Medical & Surgical Urology
ISSN: 2168-9857

Chua et al., Med Surg Urol 2014, 3:3
DOI: 10.4172/2168-9857.1000139

Research Article Open Access

Tissue Bulking Agent-Polyacrylate Polyalcohol Copolymer for Endoscopic Correction of Vesicoureteral Reflux in Children: A Comparative Study

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Abstract

Objective: To evaluate the treatment outcome of single session endoscopic treatment using Polyacrylate Polyalcohol Copolymer (PPC) (Vantris ®) compared with conservative Continuous Antibiotic Prophylaxis (CAP) and open surgical treatment among children with Vesico-Ureteral Reflux (VUR).

Methods: A retrospective cohort was undertaken in a single institution to evaluate children diagnosed with primary VUR grade 2-4 from 2006-2012 treated by a single urologist with different treatment modalities- conservative continuous antibiotic prophylaxis, endoscopic correction with PPC and open ureteral re-implantation with Cohen technique. Included patients for the study were only those who had 1-3 months and >1 year post-treatment follow- up study with Voiding Cystourethrogram (VCUG), kidney ultrasound, Dimercaptosuccinic Acid (DMSA) renal scan, and urine culture. Comparative analysis was made to evaluate the rate of VUR resolution, reflux recurrence, renal scaring and VUR treatment related hospital stay.

Results: Twenty-five children (12 girl and 13 boys) with a mean age of 3 ± 1.4 years were included. Twelve children had bilateral VUR and thirteen had unilateral VUR, a total of thirty-seven Refluxing Renal Units (RRU) were being analyzed (12 CAP, 11 endoscopic corrections and 14 open re-implantation surgery). On initial 3 months post-treatment follow-up, RRU VUR resolution observed for CAP, PPC and open surgery were 33% (4/12), 91% (10/11) and 100% (14/14), respectively. At >1 year post treatment follow-up, VUR resolution were noted in 50% (6/12) treated with CAP. For PPC treated group, 27% (3/11) had reflux recurrence or persistence and 14% (2/14) of open surgery group had ureteral obstruction with hydronephrosis. Renal scarring detected among CAP, PPC and surgery group at >1 year follow-up were 42% (5/12), 18% (2/11) and 14% (2/14), respectively. VUR treatment related mean hospital day per year was highest among the CAP group (6.25 ± 2.6 days/year) and lowest among PPC group (3.27 ± 1.2 days/year).

Conclusion: Endoscopic correction of VUR with PPC resulted to better treatment outcome when compared to CAP and was comparable to open surgical management with shorter treatment related hospital stay.

Keywords: PPC: Polyacrylate Polyalcohol Copolymer; Endoscopic; Urine culture; Renal scan; VUR: Vesico-Ureteral Reflux

Introduction

Retrograde urine flow from the bladder into the upper collecting system, also termed Vesicoureteral Reflux (VUR), is a functional and anatomical disorder that affects nearly 1% of the children [1]. This condition if treated inappropriately may result to potentially serious sequel, such as renal scarring, hypertension and renal failure [2]. The ultimate objective of VUR management is to preserve the renal function and minimize risk of long-term complications through prevention of febrile urinary tract infection. Conservative management of Continuous Antibiotic Prophylaxis (CAP) with periodic monitoring, endoscopic correction of VUR with injection of tissue bulking agent around the ureteral orifice, and surgical ureteral re-implantation into the bladder are the current options to treat VUR among children [3]. Up to date, treatment of VUR is considered the most controversial topic in pediatric urology; since spontaneous resolution may occur depending on the risk factor and severity of VUR [4]. Approximately, 80% of patient with low grade (I and II) and 30-50% in high grade (III-V) VUR will resolve within 4-5 years of follow-up [5]. Thus, a balance between risk prevention and overtreatment should be considered in providing treatment, particularly among patients with grade II-IV VUR.

Endoscopic correction of VUR has gained its popularity due to its less invasiveness associated low morbidity and short hospital stay. Although short-term follow-up had justified their efficacy, however, long-term recurrence and complications following endoscopic correction were also being reported in the literatures [6]. Currently, there are insufficient evidences on the efficacy and safety of biocompatible tissue augmenting materials used for endoscopic correction of VUR; particularly on the new tissue bulking agents [6]. Polyacrylate Polyalcohol Copolymer (PPC) - Vantris® (Promedon, Cordoba, Argentina) is a new tissue augmenting biocompatible acrylics used for endoscopic correction of VUR [7]. Several trials have been executed to determine its effectiveness and safety, however, no comparative study was available to ascertain its effectiveness and safety against conservative management antibiotic prophylactic therapy and surgical re-implantation therapy.

In this study we retrospectively evaluated a single surgeon experience of endoscopic correction using Vantris versus Cohen ureteral re-implantation and conservative antibiotic prophylaxis with initial 3 months and 1 year follow up in regard to success rate, reflux recurrences, febrile UTI, renal scarring, treatment-related hospital stay and complications.

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Received June 28, 2014; **Accepted** July 25, 2014; **Published** August 02, 2014

Citation: Chua ME, Mendoza JS, Gomez OR, Silangcruz JM, Pineda CL, et al. (2014) Tissue Bulking Agent-Polyacrylate Polyalcohol Copolymer for Endoscopic Correction of Vesicoureteral Reflux in Children: A Comparative Study. Med Surg Urol 3: 139. doi:10.4172/2168-9857.1000139

Methods

This retrospective cohort study is based from the review of case profiles and medical records of a single surgeon's experience on VUR treatment from 2006-2012. Study protocol was registered at ClinicalTrials.gov (NCT01926353). The study was reviewed and approved by the Institutional Ethics Review Committee with strict compliance to patient confidentiality according to Good Clinical Practice. All subjects diagnosed with VUR treated with conservative management, single-injection endoscopic correction or surgical management was included for comparative analysis. Patient treated with conservative antibiotic prophylaxis were managed initially with culture-guided antibiotics then maintained on 1st or 2nd generation continuous antibiotic prophylaxis for 1 year with regular follow-ups. Children who underwent endoscopic correction of VUR had single-session sub-mucosal injection of 1-1.5 mL PPC (Vantris) using a 10 Fr Storz® cystoscope double Hydrodistension Implantation Technique (HIT). Open surgery for VUR management was performed using Cohen technique ureteral re-implantation by single experienced paediatric urologist. For both groups with endoscopic correction and surgical management, antibiotic prophylaxis was given peri-operatively and maintained for 7-10 days postoperatively, which was then suspended following a normal urinalysis. All included patients had initial work-up including renal ultrasound, Voiding Cystourethrography (VCUG) and dimercaptosuccinic acid renal scan. A follow-up renal ultrasound, urinalysis/urine culture, VCUG, and DMSA scan were done at ≤ 3-month and >1-year post-treatment.

All the images of renal ultrasound, DMSA and VCUG (before, after treatment or during conservative treatment) were examined by a single radiologist and urologist who were blinded from the patient's clinical data. VCUG was read prior to the renal ultrasound and DMSA to decrease the reader's bias in rating the VCUG. The reflux was graded based on the Voiding Cystourethrogram (VCUG) according to the International Classification System (International Reflux Study Committee). Renal ultrasound was labelled as (a) no dilatation, (b) pelvocaliectasia or hydronephrosis.

Excluded cases were patients who had VUR grade I and grade V, no complete follow-up work ups, concomitant neurogenic bladder, anatomical malformation of the urinary tract (obstruction, complete duplicated pelvocaliceal system), previous surgical or endoscopic procedures, and suspected or confirmed dysfunctional voiding by clinical findings or abnormal results (irregular bladder wall, diverticulum) on VCUG or urodynamic study.

Morbidity refers to ureteral obstruction due to intervention which was defined as increasing severity of collecting system dilatation noted on ultrasound without VUR findings on follow-up VCUG, which the ultrasound finding was attributed to the treatment procedure. Post-treatment febrile bacteriuria is characterized by documented fever with ≥ 10^5 bacteria/ml microscopic finding in urinalysis or urine culture despite treatment which needs additional antibiotic management. Renal scarring is defined as consistent decreased tracer activity noted in follow-up DMSA scan. Recurrent VUR is defined as VUR noted on 1-year follow up VCUG after its resolution on 3-month follow-up. Failed treatment is defined as persistent VUR or VUR grade progression despite treatment. Treatment success is defined as VUR resolution or downgrade to VUR grade I.

Results

Twenty-five patients (13 girls and 12 boys) with a mean age of 3 ± 1.4 years old diagnosed with VUR grade II-IV, according to the International Reflux Study Classification, were included in the study. A total of 37 RRUs were managed accordingly. Twelve RRUs were managed with CAP, fourteen underwent open ureteral re-implatation with Cohen technique, and the remaining 11 RRUs underwent endoscopic correction using PPC (Vantris®). Between treatment groups, baseline characteristics and patient demographics were comparable (Table 1).

On initial 3 months post-treatment follow- up, treatment outcome observed for CAP, PPC and open surgery, the success rates were 33% (4/12), 91% (10/11) and 100% (14/14), respectively. At 1-year post treatment follow-up, cumulative success rates of 50% (6/12) and 100% were noted in patients treated with CAP and open surgery, respectively. Reflux recurrence was observed in 10% (1/10) of the RRUs under the PPC arm.

The incidence of febrile UTI at initial 3 months were reported among the treatment groups were 1 patient (9%) for endoscopic correction with PPC, 1 patient (9%) treated with Cohen re-implantation, and 3 patients (25%) who were maintained on CAP. Beyond 3 months, the occurrence of febrile UTI was noted in 3 patients (25%) treated with CAP and none of the patients from the two other treatment arms.

Renal scarring detected among CAP, PPC and surgery group at 3-month follow-up were 25% (3/12), 9% (1/11) and 14% (2/14), respectively. At 1-year follow-up however, another patient from the PPC group and additional 2 patients from the CAP group were detected to have renal scarring, hence a total cumulative rate of renal scarring of 18% and 42% were observed, respectively. Overall VUR treatment related mean hospital day per year was highest among the CAP group (6.25+2.6 days/year) and lowest among the PPC group (3.27+1.2 days/year). On the other hand, among the surgery group, the mean hospital day post treatment was 4.0 ± 2.6 days/year. Beyond 3 months follow up, one patient from surgery group was noted to have ureteral obstruction, which was considered as a complication (Table 2).

Discussion

In the past few decades, before the introduction of endoscopic correction with different bulking agents for VUR, only two treatment options were considered, the conservative continuous antibiotic prophylaxis versus open surgical approach. Conservative management basically dwells on the principle of spontaneous resolution of VUR in time, especially in younger patients with low-grade reflux [3]. This approach includes observation with regular follow-up imaging studies

Variables	Treatment		
	PPC	Surgery	CAP
Gender			
Male	4	8	8
Female	7	6	4
Mean age (y) ± SD	3.2 ± 1.03	3.2 ± 1.55	2.2 ± 1.29
Laterality			
Unilateral	5	4	4
Bilateral	3	5	4
VUR grade			
II	2	2	5
III	6	10	5
IV	3	2	2
DMSA findings			
Decreased tracer	6	10	5
Unremarkable	5	4	7
UTZ findings			
Mild hydronephrosis	1	3	1
Caliectasia	6	8	6
Unremarkable	4	3	5

Table 1: Demographic data and patient baseline characteristics.

Outcome Measure	PPC		Surgery		CAP	
	3 month	1 year	3 month	1 year	3 month	1 year
Success Rate	10/11 (91%)	9/11 (82%)	14/14 (100%)	14/14 (100%)	4/12 (33%)	6/12 (50%)
Reflux Recurrence	-	1/10 (10%)	-	0/14 (0%)	-	-
Febrile UTI	1/11 (9%)	0/11 (0%)	1/14 (9%)	0/14 (0%)	3/12 (25%)	3/12 (25%)
Renal Scarring	1/11 (9%)	2/11 (18%)	2/14 (14%)	2/14 (14%)	3/12 (25%)	5/12 (42%)
Tx related Hospital Stay (Mean ± SD) days per year	-	3.27 ± 1.2	-	4.0 ± 2.6	-	6.25 ± 2.6
Complication rate Clavien-Dindo Grade 3	-	0/11 (0%)	-	1/14 (7%)	-	-

Table 2: Comparison of outcome measures of PPC, Surgery and CAP at 3-month and 1-year follow-up.

(e.g. renal ultrasonography, VCUG, nuclear cystography, or DMSA scanning), and intermittent or continuous antibiotic prophylaxis since VUR in the absence of infection does not damage the kidney. However, in the meta-analysis of five randomized studies by Matoo, antibiotic prophylaxis did not significantly prevented UTI and renal scar development among patients with grade I-V VUR [8]. Likewise, our results have shown that among 12 RRUs (8 patients) who were given prophylactic antibiotic alone, 25% (3/12 RRUs, 2/8 patients) have developed urinary tract infection, both at 3-month and 1-year follow-up. Twenty-five percent and forty two percent of these patients had progression of renal scarring on 3-month and 1-year follow up, respectively.

Although surgical correction by ureteral re-implantation has been considered as the gold standard in the management of reflux with an efficacy rate of almost 100% [9], endoscopic correction of VUR using different bulking agents has progressively been used and widely offered over the past 30 years. It has become a promising procedure that offers minimal-invasiveness with good clinical outcome. Several bulking agents such as poly-tetra-fluoroethylene (Teflon), collagen, autologous fat, poly-di-methylsiloxane, silicone, chondrocytes, dextranomer/hyaluronic acid (Deflux) have been used since their introduction in the early 1980s [10]. According to the systematic review by Chertin et al., among the widely used bulking agents, Poly-tetra-fluoroethylene (PTFE) had the highest long-term success rate of 95% but due to high rate of particle migration was subsequently abandoned; while dextranomer/hyaluronic acid, on the other hand, have a high success rate of up to 92% with only short-term efficacy and high recurrence rate of 26% [6]. The high recurrence rate is probably secondary to the biodegradable property of dextranomer/hyaluronic acid [6].

A recent study done in a tertiary hospital in Canada which used a non-biodegradable polyacrylamide hydrogel injection demonstrated that use of this substance was comparable to the most popular bulking agent, dextranomer/hyaluronic acid with a success rate of 87% for VUR grades I-III at 3 months and 81.2% overall success rate for all VUR grades [7]. Newer bulking agent, Polyacrylate Polyalcohol Copolymer (PPC)-Vantris® a synthetic non-biodegradable compound that belongs to the acryl family was recently introduced for treatment of VUR and showed promising results when compared to other bulking agents [11]. Our results have been consistent and have shown similar findings. Among patients with grades II-IV VUR (Table 1), 82% of RRUs have been successfully treated using PPC injection as seen on repeat VCUG after 1 year. Only one patient had VUR recurrence after 1 year. The result is further supported by another prospective study involving 165 RRUs by Chertin et.al where Vantris injection have corrected 92.7% of RRUs and 4.2% of RRUs after first and second injection, respectively [12]. These results have shown a high level of reflux resolution among grades I-III VUR. In a recent publication of a randomized controlled trial by Garcia-Aparicio et al. from 2002-2004 that included 41 patients with VUR grades II-IV, short-term and long-term follow-up have shown that endoscopic treatment of VUR is as effective as ureteral re-implantation [13]. Our results when compared to the success rate among patients who underwent ureteral re-implantation using Cohen technique showed a comparable outcome between the two groups.

One patient who underwent ureteral re-implantation (7%) had complication of ureteral obstruction while no complication was observed in the PPC group. Furthermore, ultrasound findings have remained stable in all groups, except for 1 patient with grade III VUR in the PPC group who eventually had resolved caliectasia. With this data, the authors believe that among the 3 management, endoscopic correction has the lowest risk to develop post-operative ureteral obstruction. Alizadeh et al. investigated the incidence and presentations of ureteral obstruction in 88 patients with 128 RRUs following periureteral injection of PPC (Vantris) for treatment of VUR. Four patients (4 ureters; 3%) had early-onset transient hydronephrosis and another 3 patients (4 ureters; 3%) developed late-onset obstruction which appeared 3 months to 1 year after treatment [14]. On the contrary, a difference although not significant was observed based on renal scarring status of patients in our study. Renal scarring was evaluated based on DMSA done at initial 3-month and around 1-year post-treatment follow-up. At 3 months, DMSA findings showed improved renal scarring in 45.5% vs. 35.5% and stable in 54.5% vs. 64.3% in PPC group and surgery group, respectively. At 1 –year follow up however, 14% (3/14) of patients in the surgery group has progression of renal scarring as compared to 18% (1/11) in the PPC group. Our data is comparable to the study done by Chertin et al. which evaluated renal scarring using DMSA renal scan after successful correction of VUR using polytetrafluoroethylene and dextranomer/hyaluronic acid copolymer. Their results showed an insignificant 2.3% change in relative scan after successful reflux correction [15].

As previously mentioned, one of the primary advantage of endoscopic correction over the surgical ureteral re-implantation is the shorter hospital stay which was demonstrated in several studies, as such is usually performed on an outpatient basis in many institutions [6,16]. In our study, endoscopic correction with PPC has led to a shorter hospital day of 3.27+1.2 days/year when compared to surgical ureteral re-implantation of 4.0 ± 2.6 days/year.

Conclusion

Our data showed that endoscopic correction of VUR with PPC resulted to better treatment outcome among VUR grades II-IV when

compared to CAP and was comparable to open surgical management with shorter treatment related hospital stay.

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