ORIGINAL PAPER

PEDIATRIC UROLOGY

Endoscopic correction of vesicoureteral reflux in children using polyacrylate-polyalcohol copolymer (Vantris): 5-years of prospective follow-up

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Introduction The endoscopic correction of vesicoureteral reflux (VUR) in children is a currently well accepted therapy in many pediatric urology centers. Polyacrylate-polyalcohol copolymer (PPC), namely Vantris®, is one of the tissue-augmenting substances used for endoscopic reflux therapy. The aim of this study was to evaluate the results with PPC in children.

Material and methods From 2012 to 2016, 125 children (73 girls and 52 boys) aged 0.6–17.9 years (mean 4.9 ±3.58) were treated with PPC. VUR was unilateral in 64 and bilateral in 61 patients, comprising 197 renal refluxing units (RRUs) grades: II in 72, III in 50, IV in 33 and V in 42. Of these primary reflux was present in 132 RRUs and 65 were complex cases. Voiding cystourethrogram (VCUG) was done 3 months after procedure.

Results Follow-up was completed in 89.6% of patients (112 children), and 89.8% of RRUs (177 out of 197). Reflux resolved in 86.4% of RRUs after single injection, in 99.4% after second and in 100% after the third. The only significant, but serious complication observed was late ureteral obstruction after PPC injection correcting high grade reflux, which required ureteral re-implantation. This complication was found in 9 out of 112 children (8%), and in 11 out of 177 RRUs (6.2%), 1.1-2.9 years (mean 2 ±0.7) after the PPC injection. The longest follow-up reaches 4.5 years.

Conclusions Our data show that the PPC injection is an effective procedure for treating all grades of VUR with high success rate. However, because of the possibility of late ureteral obstruction, which requires ureteroneocystostomy, long-term follow-up is mandatory.

Key Words: vesicoureteral reflux ‹› endoscopic correction of reflux ‹› Vantris® ‹› polyalcohol-polyacrylate copolymer ‹› ureteral obstruction ‹› pediatric urology

INTRODUCTION

In 2008, a new tissue-augmenting substance, polyacrylate–polyalcohol copolymer (PPC), was presented [1]. PPC, namely Vantris® (Promedon, Cordoba, Argentina) is a biocompatible, synthetic, non-absorbable bulking agent. The first clinical experience with PPC was published in 2010 [2]. Since that time PPC was introduced into clinical practice and is currently used in some centers around the world. So far, 19 publications of endoscopic treatment of vesicoureteral reflux (VUR) using PPC are available in the literature [2–19]. The general objective of this paper was to present 5-year experience with PPC and to evaluate its efficacy in the management of reflux in children. This was an observational, descriptive, prospective study.

MATERIAL AND METHODS

Over the last 5 years (2012–2016), 125 children (73 girls and 52 boys) aged 0.6–17.9 years (mean 4.91 ±3.58) underwent endoscopic correction of persisting VUR using PPC. VUR was unilateral in 64 and bilateral in 61 patients, comprising 197 renal refluxing units (RRUs) grades: II in 72, III in 50, IV in 33 and V in 42. In 132 (67%) RRUs primary reflux was present, and the remaining 65 (33%) RRUs were complex cases (reflux in duplex system: 21 RRUs, in bifidus system: 14 RRUs, in boys with posterior urethral valves: 18 RRUs, persistent VUR after failed Dx/HA (Deflux®) injection: 9 RRUs, and postoperative reflux after ureteral re-implantation because of megaureter: 3 RRUs). Reflux coexisting with duplicating system was presented as in the bifidus system (incomplete duplication) where reflux can affect both upper and lower renal moiety or only one of them – usually lower, and reflux in the duplex system (complete duplication) where reflux affects almost exclusively the lower pole of the duplicating system.

In the majority of children reflux was diagnosed as a result of urinary tract infection. In some cases (boys with posterior urethral valves and children with duplicating system), a voiding cystourethrogram (VCUG) was done as one of the diagnostic procedures and revealed the presence of VUR. Table 1 and 2 displayed reflux characteristic.

Indications for endoscopic treatment included persistent VUR grade II–V in patients with a history of previous medical treatment for at least 12-months, with the presence of renal scarring (renal scintigraphy) and with no bladder dysfunction (urodynamic study) at the time of injection. Those indications were reached in all patients. Initial cystometry was done in all children after VUR was diagnosed and the repeated study after 6–8 months of pharmacological treatment of bladder dysfunction. In toilet trained children uroflowmetry was applied as a control study and if not possible control cystometry was performed.

All procedures were done during cystoscopy under general anaesthesia using a pediatric operating cystoscope (Storz® 9.5 FR or Wolf® 8/9.8 FR). A mean 0.8 ml of PPC was injected under the ureteral orifice using Sting technique. After injection of the bulking agent, apparent bulge at the site of injection was visible (Figure 1). All injections were performed by a single surgeon as a part of the study protocol.

Two types of injection needles were used: RIN type ('concave side opening') with a laterally located injection hole to treat high grade primary VUR (IV–V) and for complex cases (excluding reflux in bifid/duplex system) (Figure 2) and standard needle, i.e. RINS type ('bevel tip') with injection hole at the end of the needle for the remaining cases (Figure 3).

Perioperative antibiotic prophylaxis was administered (four doses of amoxicillin and clavulanic acid – first before cystoscopy and consecutive three doses after the procedure) and the child was discharged home the next day after cystoscopy. Each patient underwent ultrasound scan (US) 2 weeks after injection and voiding cystourethrogram (VCUG) 3 months after the injection. In case of immediate post-injection flank/abdominal pain, an US was performed to evaluate the degree of possible obstruction of the upper urinary tract. Further follow-up protocol included: US scan and radionuclide examination

Table 1. *Reflux grades regarding primary and complex reflux treated with polyacrylate-polyalcohol copolymer (PPC)*

VUR Grade	RRUs (no) Primary rteflux	RRUs (no) Complex reflux	RRUs (no) Total
II	49	23	72
III	40	10	50
IV	17	16	33
V	26	16	42
Total	132	65	197

VUR – vesicoureteral reflux; RRU – renal refluxing unit

Table 2. *Reflux grades in complex reflux cases treated with polyacrylate-polyalcohol copolymer (PPC)*

VUR Grade	RRUs (no) VUR in duplex system	RRUs (no) VUR in bifidus system	RRUs (no) VUR in PUV	RRUs (no) VUR after failed Deflux®	RRUs (no) postoperative VUR	RRUs (no) Total
II	10	3	3	7		23
III	3	2	3	2		10
IV	6	6	1		3	16
V	2	3	11			16
Total	21	14	18	9	3	65

VUR – vesicoureteral reflux; RRU – renal refluxing unit; PUV – posterior urethral valves

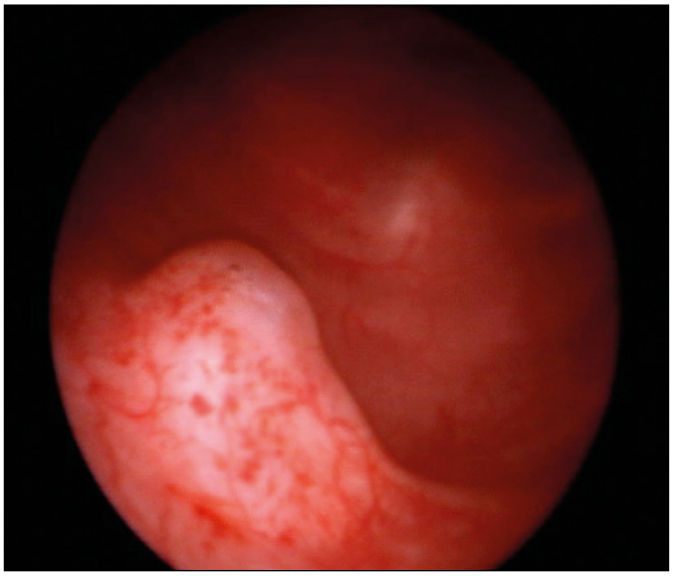

Figure 1. *Cystoscopic view of ureteral orifice after polyacrylate-polyalcohol copolymer (PPC) injection.*

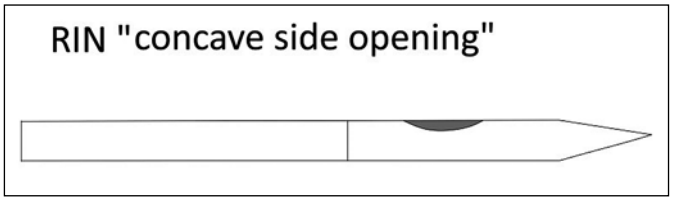

Figure 2. *Injection needle with laterally located injection hole: RIN type ('concave side opening').*

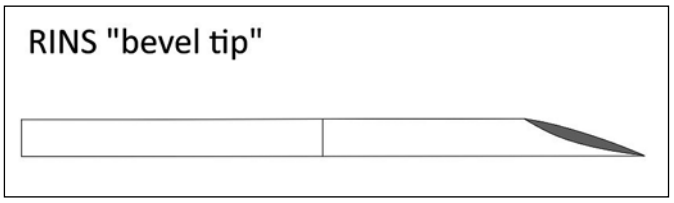

Figure 3. *Standard injection needle with the injection hole located at the end of the needle: RINS type ('bevel tip').*

(dynamic scintigraphy) 6 months after the injection. Then the ultrasound scan was done every six months in each patient and in selected cases, in addition a radionuclide scan was performed on individual basis.

RESULTS

The results of the endoscopic treatment was evaluated in terms of the number of required injections to achieve resolution of reflux and observed postoperative complications.

A mean 0.8 ml of PPC was injected under the ureteral orifice using Sting technique.

Table 3. *Reflux resolution after polyacrylate-polyalcohol copolymer (PPC) injection*

VUR Grade	RRUs	After 1st injection % (no)	After 2nd injection % (no)	After 3rd injection % (no)
II	69	97.1% (67)	100% (69)	
III	44	81.8% (36)	100% (44)	
IV	30	73.3% (22)	100% (30)	
V	34	82.4% (28)	97.1% (33)	100% (34)
Total	177	86.4% (153)	99.4 % (176)	100% (177)

VUR – vesicoureteral reflux; RRU – renal refluxing unit

Table 4. *Primary reflux resolution rates after polyacrylate-polyalcohol copolymer (PPC) injection*

Primary VUR Grade	RRUs	After 1st injection % (no)	After 2nd injection % (no)	After 3rd injection % (no)
II	46	95.7% (44)	100% (46)	
III	34	79.4% (27)	100% (34)	
IV	14	71.4% (10)	100% (14)	
V	20	90% (18)	100% (20)	
Total	114	86.8% (99)	100 % (114)	

VUR – vesicoureteral reflux; RRU – renal refluxing unit

Table 5. *Complex reflux resolution rates after polyacrylate-polyalcohol copolymer (PPC) injection*

Complex VUR Grade	RRUs	After 1st injection % (no)	After 2nd injection % (no)	After 3rd injection % (no)
II	23	100% (23)		
III	10	90% (9)	100% (10)	
IV	16	75% (12)	100% (16)	
V	14	71.4% (10)	93.8% (13)	100% (14)
Total	63	85.7% (54)	98.4% (62)	100 % (63)

VUR – vesicoureteral reflux; RRU – renal refluxing unit

In 112 out of 125 children (89.6%) and 177 out of 197 RRUs (89.8%) control voiding cystourethrography showed reflux resolution. Seven patients (10 RRUs) are before VCUG after first PPC injection, 4 (6 RRUs) with persistent reflux await the second procedure and 2 (4 RRUs) are before cystography after the second PPC injection.

Reflux resolved in 153 out of 177 RRUs (86.4%) after the first PPC injection, in 23 (13%) after the second injection, and in 1 (0.6%) after the third injection. Tables 3, 4 and 5 present VUR resolution rate after PPC injection regarding reflux grade and type.

Primary VUR was corrected in 86.8% RRUs after single injection and in 100% after the second. Complex VUR resolved in 85.7% RRUs after the first, in 98.4% after the second and in 100% after the third injection.

In 115 out of 125 children after the PPC injection, the ultra sound showed an injected substance deposit within the bladder wall visible as an apparent bulk (Figure 4).

Transient, mild and self-limiting dilatation of the upper urinary tract was observed in 12 out of 125 of treated children. The mean degree of dilatation was 10–12 mm of renal pelvis in AP diameter together with dilated ipsilateral ureter up to 5–7 mm along its whole length. The dilation was detected within the first hours after the injection of PPC and indication for early US was back pain in all children. Then the pain and dilatation resolved spontaneously within the next 12–24 hours. In all those children, a control US exam showed no further visible dilatation.

Progressive dilatation of renal collecting system and megaureter (US study) as well as deterioration of renal function with delayed excretion (radionuclide study) was found 1.1–2.9 years (mean 2 ±0.7) after PPC injection in 8 children, in the 9th child after 0.9 yrs, comprising 11 RRUs, all with initial Grades IV and V. In all of them this new dilation became obstructed in time. All nine were qualified for operative treatment. Politano-Leadbetter antireflux procedure after excision of the stenotic intravesical part of ureter was performed in 7 children: unilaterally in 5, bilaterally in 2. Two children did not show up for the planned surgery and they no longer participated in further follow-up. The remaining seven operated children are under control. Postoperative US and dynamic scintigraphy (mean follow-up 1 year) showed gradual decrease of dilatation of the upper urinary tract and permanent improvement of drainage and renal function.

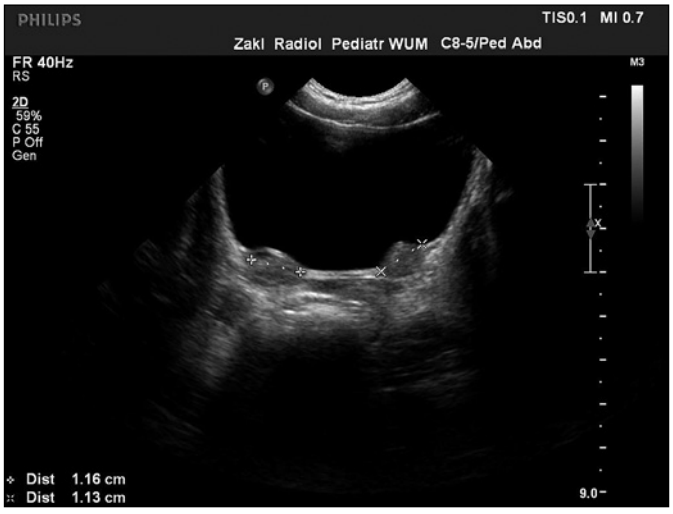

Figure 4. *Ultrasound picture of polyacrylate-polyalcohol copolymer (PPC) deposit within the bladder wall.*

DISCUSSION

Endoscopic management of VUR in children since the introduction of subureteric injection of polytetrafluoroethylene (Teflon®) in 1983, has become as a first-line procedure for the interventional treatment of all grades of reflux in children in some institutions [20–23]. In EAU recommendations for the management of VUR in children, children with persistent low grade reflux may be candidates for endoscopic treatment and surgical correction should be considered in patients with high grade reflux (grades IV/V) [24].

Many tissue augmenting, i.e. bulking substances have been used in the past and their safety as well as efficacy have been the major concerns [25, 26, 27]. Dextranomer/hyaluronic acid copolymer (Dx/HA, Deflux Q-Med Scandinavia, Uppsala, Sweden), which is a biodegradable material, has been commonly used throughout the world since 2000 [22, 23, 28, 29, 30]. The overall success rate reported in the literature after endoscopic treatment of VUR in children with Dx/HA as the most widely used bulking agent, ranges between 68% and 92%, depending mainly on the reflux grade, however, with only 50–70% success rate after single injection [20, 22, 24, 25, 27, 29, 30].

In our experience with Dx/HA, used from 2000 to 2012, the success rate was similar to that published: 63% after the first injection and 90.7% after the second [18].

The reported possibility of recurrence of VUR after successful Dx/HA treatment, failures of endoscopic correction with Dx/HA with the need for repeated injection or operative treatment, led to introduce the new synthetic, non-biodegradable tissue-augmenting substance polyacrylate-polyalcohol copolymer (PPC). The biodegradable nature of dextranomer/hyaluronic acid copolymer together with migration mound on re-operation are suggested as a factors responsible for the eventual reflux persistence and recurrence [2, 3, 13, 14, 28, 31].

A high level of reflux resolution using PPC is noted. The results showed that reflux was corrected in about 90% of cases after single PPC injection, with no recurrence during prospective follow-up [5, 13, 14, 15, 16, 18, 19].

Recently, in 2016, were published 4 papers, which compared retrospectively the outcomes of endoscopic reflux correction using two bulking agents: dextranomer/hyaluronic acid copolymer versus polyacrylate-polyalcohol copolymer. The results revealed that

success rate of PPC was significantly higher than that obtained with Dx/HA [16, 17, 18, 19].
PPC is used successfully to treat primary reflux and also for complex cases [9, 10, 13, 14, 16, 18, 19]. The use of PPC to correct grades IV and V is also very efficient with an overall success rate achieved of over 80% [8, 11, 13, 15, 17].
Our results with PPC confirm that this new augmenting substance is very effective for treating all grades of primary and also complex VUR in children. Reflux is resolved in almost 87% of all treated RRU's after the first procedure and in 99.4% after the second procedure. Primary VUR was corrected in 86.6% RRUs after first injection and in 100% after repeated procedure, while for complex cases 85.7% success rate was noted after single injection, 98.4% after second and 100% after the third. For high grade VUR, i.e. IV and V, which represented more than 1/3 of cases, success was achieved in 78% RRUs after the first injection, in 94.4% after the second and in all after the third injection.
Postoperative obstruction after endoscopic treatment of VUR using bulking substances is a well known reported phenomenon [32–35]. This complication can occur even many years after procedure, in an adult [36].
Acute and delayed ureteral obstruction is also described after PPC injection and is estimated as the main postoperative complication. Early obstruction is managed expectantly, late is treated with insertion of the double J stent or requires open ureteroneocystostomy [2, 4, 5, 8, 11–16].
In our experience the only significant and serious complication encountered with PPC was late ureteral obstruction, requiring ureteral re-implantation in all cases. All those patients were treated successfully with high grade, i.e. IV and V, reflux. Late-onset ureteral obstruction (megaureter on US and deterioration on renal function on radionuclide study) was noted in 8 out of 9 of our patients 1.1–2.9 years (mean 2 ±0.7) after PPC .
Various injection methods including subureteral transurethral injection (STING), hydrodystention implantation technique (HIT) and double HIT are used for endoscopic treatment of VUR [11, 28, 37, 38]. In 2014 Kirsch and co-workers reported that double HIT method for Dx/HA implantation is the most commonly performed technique by paediatric urologists in the United States [30]. Recently published systematic review and meta-analysis concluded that HIT is superior to STING technique for resolution of VUR after Dx/HA injection [38]. Regardless, the injection method standard needle with the injection hole located at the end of the needle is used with a single puncture for STING or HIT procedure or two punctures for double HIT.
For PPC injection we used two types of needles: standard needle as described above named the RINS type and the RIN type with laterally located injection hole. The RIN type of the needle was used by us to treat high grade primary VUR (IV–V) and for complex cases (excluding reflux in bifid/duplex system) and in our experience a very high resolution rate with one puncture observed.

CONCLUSIONS

In conclusion, our experience with the use of PPC has been favorable. Our data showed that the PPC injection is an effective procedure for treating all grades of VUR with high success rate. However, the development of late ureterovesical obstruction several months or years after injection, should be taken into account in PPC treatment. Therefore, long-term follow-up, despite complete reflux resolution is recommended.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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