"Efficacy and Safety of Polyacrylate Polyalcohol Co-polymer (Vantris) Injection Material in the Endoscopic Treatment of VUR in Children: 3 Years of Prospective Follow Up "

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ABSTRACT:

BACKGROUND:

To evaluate the safety, efficacy and durability of Vantris injection over a period of 3 years.

PATIENTS AND METHOD:

From 2015 to 2018 we followed 40 patients {male 14, female 26} with a mean age of 4.2±3.4 years (mean ± SD) underwent endoscopic Vantris injection therapy for treatment of primary vesicoureteral prospectively by voiding cystourethrogram at 3months, 1 year and 3 years. Those 40 patients comprising 70 refluxing renal unit (RRU), were unilateral in 10 patients and bilateral in 30 patients. Those were grade II in 10 RRU, grade III in 35 RRU and grade IV in 25 RRU. The volume of injected Vantris material was 0.8ml (range 0.4-1.2 ml) per refluxing unit. The patients were followed. Ultrasound was used at 1 week, 1 month and yearly for 3 years.

RESULTS:

All patients completed 3 years follow up by voiding cystourethrogram. At 3months VCUG 1 was done and shows: 10/10 RRU of grade II, 32/35 RRU of grade III and 23/25 RRU of grade IV show complete resolution of reflux, Success rate is 92.85%. At 1year VCUG 2 was done and shows: 10/10 RRU of grade II, 32/32 of grade III and 21/23 of grade IV show complete resolution of reflux, Success rate is 96.92%. At 3years VCUG 3 was done and shows: 10/10 RRU of grade II, 32/32 of grade III and 21/21 of grade IV show complete resolution of reflux, Success rate is 100%. The overall success rate is 63/70 (90%).

CONCLUSION:

Endoscopic injection of Vantris material for treatment of vesicoureteral reflux in children is very effective, safe and durable, and can be considered as first line treatment of grade II -IV vesicoureteral reflux.

KEYWORD: Vantris, Injection therapy, VUR.

INTRODUCTION:

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder to the upper urinary tract. VUR is the most common abnormality of the urinary tract in the children, affecting 1% of all children [(1)].

Vesicoureteral reflux is believed to be present in 1% or less of normal children, although the incidence is likely to vary depending on the age of screening because VUR mostly resolved over time. Most cases of VUR are diagnosed after occurrence of urinary tract infection (UTI) [(2)]. In children with UTIs, the reported frequency of VUR varies from 20% to 40% [(3-5)]. More recent guidelines specifically for children under 2 years of age from the American Academy of Pediatrics(AAP) tighten the recommendation for voiding cystography to follow a second rather than the initial febrile UTI, with infection based on stricter culture criteria. Males and females are equally to have VUR after UTI, but males are more likely to have higher grade VUR [(3)]. Females are more commonly diagnosed with VUR because they are more likely to have UTIs [(6)]. The widespread use of prenatal ultrasound leads to more frequent detection of antenatal hydronephrosis. When screened, approximately 10%-20% of these children have VUR.

Patients who have prenatally detected VUR have higher grade VUR than children detected after UTI. There is a genetic predisposition to VUR, with some studies suggesting an autosomal dominant inheritance with variable penetrance although no specific genetic loci have been defined [(7)]. These findings are dramatically illustrated by high incidence of reflux in siblings

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and offspring's of patients have VUR [8,9] , which lead to recommendation of screening children who have first degree relative with VUR [10,11].

Diagnosis

A voiding cystourethrogram (VCUG) is the gold standard diagnostic approach, it allows for grading of VUR and provides excellent anatomic details. VCUG is able to diagnose posterior urethral valve and bladder abnormalities. The disadvantages are radiation exposure and need for catheterization. In contrast, direct radionuclide cystography, which also requires catheterization, has excellent sensitivity for detecting VUR and much lower radiation exposure than VCUG [12].

Radionuclide cystogram (RNC) a nuclear study which uses solution contain radioactive tracer Technetium-99m (99mTc) which provide less anatomical details than VCUG and typically involve less overall radiation exposure [11]. RNC is usually used after initial VCUG examination to follow/monitor a patient's progress. VUR grading is less detailed with a RNC and is usually graded as mild, moderate or severe VUR [13].

Management: -

Principles of management:

1. Spontaneous resolution of reflux is common.
2. High-grade reflux is less likely to resolve spontaneously.
3. Extended use of prophylactic antibiotics & "Watchful waiting".
4. The success rate with surgical correction is very high.

Management of VUR is divided into medical (conservative) and surgical management which is divided into open or laparoscopic reimplantation, and endoscopic approach [14].

Endoscopic injection therapy of VUR

Matouschek (1981) was the first who describes the injection of polytetrafluoroethylene (PTFE) at the ureteral orifices to correct VUR [15]. O'Donnell and puri (1986) popularized the technique when they published their initial report on the successful endoscopic correction of primary VUR with success rate of 75% after one injection [16]. The overall success rates which were reported by the different groups ranged between 68–92%, depending mainly on the VUR grade [17-19].

Materials used for endoscopic correction of reflux

A. Non autologous materials:

1- Polytetrafluoroethylene paste (PTEF - Teflon paste)
2- Polydimethylsiloxane (Macroplastique)
3- Cross liked bovine collagen.
4- Coaptite.
5-Dextranomer/Hyaluronic acid copolymer; Dx/HA (Deflux).
6- Polyacrylate polyalcohol copolymer/ PPC (Vantris), Non-biodegradable agents of synthetic origin lead to the formation of a fibrotic capsule, giving stability and long-term permanence. It belongs to the family of Acrylics, particles of polyacrylate polyalcohol copolymer immersed in a glycerol and physiological solution carrier. Molecular mass is very high. When injected in soft tissues, this material causes a bulkiness that remains stable through time. The carrier is a 40% glycerol solution with a pH of 6. Once injected, the carrier is eliminated by the reticular system through the kidneys, without metabolizing. Particles of this polyacrylate polyalcohol with glycerol are highly deformable by compression, and may be injected using a 23-gauge needle. The average of particles size is 320 mm. Once implanted, particles are covered by a fibrotic capsule of up to 70 microns. Particles of this material are anionic with high superficial electronegativity, thus promoting a low cellular interaction and low fibrotic growth [20]. The only significant and serious complication of vantris injection is ureteral obstruction which may need ureteral re-implantation [21].

B. Autologous materials

Fat, collagen, muscle, and chondrocytes have all been evaluated as bulking agents [22].

Patients and method

We prospectively followed patient who had primary VUR and treated by endoscopic Vantris injection from October 2015 to September 2018. They were 40 patients (with 70 RRUs); 14 males (35%) and 26 females (65%), with a mean age of 4.2 ±3.4 years (mean ± SD). The baseline characteristics of the patients are shown in table (1) and table (2). Follow up includes clinical and radiological assessments (ultrasonic examination and voiding cystourethrogram VCUG) for 3 years. Intravenous urogram (IVU) was done for most of patients before the procedure and DMSA scan was done for two patients to insure adequate function of the kidneys. The reflux grade was based on the voiding cystourethrogram (VCUG) before and after the surgery, according to the International Classification System (International Reflex Study Committee). For patients with grade II - III VUR, cystoscopic sub-ureteric transurethral injection (STING) technique was used, while patients with grade **IV** VUR or those with widely opened orifice, the injection was performed inside the orifice {hydrodestention injection therapy (HIT)}.

All families were informed and consent taken; regarding the procedure and tissue augmented substance used for reflux correction. All patients should have urinalysis to exclude a UTIs prior to injection therapy and before doing a VCUG.

Inclusion criteria: -

1- All children with grade II -IV primary VUR treated by single injection of Vantris.

Exclusion criteria: -

1- Secondary and complex VUR.
2- Injection on re-implanted ureter.
3- More than one injection.
4- Grade V VUR.

First visit is at 1-week post-injection for clinical assessment and Ultrasonic examination. Clinical assessment includes: - Urine output, temperature and general condition of child.

Then Ultrasound examination to be done at 1 month after injection and then yearly for 3 years.

Ultrasound examination used for assessment of: -

1- Degree of hydrouretronephrosis.
2- Parenchymal thickness.
3- Bladder capacity (full capacity and post void residue).

Voiding cystourethrogram was done at 3 months after injection therapy, then 1 year and 3 years after injection therapy. Antibiotic prophylaxis stopped if VCUG shows no reflux. {Reflux considered cured if VCUG did not demonstrates VUR of any grade}. Ultrasound study was done at 1 week, 1month and yearly for 3 years for follow up of parenchymal thickness and degree of hydrouretronephrosis as predictor of residual reflux if present. As grading of VUR depends mainly on VCUG (International classification of vesicoureteral reflux), the results of our study depend mainly on VCUG findings. As shown in table 3, it can easily be noticed that breakthrough UTI was the most frequent indication for surgery (in 62.5% of patients), followed by high-grade VUR (in 25% of patients), and family preference was the indication for surgery in 5 patients (12.5%).

Table 1 : The baseline characteristics of the studied group.

Variables		Values %
Age	Mean ± SD Range	4.2 ±3.4 2 – 9
Gender	Male Female	35 14 65 26
Laterality	Unilateral Bilateral	25 10 75 30
Renal reflexing unit (RRU)	Primary Complex Total	100 70 0 0 100 70
Grades	II III IV	14.3 10 35 50 35.7 25
Injection volume	Mean ± SD Range	0.8 ± 0.56 0.4 – 1.2

Table 2 : The characteristics of studied group according to gender and laterality.

Grade	Gender/40			RRU No./70	Laterality/40					
		No	%		Left No	%	Right No	%	Bilateral No	%
Grade II	Male	2	5	3	1	2.5	0	0	1	2.5
	Female	4	10	7	1	2.5	0	0	3	7.5
Grade III	Male	8	20	14	2	5			6	15
	Female	13	32.5	21	4	10	1	2.5	8	20
Grade IV	Male	4	10	8			0	0	4	10
	Female	9	22.5	17	1	2.5	0	0	8	20
Total	Male	14	35	25	3	7.5			11	27.5
	Female	26	65	45	6	15	1	2.5	19	47.5

Table 3 : Indications for endoscopic correction of VUR.

Indications	No.	%
Breakthrough UTI	25	62.5
High-grade VUR	10	25.0
Family preference	5	12.5

RESULTS:

The baseline characteristics of our study reveal that the mean age of patients was 4.2 ± 3.4 (range: 2-9 years). Females were dominant representing (65%) of the patients. Majority had bilateral RRUs, representing 30/40 (75%) of patients. All patients had primary VUR. RRU were grade II in 10/70 (14.3%), grade III in 35/70 (50%) and grade IV in 25/70 (35.7%). The injected volume of Vantris ranges from 0.4 to 1.2 ml with a mean of 0.8 ml. The outcomes of first VCUG done at 3 months after single injection of Vantris material, shows complete resolution of grade II VUR (10/10 RRUs), 32/35 RRUs of grade III had no VUR and 23/25 RRUs with grade IV had no VUR. In total 65/70 RRUs had resolved VUR as shown in table (4), while those RRU who downgraded to grade I kept on conservative therapy for 3 months then VCUG was done; 4 of them reached complete resolution of VUR and only 1 RRU required second injection. Second VCUG done 1 year after injection therapy, all 10/10 RRUs with grade II had no VUR, 32/32 RRUs of grade III had no VUR, and 21/23 RRUs with grade IV had no VUR. In total 63/65 RRUs had no VUR as shown in table (5). Those who failed to reach complete resolution (2 RRUs) were kept on conservative therapy for 3 months and further VCUG was done and shows spontaneous resolution of VUR. Third VCUG done 3 years after injection therapy, all 10/10 RRUs with grade II had no VUR, 32/32 RRUs of grade III had no VUR, and 21/21 RRUs with grade IV had no VUR. In total 63/63 RRUs had no VUR as shown in table (6).

So, totally 63/70 (90%) RRUs show complete resolution, with 7/70 (10%) show downgrade to grade I. Ureteral obstruction developed in 1 patient (2.5%) treated by Vantris injection for grade III left side VUR, and was diagnosed immediately within two days as low urine output and patient's complain of pain and was treated by double J insertion which is removed after three weeks with no squeal. Apart from ureteral obstruction, no fever or allergic reaction developed in any patient as shown in Table (8).

Table 4 : Outcomes of endoscopic correction of RRUs according to first VCUG (3 months after single injection of Vantris) .

Grades	(RRU) No.	Downgrade to Grade 0 No. %	Downgrade to Grade Ⅰ No. %	GENDER/40		LATERALITY/40					
					No. %	Left No. %		Right No. %		Bilateral No. %	
Grade Ⅱ	10	10 100	0 0	Male	2 5	1	2.5	0	0	1	2.5
				Female	4 10	1	2.5	0	0	3	7.5
Grade Ⅲ	35	32 91.4	3 4.3	Male	7 17.5	1	2.5	0	0	6	15
				Female	12 30	4	10	1	2.5	7	17.5
Grade Ⅳ	25	23 92	2 2.8	Male	3 7.5	0	0	0	0	3	7.5
				Female	9 22.5	1	2.5	0	0	8	20
Total	70	65 92.9	5 7.1	Male	12 30	2	5	0	0	10	25
				Female	25 62.5	6	15	1	2.5	18	45
Success rate	92.9%			92.5%		88.9%		100%		93.3%	
P value	* < 0.001			** 0.57							

* P value of result in VCUG 1 (at 3 months) is <0.001 (highly significant).
** P value between both gender of our study is not significant.

Table 5 : Outcomes of endoscopic correction of RRUs according to second VCUG (1 year after single injection of Vantris).

Grades	NO. (RRU)	Downgrade to Grade 0 No. %	Downgrade to Grade Ⅰ No. %	GENDER/40		LATERALITY/40					
					No. %	Left No. %		Right No. %		Bilateral No. %	
Grade Ⅱ	10	10 100	0 0	Male	2 5	1	2.5	0	0	1	2.5
				Female	4 10	1	2.5	0	0	3	7.5
Grade Ⅲ	32	32 100	0 0	Male	7 17.5	1	2.5	0	0	6	15
				Female	12 30	4	10	1	2.5	7	17.5
Grade Ⅳ	23	21 91.3	2 3.1	Male	2 5	0	0	0	0	2	5
				Female	9 22.5	1	2.5	0	0	8	20
Total	65	63 96.9	2 3.1	Male	11 27.5	2	5	0	0	9	22.5
				Female	25 62.5	6	15	1	2.5	18	45
Success rate	96.9%			90%		88.9%		100%		90%	
P value	* < 0.001			** 0.22							

* P value of result in VCUG 1 (at 3 months) is <0.001 (highly significant).
** P value between both gender of our study is not significant.

Table 6 : Outcomes of endoscopic correction of RRUs according third VCUG (3 years after single Vantris injection).

Grade	NO. (RRU)	Downgrade to Grade Ⅰ No.	%	Downgrade to Grade Ⅰ No.	%	GENDER / 40	No.	%	LATERALITY / 40	Left No.	%	Right No.	%	Bilateral No.	%
Grade Ⅱ	10	10	100	0	0	Male	2	5		1	2.5	0	0	1	2.5
						Female	4	10		1	2.5	0	0	3	7.5
Grade Ⅲ	32	32	100	0	0	Male	7	17.5		1	2.5	0	0	6	15
						Female	12	30		4	10	1	2.5	7	17.5
Grade Ⅳ	21	21	100	0	0	Male	2	5		0	0	0	0	2	5
						Female	9	22.5		1	2.5	0	0	8	20
Total	63	63	100	0	0	Male	11	27.5		2	5	0	0	9	22.5
						Female	25	62.5		6	15	1	2.5	18	45
Success rate	100%					90%				88.9%		100%		90%	
P value	* < 0.001					** 0.22									

* P value of result in VCUG 1 (at 3 months) is <0.001 (highly significant).
** P value between both gender of our study is not significant.

Table 7: Outcomes of endoscopic correction of RRUs according to 1ST, 2nd and 3rd VCUG.

Grade	1st VCUG					2nd VCUG					3rd VCUG				
	NO.	MALE No.	%	FEMALE No.	%	NO.	MALE No.	%	FEMALE No.	%	NO.	MALE No.	%	FEMALE No.	%
Grade II	10	2	5	4	10	10	2	5	4	10	10	2	5	4	10
Grade III	32	7	17.5	12	30	32	7	17.5	12	30	32	7	17.5	12	30
Grade IV	23	3	7.5	9	22.5	21	2	5	9	22.5	21	2	5	9	22.5
TOTAL	65	12	30	25	65.5	63	11	27.5	25	62.5	63	11	27.5	25	62.5
P value	0.001				0.57	<0.001				0.22	0.001				0.22

Table 8: Postoperative complications.

Complication	No.	%
Ureteral obstruction	1	1.4
RRUs failed to reach con resolution	7	10

DISCUSSION:

Although surgical correction by ureteral re-implantation has been considered as a gold standard in the management of VUR with efficacy rate of almost 100% [23], endoscopic correction of VUR using different bulking agents has been progressively used and widely offered in the last three decades and has become a promising procedure which is minimally invasive with good clinical outcomes.

Vantris (polyacrylate polyalcohol copolymer (PPC)) is a synthetic non-absorbable compound that belongs to acryl family was introduced for treatment of VUR and shows a promising results when compared to other bulking agents [24].

In our study, we prospectively followed forty patients {male 14 (35%), female 26 (65%)} with a mean age of 4.2(±3.4) years (mean ± SD) who underwent endoscopic Vantris injection therapy for treatment of primary VUR with a mean injected volume of 0.8ml (range 0.4- 1.2 ml).

The follow up includes clinical assessment (temperature, urine output and general condition of patient) in addition to radiological assessments including ultrasonic examination at (1 week, 1

month, then yearly for 3 years) and voiding cystourethrogram (VCUG) at (3 months, 1 year and 3 years) following the injection therapy, ultrasound examination was done on regular basis as a part of general assessment, and to follow the degree of hydrouretronephrosis. The success was defined as complete resolution of VUR on post-injection VCUG. Our results in first VCUG at 3 months show success rate of 92.9% with p. value <0.001 with 3 RRUs of grade Ⅲ and 2 RRUs of grade Ⅳ downgraded to grade Ⅰ as shown in table 4, which indicates efficacy of Vantris injection in treatment of VUR on short term follow-up. No patient develops post injection fever or allergic reaction which indicate that Vantris as a bulking agent used for treatment of VUR had minimal or low cellular interaction. Only 1 patient develops ureteral obstruction on injected side which was diagnosed immediately within two days' post injection because ipsilateral pain and decreasing urine output necessitated DJ stent insertion within two-days which is removed after 3 weeks without any sequelae, this may indicate that the Vantris doesn't loss its volume after injection.

The second VCUG was done 1 year after injection shows success rate of 96.9% with p. value < 0.001. Two RRUs of grade Ⅳ show downgraded to grade Ⅰ as shown in table 5. No patient developed late ureteral obstruction. So these results can give a promising idea about the durability and efficacy of Vantris. The third VCUG was done 3 years after injection shows cure rate of 100% for all grades with p. value <0.001 as shown in table 6. The success rate of our study is 90%, which indicates Vantris as an effective bulking agent used for correction of VUR as shown by few cases of VUR downgrade to grade Ⅰ after single injection. High success rate through a period of follow up for 3 years after single injection indicates high durability of Vantris which may attributed be to physical properties of being non-biodegradable, non-migrating and keeping of injected volume for long period while low complications rate including (ureteral obstruction, fever or allergic reaction) can gives an idea about safety of Vantris for correction of VUR for long time. Only 10% of RRUs (3RRUs of grade Ⅲ and 4 RRUs of grade Ⅳ) shows downgrade to grade Ⅰ, all those patients with downgraded VUR had conservative treatment with antibiotics for 3 months, then another VCUG was done which shows only 6 RRUs have complete resolution of VUR and only 1 persistent RRU required second Vantris injection. This downgrading on VCUG occur due to either partial response to Vantris because of its early degradation or improper VCUG (high pressure VCUG). So failure to reach complete resolution of VUR after 3 years follow up by VCUG increases as the grade of primary reflux increase (grade Ⅳ> grade Ⅲ> grade Ⅱ).

There was no statistical change in response to vantris injection between both sexes (p. value of 0.22)

In multicenter survey of endoscopic treatment of VUR using Vantris from 2009-2013, 611 patients (210 males and 401 females) with 809 RRUs with mean age of 3.5 years were treated at 7 centers worldwide endoscopically with Vantris injection, of these (83.3%) RRUs are primary and (16.7%) RRUs are complex, the reflux was grade Ⅰ-Ⅴ and the mean injected volume of 0.4 ml (range) (0.2-1.3). The patients monitored by ultrasound study and VCUG at 3 months, 1 year, and 3 years. The result show resolution of VUR in 759 RRUs (93.8%) after first injection [25]. In comparison to our study the number of patients enrolled in this study is higher involving both primary and secondary VUR of grade Ⅰ-Ⅴ; while our results depend on data of 40 patients, only primary VUR of grade Ⅱ-Ⅳ: however, the overall results appear to be similar taking in consideration we are dealt only with grade Ⅱ-Ⅳ. Stanislaw warchol et al. followed up 125 children (52 males, 73 females) with mean age (4.9 ±3.6) were treated with Vantris, with 186 RRUs (64 unilateral and 61 bilateral). Follow up was completed in 89.6% of patients (167 RRUs) of those the primary reflux was found in 126 RRUs and complex reflux in 40 RRUs. VCUG was done 3 months after the procedure. Reflux was resolved in 86.4% of RRUs after single injection [21]. Compared to our study, this study had shorter follow-up period (VCUG done 3 months after injection), number of patients are higher, involving both primary and complex VUR. Complication were reported in this study including ureteral obstruction in 9 patients which were treated by ureteral re-implantation. The results of our study appear to be more promising for long term durability of Vantris 92.9% cure rate shown in first VCUG of our study compared to 86.4% cure rate of this study and complication rate is much lower compared to this study.

Ormaechea et al treated 61 patients (18 males, 43 females) with 88 RRUs during a multicenter trial, with average age of 58 months completed follow-up for 20 months. The grade of VUR treated in this study was Ⅱ-Ⅴ of those 83%

were grade Ⅱ-Ⅲ with a mean injected volume of 0.76 ml. Vesicoureteral reflux was cured in 88.6% RRUs and downgrade to grade Ⅰ in 6.8% RRUs [26]. The cure rate and the injected volume in our study appear to be similar to this study. The postoperative complication was also low including mainly ureteral obstruction in one patient treated by ureteral re-implantation; while our results had one patient with ureteral obstruction discovered and treated immediately by DJ stenting.

Chertin et al in 2013 reported 3 years prospective follow up for patients treated by endoscopic Vantris injection. A total of 109 patients (37 males, 72 females) with 165 RRUs underwent the procedure. The mean age was 6.2±3.4 years. VUR was unilateral in 53 patients and bilateral in 56 patients with total 165 RRUs. Mean injected volume of Vantris is 0.85 ml. Of those 84.2% RRUs were primary VUR and 15.8% RRUs were complex cases. The same protocol taken in our study was applied in chertin's study including ultrasound examination in 1 month, 1 year and 3 years after injection. VCUG was performed in 3 months, 1 year and 3 years after injection. The reflux was corrected in 153 RRUs (92.7%) after single injection [27]. The result of our study regarding the cure rate (90%), duration of follow up (3 years) and injected volume of Vantris (0.8ml) appear to be similar to this study although in our study we excluded the complexes cases of VUR and the number of cases of our study is lower than this study. Ureteral obstruction was reported in two patients, resolved by insertion of stent in one case and open ureteral re-implantation in the other one while our complication is only one patient with ureteral obstruction treated by DJ stent insertion.

CONCLUSION AND RECOMMENDATIONS:

Endoscopic injection of Vantris material for treatment of children with vesicoureteral reflux is very effective, safe, durable with less complications compared to conventional open procedures. It can be considered as first line treatment of grade Ⅱ-Ⅳ vesicoureteral reflux.

Further studies are required to evaluate long term efficacy and possible complications.

REFERENCES:

1. Lebowitz RL, Olbing H, Parkkulainen KV, et al. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol 1985;15:105–9.
2. Greenfield SP, Ng M, Wan J. Experience with vesicoureteral reflux in children: clinical charac-teristics. J Urol 1997;158:574–7.
3. Jakobsson B, Soderlundh S, Berg U. Diagnostic significance of 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy in urinary tract infection. Arch Dis Child 1992;67:1338–42.
4. Wennerstrom M, Hansson S, Jodal U, et al. Disappearance of vesicoureteral reflux in children. Arch Pediatr Adolesc Med 1998;152:879–83.
5. Jacobson SH, Hansson S, Jakobsson B. Vesico-ureteric reflux: occurrence and long-term risks. Acta Paediatr Suppl 1999;88:22–30.
6. Hansson S, Martinell J, Stokland E, et al. The natural history of bacteriuria in childhood. Infect Dis Clin North Am 1997;11:499–512.
7. Devriendt K, Groenen P, Van Esch H, et al. Vesico-ureteral reflux: a genetic condition? Eur J Pediatr 1998;157:265–71.
8. Jerkins GR, Noe HN. Familial vesicoureteral reflux: a prospective study. J Urol 1982;128:774–8.
9. Noe HN, Wyatt RJ, Peeden Jr JN, et al. The transmission of vesicoureteral reflux from parent to child. J Urol 1992;148:1869–71.
10. Scott JE, Swallow V, Coulthard MG, et al. Screening of newborn babies for familial ureteric reflux. Lancet 1997;350:396–400.
11. Kaefer M, Curran M, Treves ST, et al. Sibling vesicoureteral reflux in multiple gestation births. Pediatrics 2000;105:800–4.
12. Rothwell DL, Constable AR, Albrecht M. Radionuclide cystography in the investigation of vesicoureteric reflux in children. Lanc1997;1:1072–5.
13. Edwards D, Normand IC, Prescod N, et al. Disappearance of vesicoureteric reflux during long- term prophylaxis of urinary tract infection in children. BMJ 1997;2:285–8.
14. Walker RD. Vesicoureteral reflux update: effect of prospective studies on current management. Urology 1994;43:279 –83.
15. Matouschek E: Treatment of vesicorenal reflux by transurethral teflon-injection (author's transl). 1981 *Urologe A*. 20:263-264.
16. O'Donnell B, Puri P: Endoscopic correction of primary vesicoureteric reflux. *Br J Urol.* 58:601-604 1986. 29.

17. Kirsch A. J., Perez M. -Brayfield, E. A. Smith, and H. C. Scherz ,"The modified sting procedure to correct vesicoureteral reflux:improved results with submucosal implantation within theintramural ureter," *Journal of Urology*, 2004 ;171:2413–16. 2003 ; 170: 1541–44.

18. P. Puri, B. ChertinM.Velayudham, L. Dass, E. Colhoun, and H. Snyder,"Treatment of vesicoureteral reflux by endoscopic injection of dextranomer/hyaluronic acid copolymer: preliminaryresults," *Journal of Urology*, 2003;170:1541–44.

19. B. Chertin, E. Colhoun, M. Velayudham, and P. Puri, "Endoscopic treatment of vesicoureteral reflux: 11 to 17 years of followup," *Journal of Urology*, 2002;167:1443–45.

20. M. Ormaechea, E. Ruiz, E. Denes, F. Gimenez, F.T. Dénes, J. Moldes, A. Amarante, G. Pioner, S. Dekermacher, F. de Badiola. New Tissue Bulking Agent (Polyacrylate Polyalcohol) for Treating Vesicoureteral Reflux: Preliminary Results in Children. The Journal of Urology - February 2010;183: 714-718, DOI: 10.1016/j.juro.2009.10.047)

21. Warchoł W, Krzemień G, Szmigielska A, Bombiński P, Toth K, Dudek-Warchoł T. Endoscopic correction of vesicoureteral reflux in children using polyacrylate polyalcohol copolymer (Vantris): 5-years of prospective follow-up. Cent European J Urol. 2017; 70: 314-19.

22. Matthews RD, Christensen JP, Canning DA: Persistence of autologous free fat transplant in bladder submucosa of rats. *J Urol.* 1994;152:819-21.

23. Caillaud C, Lacreuse I, Fothergill H, Becmeur F, Fischbach M Observational, medical or surgical management of vesicoureteric reflux. Acta Paediatr 2013;102: 222-25.

24. Cloutier J, Blais AS, Moore K, Bolduc S Prospective study using a new bulking agent for the treatment of vesicoureteral reflux: polyacrylamide hydrogel. J Urol 2013;190:1034-37.

25. Kocherov, S., Ulman, I., Nikolaev, S., Corbetta, J. P., Rudin, Y., Slavkovic, A., & Skliarova, T. Multicenter survey of endoscopic treatment of vesicoureteral reflux using polyacrylate-polyalcohol bulking copolymer (Vantris). *Urology*, 2016; 84: 689-93.

26. Ormaechea M, Ruiz E, Denes E, Gimenez F, Denes FT, Moldes J, et al. New tissue bulking agent (polyacrylate polyalcohol) for treating vesicoureteral reflux: preliminary results in children. J Urol 2010; 183:717.

27. Chertin, B., Arafeh, W. A., Zeldin, A., Ostrovsky, I. A., & Kocherov, SEndoscopic correction of VUR using vantris as a new nonbiodegradable tissue augmenting substance: three years of prospective follow-up. *Urology*,2013; 82:201-204.