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POLYACRYLATE POLYALCOHOL COPOLYMER (VANTRIS®) AS AN OPTION FOR MINIMALLY INVASIVE MANAGEMENT OF VESICOURETERAL REFLUX: OUR EXPERIENCE

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Minimally invasive treatment of vesicoureteral reflux (VUR) has gained popularity in recent decades for numerous advantages of the procedure itself: easy to perform, short inpatient care time compared to open techniques, a rare occurrence of serious complications, and short duration of stay in hospital. There are two groups of injectable tissue augmentation agents: biodegradable and non-biodegradable. Vantris® is a combination of two groups.

The aim of the study was to determine the effectiveness of Vantris® as an option in the minimally invasive treatment of VUR.

We conducted a prospective study for a period of five years (2015–2019). A total of 24 patients, or 39 renal reflux units (RRJ) were treated with Vantris®.

Reflux was unilateral in 9 patients (37.5%), and bilateral in 15 patients (62.5%). Reflux grade was V in two ureters (5.12%), IV in 6 ureters (15.38%), III in 22 (56.42%), II in three (7.69%) and I in 6 (15.38%). Median follow-up was 12 months and included urinalysis, urinary tract ultrasound, and voiding cystoureterography at one year. Reflux was eliminated in 36 ureters (92.31%). Two patients developed ureterovesical junction obstruction, while one patient required another injection treatment.

Vantris® can be used to treat VUR successfully and with a low percentage of complications. The application is simple, the rate of complications is reduced to a minimum, and therefore it could become the treatment of choice for the treatment of VUR.

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Key words: *vesicoureteral reflux, children, Vantris®*

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Introduction

Vesicoureteral reflux (VUR) is a condition described even in the early beginnings of pediatric urology. It was reported back in 1893 by Pozzi. It is the retrograde flow of urine from the urinary bladder to the upper urinary tract, caused by abnormalities of the vesicoureteral junction, in the case of primary VUR. There is also secondary VUR, occurring as a consequence of an increased intravesical pressure which can result from numerous causes. It is more common in white children, predominantly boys up to the age of one year, but after the age of 1, it is more frequent in girls. Available literature data show the incidence of 0.4–1.8% in patients without urinary tract infection and 10–40% in patients with urinary tract infection (1).

Although the spontaneous resolution rate is almost 100% for grades I and II, and 20–60% for grades III–V, surgical and endoscopic management of VUR remains the treatment option in clearly defined cases: breakthrough while on antibiotic prophylaxis and recurrent urinary infection, the presence or *de novo* development of renal scarring, and persistent reflux (2).

The concept of endoscopic treatment of VUR has many advantages such as easy to perform, short duration, minimally invasive procedure, rare occurrence of serious complications, no visible scarring, low treatment cost, and short hospitalization (3). Rare complications include vesicoureteral junction obstruction and the development of contralateral reflux. The success rate of endoscopic management of VUR is defined as reflux grade reduction or complete reflux resolution.

Polyacrylate polyalcohol copolymer (PPC) (Vantris®, Promedon, Argentina) is a novel tissue-augmenting agent that is applied endoscopically.

The most significant indication of its use is the resolution of VUR.

Aim of the paper

This prospective study aimed to evaluate the Vantris efficacy in treating children with VUR.

Material and Methods

We conducted this prospective study for five years (2015–2019). The study included 24 patients with a total of 39 refluxing renal units (RRU). Apart from standard laboratory analyses (blood count, urinalysis, biochemical analyses), according to the European Society of Pediatric Urology (ESPU) Guidelines for the diagnosis of VUR, all the patients underwent ultrasound imaging and voiding cystourethrography (VCUG) to precisely determine the reflux grade. According to the American Urological Association (AUA), scintigraphy with 99m-dimercaptosuccinic acid (DMSA) is reserved for children with high reflux grade (III–V), those with high values of creatinine, and those with recurrent urinary tract infections. The study included only cases with primary VUR. All refluxing renal units (RRU) were treated with Vantris®. The study encompassed results following only one injection treatment and one-year follow-up period.

Results

Unilateral reflux was present in 9 patients (37.5%), and bilateral in 15 patients (62.5%) (Figure 1). In 19 RRU reflux was on the right side, in 20 RRU it was left-sided (Figure 2). Reflux was grade V in two RRU (5.12%), grade IV in 6 RRU (15.38%), grade III in 22 RRU (56.42%), grade II in three (7.69%), and grade I in 6 (15.39%) (Figure 3). Mean follow-up time was 12 months; the follow-up included urinalysis, and ultrasound of the kidneys and bladder. VCUG was performed only in cases of recurrent urinary infections.

Reflux was eliminated in 36 RRU (92.31%). Two patients developed vesicoureteral junction obstruction, and one patient required an additional injection treatment due to persistent VUR, nonetheless reflux grade decreased after administering one injection (Figure 4).

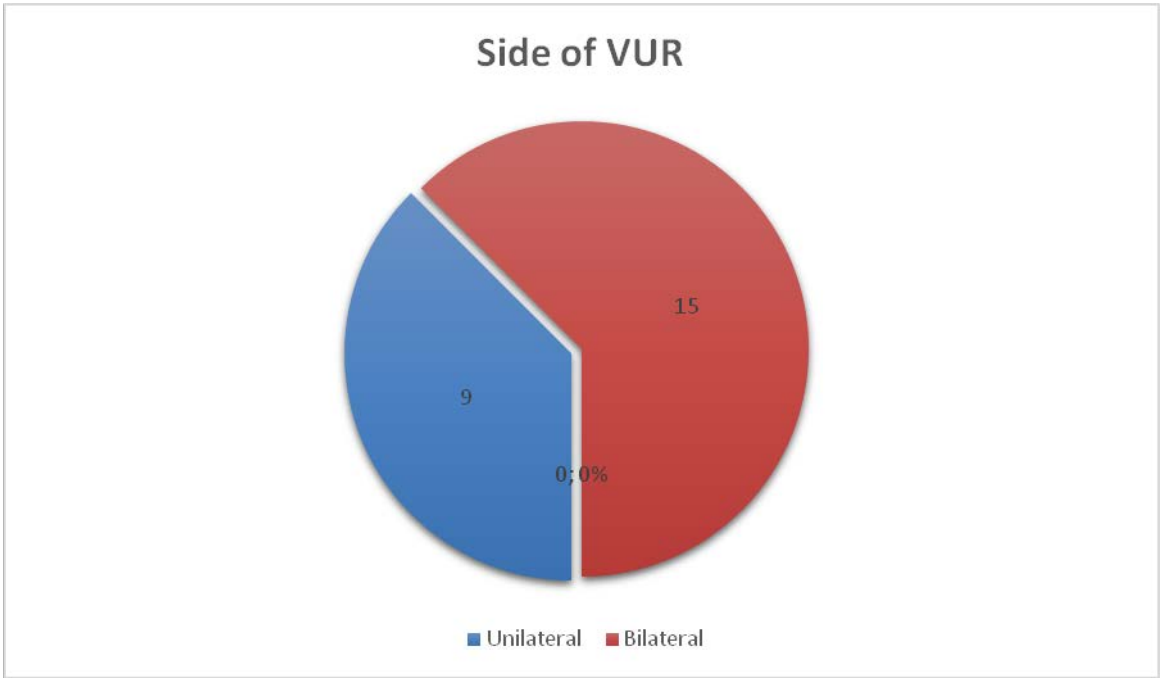
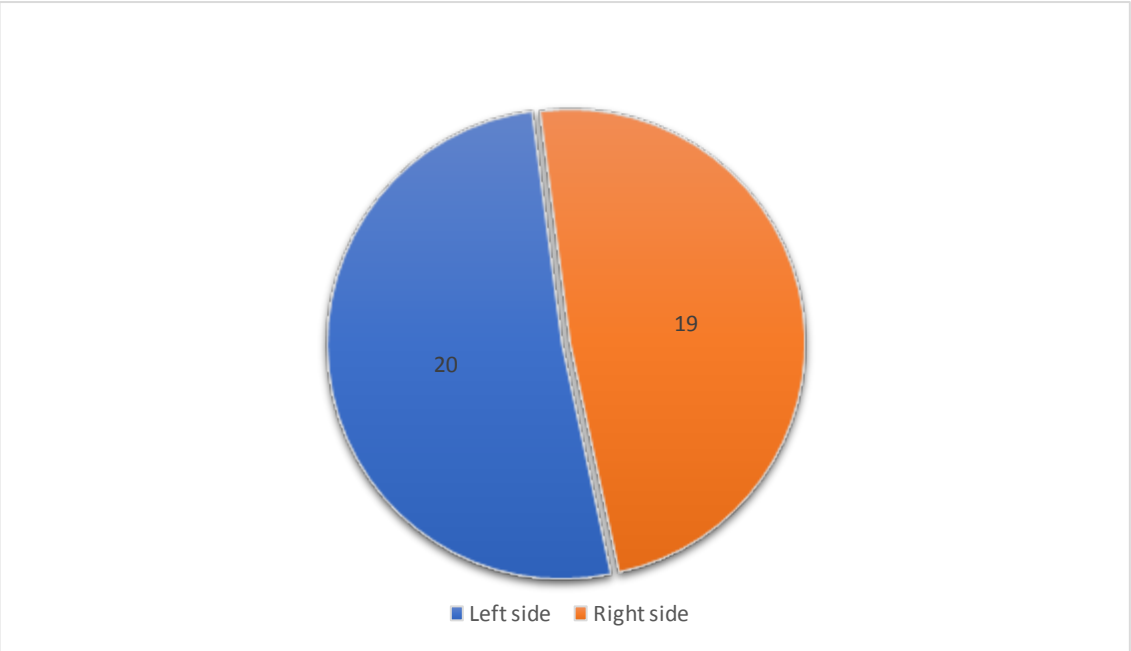


Figure 1. Distribution of VUR according to the side



Figures 2. Distribution of VUR according to the side

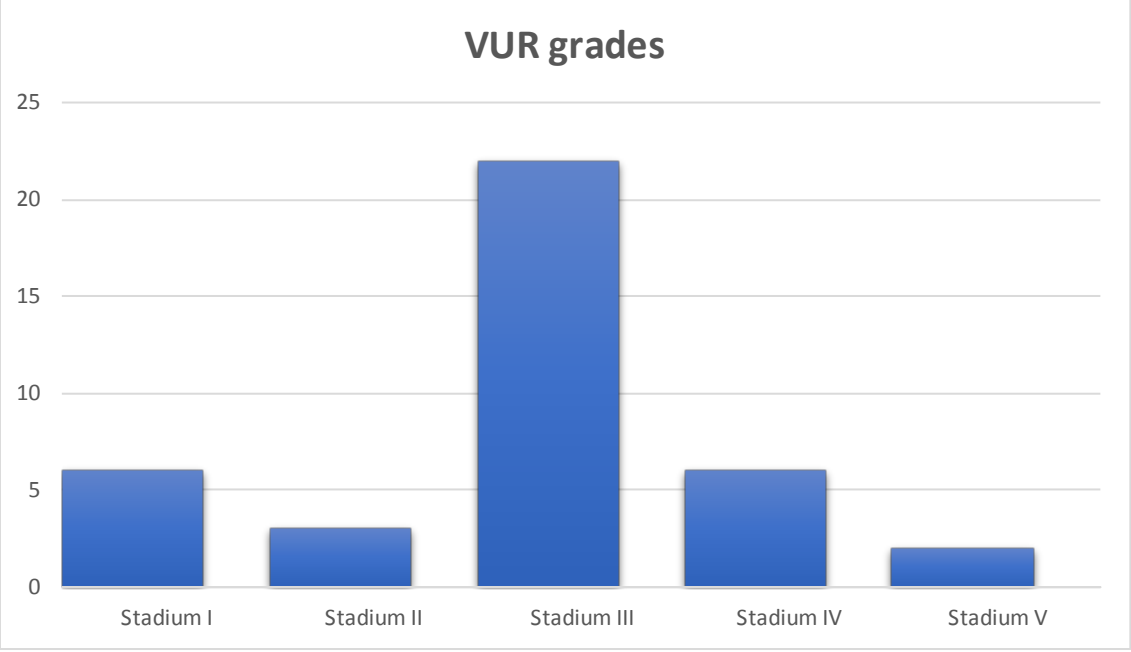


Figure 3. Distribution of patients according to the grade of reflux

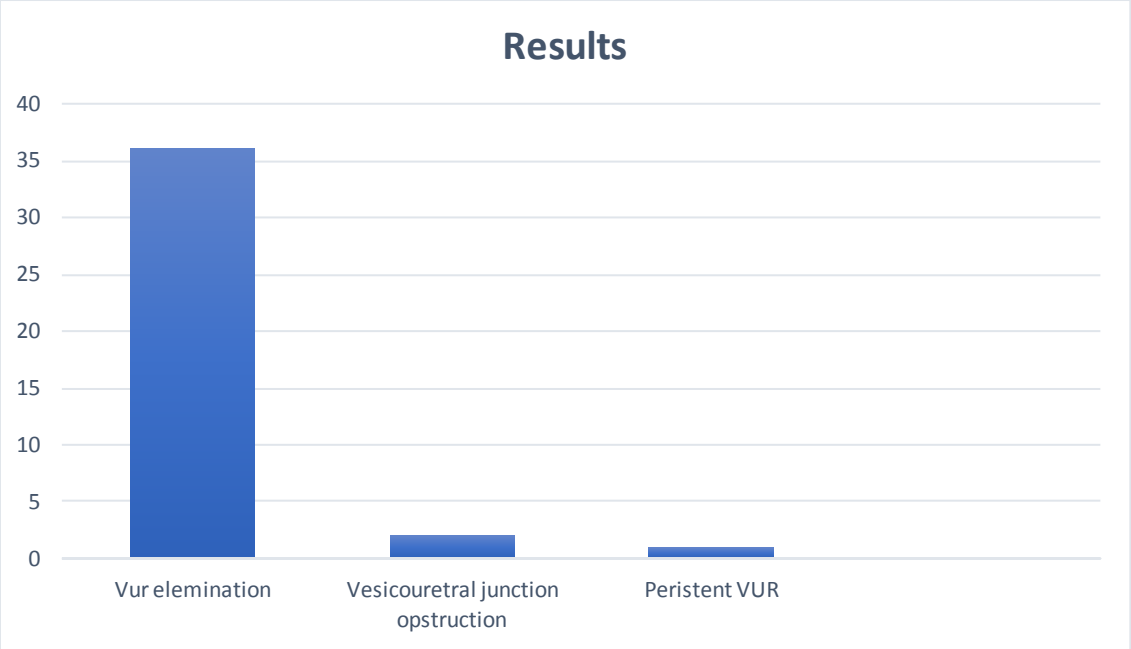


Figure 4. Results of Vantris® application in the treatment of VUR, our experiences

Discussion

According to International classification, there are V grades of VUR: grade I, reflux in lower third of the ureter only; grade II, reflux in the ureter and pyelon, without dilatation; grade III is characterised by mild dilatation/tortuous ureters and mild dilatation of pyelon; grade IV, moderate dilatation of the ureter, pyelon and calyces, but maintenance of papillary impressions in most calycles; and grade V, dilatation of the ureter, pyelon and calyces, gross tortuosity of the ureter, with loss of papillary impression (4).

The principal aim of VUR management is to preserve the renal parenchyma by preventing pyelonephritis and subsequent renal scarring. There are several options for treating VUR, watchful waiting, antibiotic prophylaxis, surgical treatment, and endoscopic procedures that, with advancements in minimally invasive procedures, pose the first line of treatment (5).

There are three surgical modalities in treating VUR: open or laparoscopic extravesical techniques, intravesical techniques, and endoscopic treatment. The introduction of the STING procedure in 1984 by O'Donnell and Puri was a huge advancement in minimally invasive treatment of vesicoureteral reflux, so that in recent years endoscopic management of VUR has become a treatment of choice for all reflux grades worldwide (6). A modified STING procedure, called the HIT (hydrodistension implantation technique) means hydrodistention of the ureter and submucosal injection into in distal ureter at the "6 o'clock position". A modified HIT procedure (double HIT) has also been introduced recently by using two injections, sub-ureteral and sub-mucosal, to coapt the ureteral orifice (7).

All the agents for endoscopic tissue augmentation are classified into two big groups: biodegradable and non-biodegradable (8). Biodegradable injectable agents have a high rate of reabsorption after a year, while non-biodegradable agents stimulate the formation of the fibrotic capsule, providing stability and long-term effects. Vantris® belongs to the latter group (a combination of both groups of injectable agents); it is composed of particles of polyacrylate polyalcohol copolymer immersed in a glycerol and physiological solution. When injected in tissues, the material remains stable throughout time (3). Injections are administered in ureteral submucosa; tissue augmentation occurs, that is, an elongation of the intramural parts of the ureters, thus providing an effective anti-reflux mechanism. The carriers of the active substance (glycerol and physiological solution) are eliminated by the reticular system through the kidneys, while the active substance remains *in situ*. We believe that the very non-biodegradable component of Vantris® and its stability through time has a favourable effect, having in mind the percentage of recurrences after endoscopic treatment with biodegradable agents such as dextranomer/hyaluronic acid copolymer (Deflux). Lee et al. reported in their retrospective study a

high recurrence rate of VUR after initial treatment with Deflux. The initial success of the treatment was similar to already reported results, with the postoperative success of 73%, while the recurrence rate in the first year was 26% (9).

Successful surgical treatment of VUR is defined as the complete elimination of reflux; however, a decrease in reflux grade is also considered as successful surgical treatment of VUR. In a meta-analysis of 5,527 patients, Elder et al. reported the success rate of first endoscopic treatment of 78.5% for VUR grades I and II, 72% in grade III, 63% in grade IV and 51% in grade V. The second treatment success rate after the first treatment failure was 68%, and the third treatment success rate was 34%. Considering all the cases, the success rate of endoscopic treatment of VUR was 85% (10). By comparing endoscopic and open surgical methods, literature data show that endoscopic treatment of reflux, which can prevent further urinary infections and renal scarring, may have equally good results as open surgical techniques (11, 12).

However, the question arises of the success rate in endoscopic treatment of high-grade reflux. In a retrospective study by Chung et al., out of a total 323 ureters, 234 were treated endoscopically, while 92 were treated by ureteral reimplantation. They reported that both methods were safe and effective in treating VUR, but with significantly higher success rate in surgical treatment of VUR grades IV and V, while, on the other hand, endoscopic treatment was characterized by shorter hospital stay and shorter recovery, so they believe that endoscopic treatment should be the first-line treatment for lower grade VUR, while surgical treatment should be reserved for more severe cases and after the failure of previous endoscopic treatment (13). Apart from being associated with treatment success rate, reflux grade is also associated with the onset of complications, and they more commonly occur in higher grade VUR—one of the complications that can occur after endoscopic treatment is vesicoureteral junction obstruction. In a large multicenter study enrolling a total of 611 patients and 6 centres worldwide, Kocherov et al. reported vesicoureteral junction obstruction of 1.2%, which is in accordance with our results. They believed that the cause of this complication occurrence is already present ureteral pathology, meaning that a certain number of their patients initially presented with already obstructed vesicoureteral reflux, and Vantris® application resolved reflux on one hand but exacerbated obstruction on the other hand. Ureter obstruction was resolved surgically. They reported a success rate for reflux after initial treatment with Vantris® of 94%, which is consistent with the results of our study, while 3.8% of patients required additional Vantris® application, which is also in agreement with our study. Patients indicated for additional Vantris® application had a more severe reflux grade (14).

The results of our study are also in accordance with the results of Dothan et al., with the overall success rate in correcting reflux utilizing Vantris® of 94.9%. Additional injections were required in 2.1% of patients, while 2.7% of patients developed ureterovesical junction obstruction (15). Also, a total of 83 patients underwent this treatment during a multicentre study in South America in the period 2006–2006. Reflux was eliminated in 88.6% of patients, and decreased to a lower degree in 6.8% of patients (1).

Our results with injection therapy of VUR using Vantris® are promising and are similar to results already published in the literature. Reflux was eliminated in 92.31% of units, but it should be pointed out that there were patients with associated anomalies of the urinary tract in the group of unsuccessfully treated patients.

This study has several limitations. All the cases were a single-centre experience, with a small sample size. Also, the SARS-CoV2 virus pandemic affected daily activities at our Institution, so the follow-up period was limited to one year, thus data on long-term results of reflux resolution by using Vantris® are lacking.

Conclusion

Utilization of polyacrylate polyalcohol copolymer (Vantris®), a tissue augmenting agent, is a simple method with a high success rate even after a single injection. The success rate depends on the severity of reflux, so the failure is mostly associated with high-grade reflux. The rate of complications after application is low, mostly in patients with already present ureteral pathology. For all aforementioned, Vantris® is one of the agents of choice for permanent resolution of VUR.

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POLIAKRILAT-POLIALKOHOL KOPOLIMER (VANTRIS®) KAO OPCIJA U MINIMALNO INVAZIVNOM ZBRINJAVANJU VEZIKOURETERALNOG REFLUKSA: NAŠE ISKUSTVO

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Minimalno invazivno zbrinjavanje vezikoureteralnog refluksa u poslednjim decenijama postalo je popularno, i to zbog brojnih prednosti same procedure, koju odlikuju jednostavno izvođenje, kraće vreme izvođenja nego kod otvorenih tehnika, retka pojava ozbiljnijih komplikacija, kao i skraćivanje boravka u bolnici. Postoje dve grupe injekcionih agenasa za augmentaciju tkiva: biorazgradivi i nebiorazgradivi. Vantris® (poliakrilat-polialkohol kopolimer) predstavlja kombinaciju ovih dveju grupa.

Cilj studije bilo je utvrđivanje efikasnosti kopolimera Vantris® kao opcije u minimalno invazivnom zbrinjavanju vezikoureteralnog refluksa (VUR).

Sproveli smo prospektivnu studiju koja je obuhvatila period od pet godina (2015–2019). Ukupno je 24 bolesnika, tj. 39 renalnih refluksivnih jedinica bilo tretirano koplimerom Vantris®

Refluks je bio jednostran kod devet bolesnika (37,5%), a obostran kod 15 bolesnika (62,5%). Stepen refluksa bio je V kod dva uretera (5,12%), IV kod šest uretera (15,38%), III kod 22 uretera (56,42%), II kod tri uretera (7,69%) i I kod šest uretera (15,38%). Srednje vreme praćenja iznosilo je 12 meseci i uključivalo je pregled urina, ultrazvučni pregled urinarnog trakta i mikcionu cistouretrografiju nakon godinu dana. Refluks je eliminisan u 36 uretera (92,31%). Kod dvoje bolesnika razvila se opstrukcija vezikoureteralnog spoja. Kod jednog bolesnika bio je potreban dodatni injekcioni tretman.

Vantris® se za tretiranje VUR-a može koristiti uspešno i sa malim procentom komplikacija. Budući da je primena jednostavna, a stopa komplikacija svedena na minimum, mogao bi postati tretman izbora za lečenje VUR-a.

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***Ključne reči**: vezikoureteralni refluks, deca, Vantris®*