical treatment, with the aim of avoiding febrile urinary tract infections in pediatric patients with VUR 8,12.

Complications	Number	%	Treatment of complications n=27					
			Doctor		Endoscopic		Surgical	
			Number	%	Number	%	Number	%
Hematuria	3	1.14	3	11.11	-	-	-	-
Transient hydronephrosis	1	0.38	1	3.70	-	-	-	-
Late ureterovesical obstruction	6	2.28	-	-	2	7.40	4	14.81
Total	27	10.26	21	77.77	2	7.40	4	14.81

Table 3: Distribution according to complications and their treatment.

Source: Clinical History

The incidence of urinary tract infection in childhood varies between genders, affecting 1 to 2% of boys and can increase up to 5% in girls. It is suggested that 25 to 70% of infants who suffer from recurrent febrile urinary tract infections are carriers of VUR 4, 8.

In most of the studies found in the international literature on endoscopic treatment of VUR, a predominance of the female gender is reported, which coincides with the results of the present investigation: 13, 14, 15, 16, 17, 18, 19, 20 and 21.

In relation to the age of patients undergoing endoscopic treatment of VUR, a predominance of mean age that ranges between 3 and 6.7 years is generally observed 11, 14, 15, 16, 17, 19, 20, 21. Results Similar results were obtained in this research.

In a systematic review on factors conditioning the success and failure of endoscopic treatment, which included 14 studies, it was observed that younger age at the time of endoscopic treatment constitutes a factor conditioning failure 11.

In the same study, when analyzing anomalies or conditions associated with VUR, several authors observed that the double excretory system is associated with less success in the endoscopic treatment of VUR, some with a statistically significant relationship and others not. They also conclude that the presence of previous kidney damage confirmed in the presurgical scintigraphy is associated with a poor response to endoscopic treatment.

Another condition found was lower urinary tract dysfunction, which acted as a predictor of failure 11.

There is little research that studies the conditions or anomalies associated with VUR. Pérez Cortaya et al 14 found 37% associated anomalies, which include ureteral duplication, ectopic ureter and ureterocele. These results correspond in part to those of the present investigation, although the percentage of conditions associated with VUR found was lower. Only patients with primary VUR were studied, so lower urinary tract dysfunction was considered an exclusion criterion in this investigation.

One of the most studied variables in the international literature is the degree of VUR and its relationship with the success of endoscopic treatment. The Food and Drugs Administration (FDA) has approved the endoscopic treatment of VUR in patients with grade II-III and IV, but there is still not enough scientific evidence for its use in patients with grade V VUR. According to the Guidelines of the European Association of Urology, endoscopic treatment of VUR has similar indications to open surgery, children from 1 to 5 years of age with grade III to V VUR 8.

Several studies demonstrate that the degree of VUR is inversely proportional to the success of endoscopic treatment. Some authors do not include grade V because it is considered a tributary of open surgery 11.

Some authors report a predominance of high grade reflux (III –V) 14. In other studies, grades II and III predominated 11, 17, 18. Similar results were obtained in this investigation where a predominance of grade III VUR is evident.

In a study on predictive factors of ureteral obstruction after endoscopic treatment of VUR, univariate analysis revealed that Grade V VUR was one of the significant independent risk factors leading to obstruction²².

Regarding the laterality of reflux, several authors report a predominance of bilateral VUR in patients undergoing endoscopic treatment; the results of the present investigation correspond with those of these authors 13, 14, 16, 18, 19. Others report a predominance of unilateral VUR 17, 23.

The first endoscopic injection technique described by O'Donnel and Puri was STING (subureteric teflon injection) and a modification of it called HIT (hydrodistention implantation technique) was later introduced. These techniques have been combined and modified giving rise to four techniques; STING, HIT, double HIT and combined STING/HIT 8.

Several authors only used the classic STING technique 13, 14, 16. Although others used several techniques interchangeably 24. These results correspond to those of this research, however, a greater use of the STING technique was observed.

García M et al 11 observed in a systematic review on factors determining the success and failure of endoscopic treatment, that in most studies they use only one technique, but some authors perform combinations of all of them. They also found that none of the studies reviewed identified the injection technique as a predictor of success or failure of endoscopic treatment.

Complications of endoscopic treatment of VUR occur in less than 10% of patients; most of them are minor and temporary complications that do not leave long-term sequelae. Among those reported in the international literature are urinary infection that can reach a 6%, transient hydronephrosis, transient hematuria and bladder edema. Epididymitis and calcification of the injected material, as well as local migration of the injected material, have also been reported. The most serious and feared complication is late or persistent ureterovesical obstruction that can occur in up to 2% of patients, requiring in some cases endourological treatment and/or mostly ureteral reimplantation, with the aim of preventing irreversible kidney damage that causes sustained obstruction 8,12.

Ureterovesical obstruction associated with early-onset endoscopic treatment of VUR is reported, which appears during the first postoperative days, disappears spontaneously and without the need for urological instrumentation. Late-onset obstruction is also described, these are the most feared, they appear 3 months to 1 year or more after surgery, it can evolve asymptotically and be diagnosed as an ultrasonographic finding of hydronephrosis in the postoperative follow-up, or present with pain lumbar and recurrent urinary infections 21.

Several authors have studied the complications of endoscopic treatment of VUR with the use of Vantris; they all agree that the most common complications are urinary infection and late ureteral obstruction. In most cases they require surgical treatment (ureteral reimplantation), although others are solved with the placement of ureteral catheters 16, 17, 19, 20. Similar results were obtained in the present investigation.

Other studies compare the results of endoscopic treatment of VUR with the use of different bulking agents, most of which report a

higher rate of ureterovesical obstruction with the use of Vantris, although this increase has not been shown to be statistically significant. However, long-term follow-up of these patients is suggested to identify asymptomatic or late obstructions that can lead to deterioration of the compromised renal unit 22, 23, 24.

In the international literature reviewed, no research was found that studies the severity of complications of endoscopic treatment of VUR according to the Clavien Dindo classification.

CONCLUSIONS

Endoscopic treatment of primary VUR in childhood with the use of Vantris is associated with few complications, the most frequent being minor ones and resolved with medical or conservative treatment. Late ureteral obstruction is the most serious complication; in these cases, surgical and/or endoscopic treatment is required. Long-term follow-up of patients is important for timely diagnosis and adequate treatment with the aim of avoiding irreversible kidney damage caused by sustained ureteral obstruction.

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