

Evaluation of the VANRIS Injection Success Rate in Vesicoureteral Reflux (VUR) Treatment in Children

Helina Janpanah¹, Mohsen Mohammad Rahimi², Ahmadali Nikibakhsh³, Rohollah Valizadeh⁴, Roya Zakeri⁵, *Mohammadreza Mohammadi Fallah⁶, Sanam Fakour⁷

¹Urology Resident, Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran. ²Kidney Transplant Fellowship, Kidney Transplant Division, Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran. ³Professor of Pediatric Nephrology, Nephrology and Kidney Transplant Research Center, Urmia University of Medical Sciences, Urmia, Iran. ⁴MSc Student of Epidemiology, Student Research Committee, Urmia University of Medical Sciences, Urmia, Iran. ⁵Pediatrics Specialist, Urmia University of Medical Sciences, Urmia, Iran. ⁶Professor of Kidney Transplant, Nephrology and Kidney Transplant Research Center, Urmia University of Medical Sciences, Urmia, Iran. ⁷Medicine Faculty and Student Research Committee, Urmia University of Medical Sciences, Urmia, Iran.

Abstract

Background: Vesicoureteral reflux (VUR) is a common condition among children. Although, subureteral injection is a minimally invasive new method for VUR treatment, ideal bulking agent in endoscopic treatment still remains controversial. We aimed to evaluate VANTRIS subureteral injection efficacy in VUR treatment in pediatric patients.

Materials and Methods: All patients who referred to Imam Khomeini hospital in Urmia-Iran, Urology ward with VUR diagnosis that had indications for open surgery, enrolled study (during Mar 2013 to Mar 2015). Prior to intervention, VUR severity, urinary tract infection (UTI) and subsequent complications determined using urine analysis and imaging. Subsequently, single injection of the VANTRIS performed for all patients and patients underwent six-month follow up including several clinical and paraclinical evaluations.

Results: 31 patients with VUR diagnosis participated; of 31 patients, 18 (58.06%) children with primary UTI who had surgery indication enrolled study; of 18 patients, seven patients (38.88%) were boy and eleven patients (61.12%) were girl with mean age of 6.88 ± 2.61 years, and out of 29 refluxing renal units (RRU), 13 (44.8%) were right and 16 (55.2%) were left kidney. In current study, patients divided to two subgroups regarding their age older than five or younger than five years old and there was no significant difference between the resolution rates following VANTRIS injection in two groups ($P > 0.05$). Eleven (38.88%) RRU detected in boy patients, nonetheless VUR resolved in all of them, postoperatively. On the other hand, of 18 RRU in female patients, complete VUR resolution observed in 16 kidneys (88.8%), but only 2 (11.11%) kidneys had incomplete, but significant VUR resolution, where no significant difference observed. The prevalence of reflux in patients with UTI was 30% and in patients without UTI was 17%.

Conclusion: The current study indicated that in all age groups of patients, the subureteral injection of the VANTRIS was an accurate and effective treatment modality for VUR.

Key Words: Children, Subureteral injection, VUR, VANTRIS, UTI.

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*Corresponding Author:

Mohammadreza Mohammadi Fallah, Professor of Kidney Transplant, Nephrology And Kidney Transplant Research Center, Urmia University of Medical Sciences, Urmia, Iran.

Email: Mohammadifallah44@gmail.com

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1- INTRODUCTION

Vesicoureteral reflux (VUR) is one of the most common hereditary urological anomalies in pediatric accounting for several complications including recurrent urinary tract infection (UTI), pyelonephritis, and renal scarring and end stage renal disease (1, 2). In 30 percent of the children who had referred with the febrile UTI, VUR was the underlying reasons however, only 17% of the children without UTI, had suffered VUR (3). Bowel and bladder dysfunction (BBD) in the setting of VUR results in a 56% risk of recurrent UTI vs. 25.4% in children with VUR only (4). Long standing untreated vesicoureteral reflux with renal tubular acidosis can leads to growth retardation and subsequently serious outcome (5).

There are three main treatment options for VUR in children including watch and wait, antibiotic therapy and surgical interventions (1, 2). Due to success rate of 95- 98%, ureteroneocystostomy is considered as the gold standard surgical approach for VUR treatment (3, 6). The overall success rate three months after a single injection is reported 71% (7). Off-label use of polyacrylamide hydrogel injection therapy for primarily low grade vesicoureteral reflux demonstrates that the technique and short-term success rates are comparable to the most popular bulking agent, dextranomer/hyaluronic acid (8).

Endoscopic subureteral Vantris injection is a simple, safe, and effective outpatient procedure for treating all grades of VUR (6). Further improvement on technique is described by O'Donnell and Puri in 1984 (1). During last decades, endoscopic subureteral injection of bulking agents for VUR treatment has been widely used by pediatric urologists, which includes submucosal injection of the some agents under ureteral opening in order to increase intramural thickness to prevent urine reflux to ureter. VUR diagnosed in early childhood has been found to resolve

spontaneously and safely in some patients after a period of observation on continuous antibiotic prophylaxis (CAP) (9). Although, in literature subureteral injection efficacy has been lower than open surgery, its simplicity, safety, less time consumption, and minimally invasiveness provides promising alternative to ureteroneocystostomy. Since 35 years ago, several bulking agents have been used to obtain optimal treatments goals. There are several characteristics for ideal bulking agent in order to subureteral inject such as, easy injection, sufficient durability and biocompatibility (1, 10).

The success rate with Dextranomer/hyaluronic acid copolymer (Deflux) ranges between 68% and 92% (only 50-70% after single injection). The reported possibility of reflux recurrence after successful Deflux treatment, and the need for repeated injection led to introduction of the new substance Vantris (11). Dextranomer/hyaluronic acid copolymer was the first bulking agent to receive Food and Drug administration approval to be used for grade II – IV VUR treatment in children (12, 13). Since that time, several other agents introduced to be used for subureteral injection, but different defects observed postoperatively such as substance migration to organs, lack of durability, local inflammation and immunogenicity (14, 15). Moreover, despite Deflux's rare antigenic reaction and high success rate, during long term follow up, recent studies demonstrated high VUR recurrence in patients underwent subureteral injection with Deflux (16).

In order to achieve ideal treatment, VANTRIS is the latest agent introduced to be effective in VUR subureteral injection therapy. VANTRIS is non-biodegradable agent of the acrylics with molecular weight of 320 μ m, which is composed of anionic microparticles of polyacrylate polyalcohol copolymers (PPC) (5, 10, 17). Its low

molecular weight makes particles unable to migrate through other organs. In addition, a fibrotic capsule formation around tissue following VANTRIS injection provides enhanced stability and longer performance. On the other hand, laboratory studies on VANTRIS described its non-cytotoxicity and non-mutagenicity. There are few studies on VANTRIS efficacy in endoscopic treatment of the VUR. In current study, we aimed to evaluate short-term results of the VANTRIS subureteral injection for VUR treatment.

2- MATERIALS AND METHODS

2-1. Study Design and Population

This research is an interventional prospective study that was conducted from March 2013 to March 2015. The study participants were 18 patients who were selected randomly in the Urmia city, North West of Iran. All patients referred with VUR diagnosis that had indications for open surgery, enrolled study. Prior to intervention, VUR severity, UTI and subsequent complications determined using urine analysis and imaging. Subsequently, single injection of the VANTRIS performed for all patients and patients underwent six-month follow up including several clinical and paraclinical evaluations.

2-2. Methods

From March 2013 to March 2015, a prospective study was carried out in a single center in Urmia, West Azerbaijan, and Iran. During this period, all children, who were older than 1 year-old and received prophylactic antibiotic, with primary VUR based on voiding cystourethrogram (VCUG), Dimercaptosuccinic acid (DMSA) scan or Direct radionuclide cystography (DRC) scan report, enrolled study. Prior to intervention, complete information about study process and probable complication

provided for the parents so that they could choose the current endoscopic intervention actively. Then all parents gave their written informed consent. This study approved by ethics committee of the research and innovation chancellor of the Urmia University of Medical Sciences.

Patients admitted to hospital in the operation day and subsequent to general anesthesia, using rigid cystoscope and 3.7 Fr injection catheter, patients underwent endoscopic subureteral VANTRIS injection by study supervisor who was experienced pediatric urologist. Patients discharged one day after the operation and parents informed to telephone contact in case of any emergent problem. During follow up period, patients underwent kidney and urinary tract ultrasonography, urine analysis and urine culture one week and one month after the intervention. In a three-month period between third to sixth months postoperative, patients underwent DRC scan in order to evaluate VUR resolution depend on the RRU and probable complications

2-3. Measuring tests

Actually we did not use any questionnaire, but we evaluated changes with observation in process after intervention.

2-4. Inclusion Criteria

All patients should have these inclusion criteria as follows: incomplete VUR resolution, new scar formation or recurrent UTI while antibiotic consumption, increased renal scarring, patient or parents' dissatisfaction, and upper grade VUR. The age ranges of patients were 13 months to 11 years old.

2-5. Exclusion Criteria

Our exclusion criteria include children less than one-year-old and patients with VUR secondary to other underlying diseases.

2-6. Ethical Considerations

This study was approved by the Ethics Committee of Urmia University of Medical Science (based on the second paragraph of hundred article dated 11/10/91) and objectives of the study were explained to all participants and all of them accepted to participate and were assured of the confidentiality of their individual information as well as the voluntary nature of participating in the study.

2-7. Data Analyses

All data were analyzed using SPSS version 18 Software (SPSS Inc. Chicago, IL). In order to express quantitative values, we used mean \pm standard deviation (SD). Comparison between groups was performed using student t-test and Chi-squared (X^2) test for paired data and results with $p < 0.05$ were considered as statistically significant.

3. RESULTS

In current study, 31 patients with VUR diagnosis participated. Of 31 patients, 18 (58.06%) children with primary UTI who had surgery indication enrolled study and 13 (41.93%) patients excluded. Out of 18 patients, seven patients (38.88%) were boy and eleven patients (61.12%) were girl. Mean age was 6.88 ± 2.61 , ranging from 13 months to 11 years old. Surgery indications for patients were as follows: 7 children (38.9%) for recurrent UTI, 4 children (22.2%) for increased renal scarring despite controlled UTI, 3 patients (16.7%) had persistent UTI till 9 years old, and 4 patients (22.2%) had higher grades of VUR. Of 18 patients, seven patients (38.88%) had unilateral VUR and eleven patients (61.12%) had bilateral VUR, therefore, 29 RRU observed during study that 11 (41.4%) and 18 (58.6%) detected in boy and girl patients, respectively.

Of 29 RRU, 13 (44.8%) were right kidneys and 16 (55.2%) were left kidney. During preoperative evaluations, 3 RRU (10.3%)

had Grade I hydronephrosis, however 26 RRU (89.7%) had no significant hydronephrosis. During first follow up session one month after surgery, Grade I hydronephrosis detected in 1 kidney (3.4%). In addition, postoperatively onset hydronephrosis reported in none of the patients. However, de novo reflux observed in contralateral kidney in one (5.55%) of the cases. Fifteen patients (83.3%) had urine analysis positive for UTI, preoperatively. Nonetheless, during first week post-operative none of the patients had positive urine analysis, whereas in first month and second months subsequent to surgery, only 1 patient (5.6%) had positive urine analysis for UTI. The urine analysis was negative for all patients during third, fourth and fifth months, but it was positive for UTI during sixth month in 2 patients (11.1%).

While urine culture examinations, preoperative tests were positive in 15 children (83.3%); however, during follow up period all patients had negative urine culture in first week and first month postoperative, same as results in third, fourth and fifth months. Adversely, results during second and sixth months were positive in one (5.6%) and two (11.1%) patients, respectively.

Preoperative and postoperative VUR severity obtained with due attention to VCUG and DRC scan reports listed in **Table.1**. During DMSA scan, mild cortical lesions reported in 6 kidneys (4 right side and 2 left side kidney), moderate cortical lesions in 3 kidneys (1 right side and 2 left side kidneys) and sever cortical lesions in 2 kidneys (1 left and 1 right side kidney). Recovery rate considering VUR severity is mentioned in **Table.2**. Using Chi square test, there were no significant correlation between VUR postoperative resolution and preoperative VUR severity ($P: 0.41$).

In current study, patients divided to two subgroups regarding their age whether were older than five or younger than five

years old. In patients aged younger than five years old, 7 RRU had (77.8%) complete resolution and 2 RRU (22.2%) had incomplete but significant resolution. In patients' group aged >5 years old, 20 RRU (100%) had complete resolution without any reflux report. However, Fischer exact test showed no significant difference between the resolution rates following VANTRIS injection in two groups (P= 0.56).

Eleven (38.88%) RRU detected in male patients, nonetheless VUR resolved in all of them (100%) postoperatively. On the other hand, of 18 (100%) RRU in female patients, complete VUR resolution observed in 16 RRU (88.8%), but only 2

(11.11%) RRU had incomplete, but significant VUR resolution. Using Fischer exact test, no significant difference observed between males and females in VUR resolution after VANTRIS injection (P= 0, 64).

Of 18 children, seven (38.88%) had unilateral VUR and 11 (61.11%) had bilateral VUR. VANTRIS injection provided complete resolution in all patients (100%) with unilateral VUR, however, 2 patients (18.1%) with bilateral VUR failed to have complete resolution. However, Fischer test showed no significant difference in treatment response between the groups (P= 0.59).

Table-1: Preoperative and postoperative VUR severity

| Reflux severity | Preoperative | Postoperative | P- value |
|-----------------|--------------|---------------|----------|
| Mild | 1 (3.4%) | 2 (6.9%) | 0.001 |
| Moderate | 16 (55.2%) | ·(%·) | |
| Severe | 12 (41.4%) | ·(%·) | |

Table 2: Recovery rate considering VUR severity

| Reflux severity | Successful | Un-successful | P- value |
|-----------------|------------|---------------|----------|
| Mild | 1 (100%) | ·(%·) | 0.41 |
| Moderate | 14 (87.5%) | 2 (12.5%) | |
| Severe | 12 (100%) | 0 | |

4- DISCUSSION

In current study, our results showed that endoscopic subureteral injection of the VANTRIS as a bulking agent for VUR treatment provides resolution rate of the 93.1%. In the other word, we demonstrated that during 6 months follow up, subureteral injection of the VANTRIS results in VUR correction and UTI prevention was as effective as the ureteroneocystostomy, which is considered as the gold standard treatment for VUR. In addition, there were no significant difference between patients' response to

treatment considering their ages, gender and unilateral or bilateral involvement of the kidneys. VUR is a common condition in pediatric urology, leads to serious complications including recurrent UTIs, renal damages and developmental injuries (1, 3). Although, spontaneous resolution occurs in approximately 15% of the patients, the median time of the spontaneous resolution has been reported to be 5 years, which in Grade III – IV VUR can take up to 8 years or more (5, 17). Therefore, in lower grades of the VUR, it is recommended to use

prophylactic antibiotic during observational therapy to prevent UTIs. According to some studies, pyelonephritis is more common in patients who received prophylactic antibiotics compared to patients underwent surgical therapy (1, 2).

Although, surgery is indicated in patients with breakthrough UTI and sever renal scarring, several complications occur in patients following open surgery including urinary tract obstruction and persistent reflux (2, 3). Minimally invasive endoscopic subureteral injection of the bulking agents for VUR treatment has been introduced as a competitive alternative for open surgery. Although, several studies reported lower success rate for subureteral injection comparing to open surgery, several benefits including short hospital stay, decreased operation time and lower postoperative complications made it popular intervention among pediatric urologists (10).

Since three decades ago that Deflux used for the first for subureteral injection, different bulking agents including polytetrafluoroethylene (PTFE), chondrocytes, polydimethylsiloxane (Macropastique), and silicone, have been tried to improve surgery results. However, due to several defects following these substances use in injection such as immunogenicity, local inflammation, granuloma formation, lack of durability and malignancies secondary to substances implantation, results did not meet the surgeons' expectations (14, 15).

Although, Deflux is widely accepted for subureteral injection treatment of the VUR and several reports has approved its efficacy worldwide, some studies showed Deflux short permanence during long term follow up, that leads to VUR recurrence in patients underwent endoscopic surgery (16). VANTRIS is a new bulking agent composed of polyacrylate polyalcohol polymers that has been used for several indications including treatment of the

gastroesophageal reflux disease (GERD), fecal incontinency, aesthetic surgeries and VUR and urine incontinency treatment (5, 10, 17). In a study by Ormaechea et al. VANTRIS, short term and long term local tissular reaction and localized migration following subureteral injection evaluated (10). Results showed that not only VANTRIS leads to high success rate, but also provides long durability and low localized migration. In a recent study by Corbetta et al. endoscopic Polyalcohol Copolymer (PPC) hydrogel injection provided a success rate of 92.3% among 117 reflux units during short term follow up (18). In current study, clinical presentations and resolution of the VUR evaluated following subureteral injection of the VANTRIS. Results showed success rate of 93.1%, which is in the range of the ideal success rate of 83-94%.

In another study by Ormaechea et al., results showed VUR resolution rate of 83.6% by VANTRIS injection, which had lower rate of success in comparison to previous study by the author (5). In current study we reported higher rate of success and lower incidence of the postoperative complications in VUR treatment by VANTRIS injection comparing to Ormaechea study(5), but we believe lower number of the patients and short term follow up are the underlying reasons for current results. Chertin et al. evaluated surgical outcomes in VUR patients following single VANTRIS injection during three months follow up and result showed higher level of the reflux resolution in study group (19).

In current study, we divided patients into two groups regarding their age (>5 and <5 years old). However, results showed 100% of the resolution in patients who had the age range similar to Chertin study (19). In addition, Ormaechea et al. (5) suggested that subureteral VANTRIS injection could be a good alternative for prophylactic antibiotic and observational therapy in

patients have few possibilities for spontaneous cure. Nonetheless, we compared VUR resolution between two groups of the study regarding their age, but there was no significant difference between injection success rate between patients who were younger than 5 years old and patients older than 5 years old. In addition, in present study we compared VUR resolution rate among girls and boys, that there was no significant difference between two groups.

On the other hand, considering the side of the involvement, there was no difference between VUR resolution rates between groups. Considering postoperative complications following VUR subureteral injection, Bae et al. (10) reported ureteral obstruction and a single case of de novo reflux in patients underwent endoscopic correction of the VUR by Deflux injection. In our study, authors demonstrated that although PPC provides better VUR resolution rate comparing to dextranomer/hyaluronic acid, it leads to higher incidence of the vesicoureteral junction obstruction (VUJO) (20). However, in our study, de novo reflux in a girl patient was the single complication report, we believe small study group and few patients' number leads to few rate of the complications incidence.

4-1. Limitations of the study

Our study was of some limitations. First, not many patients were referred by VUR diagnosis, therefore we had small study group. Second, we believe that multi-centric study can provide much more reliable results. Third, long term follow is needed to recognize any potential complications following VANTRIS injection. Forth, in future studies role VUR grade on VANTRIS injection success rate should be taken in to consideration. . There is still need to further studies to access additional information about evaluation of the VANTRIS injection success rate in

vesicoureteral reflux (VUR) treatment in children.

5- CONCLUSION

At current study, the subureteral injection of the VANTRIS was an accurate and effective treatment modality for VUR, with due attention to its high success rate and rare complications. In addition, patients can be candidate for VANTRIS injection without considering ages and gender.

6- AUTHORS CONTRIBUTIONS

- Study design: HJ, MMR, MMF.
- Data Collection and Analysis: RV, SF, AN.
- Manuscript Writing: R V, RZ.

7- CONFLICT OF INTEREST: None.

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