Original Article

Access this article online
Website: www.afrjpaedsurg.org
DOI: 10.4103/0189-6725.132829
Quick Response Code:

Longterm outcome of Macroplatique injection for treatment of vesicoureteral reflux in children

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ABSTRACT

Background: This study examined our experience with one year follow-up of 20 cases of vesicoureteric reflux in children after treatment with Macroplastique® injection. **Patient and Methods:** A total of 20 children (31 ureters) with primary grades II to V vesicoureteral reflux were treated with subureteral Macroplastique® injection from 2010 to 2011 and followed for an average of 12 months (range 3 to 24). Vesicoureteral reflux was grade II in 3, III in 7, IV in 9 and V in 12 ureters. Each child underwent pre-operative voiding cystourethrography, abdominopelvic ultrasound, urine analysis/culture, S. creatinine and CBC. Dimercapto-succinic acid scan (DMSA scan) and magnetic resonance urography (MRU) were done in some patients. Voiding cystourethrography at 3 months was done to rule out persistent reflux. **Results:** Overall, reflux was corrected in 11 (35.5%) ureters and 9 (45%) children after a single injection. With repeat injection, reflux was corrected in 16 (51.6%) ureters and 11 (55%) children, reflux improved/downgrade in 4 (12.9%) ureters and 2 (10%) children. Correction by grade was 100%, 100%, 9.7%, 9.7% for grades II to V, respectively. There were no surgical complications. None of the cured patients had recurrent reflux during follow-up. There were 9 (45%) children who required open ureteral re-implantation for failed injection.**Conclusion:** Sub-ureteral Macroplastique® injection therapy could be a primary treatment for low grade VUR (grade III or less) in children because it is simple, safe, effective, less invasive, decreased.

Key words: Children, injection, Macroplastique®, polydimethylsiloxane, vesico-ureteral reflux

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INTRODUCTION

Vesicoureteric reflux (VUR) is the most common urological anomaly in children, and a predisposing factor for urinary tract infection (UTI) and pyelonephritis, which can result in renal injury, renal impairment or end-stage renal disease.[1] The primary goals of management of VUR in children are to prevent pyelonephritis, renal injury, and other complications of reflux. Children with reflux may be managed either medically or surgically. The rationale for medical management is prevention of UTI using daily antibiotic prophylaxis, regular timed voiding and, in some cases, anticholinergic medication, surgical management of reflux consists of repair of the ureterovesical junction abnormality.[2]

Endoscopic correction of VUR has revolutionized the treatment of VUR. It has become an established alternative to long-term antibiotic prophylaxis and ureteral reimplantation. It was first utilized in 1981 by Matouschek[3] and was applied to both the bladder neck and periurethral tissues by politanoin 1982.[4] The method was further developed by O'Donnell and Puriwho in 1984 reported results in both pigs and humans with subureteric Teflon injection (STING).[5] However, the technique was not used widely because of concerns regarding particle migration.[6]Subsequently, cross-linked collagen was used for sub-ureteral implantation but there were no concerns regarding absorption of the material.Because of the inconsistency and questionable durability of cross-linked collagen, most centers have abandoned its use for correction of reflux.[7,8] PDS (Macroplastique®) was introduced clinically by Azmy *et al.* in 1993.[9]

In this study we document our experience with endoscopic subureteral polydimethylsiloxane (Macroplastique®) injection in 20 children as treatment of primary vesicoureteral reflux.

PATIENTS AND METHODS

From January 2010 to December 2011, 20 consecutive patients (14 girls, 6 boys; aged 2-10 years with mean age of 4.9 years) presenting to our hospital with primary VUR. The inclusion criteria included consent by the parents/guardians, and persisting reflux after treating the underlying condition of grade II-V. Exclusion criteria included secondary reflux, UTI at the time of treatment, malignancies of the bladder or ureters, previous injection therapy. All patients were graded according to the international classification system.[10] All patients were implanted with PDS (Macroplastique®).

Preoperative voiding cystourethrography, abdominopelvic ultrasound, urine analysis/culture, serum creatinine and complete blood count evaluation were carried out in all patients. Dimercapto-succinic acid scan (DMSA scan) and magnetic resonance urography (MRU) were done in some patients.

Indications for surgery were:

- Grades IV and V reflux
- Persistent reflux Despite Medical therapy (Beyond 3 Years)
- Break through UTIs while antibiotic prophylaxis
- Medical non-compliance with medical therapy
- Progressive renal scarring on antibiotic prophylaxis
- Associated ureterovesical abnormality
- Multiple drug allergies that preclude use prophylaxis

Surgery was performed on an outpatient basis under general anaesthesia and standard aseptic conditions. A 14/14. 5 Fr pediatric operating cystoscope with an offset lens is used to fill the bladder to approximately three-quarter capacity, and a 3Fr ureteral catheter is used to cannulate the refluxing ureter to assess the axis and length of the intramural ureter. Urine forculture was obtained before parenteral prophylactic antibiotics were given. A 5 Fr flexible endoscopic injection needlealready primed with polydimethylsiloxane was used with apolydimethylsiloxane administration gun to deliver the implant. The needle was passed through the working channel ofthe cystoscope into the bladder. The puncture site is made at the inferior medial aspect of the verge of theureteral orifice "1 cm distal to the ureteric orifice" at the 6 o'clock position and tunneled submucosally along the direction indicated by the ureteral catheter, which is maneuvered to tent the ureter upwards. Injected volumes vary from 0.2 to 1.0 ml per refluxing ureter, depending on surgeon judgment of an adequate subureteral mound. The injection process was judged to be complete when the ureteral orifice was elevated (mounding) and assumed a crescent-shaped appearance. Attempts were madeto avoid multiple needle perforations of the bladder mucosa to avoid the possibility of implant extrusion. The contra lateral orifice was injected at the same setting when the patient had bilateral reflux. After the last injected bolus of polydimethylsiloxane the needle is held in place for 30 seconds and then slowly removed. The injection site is inspected for escape of the implant. The ureteral catheter isthen removed, bladder drained and procedure terminated.

Each child had a short convalescence in the recovery room and is sent home in 4 hours with routine analgesia. Patients were maintained on antibiotic regimen for 3 months until reflux resolution was documented by post operative voiding cystourethrography (VCUG). If the VCUG indicated no reflux the prophylactic antibiotic was discontinued. If reflux was persistent, the parents were offered 2nd injection or continued observation on prophylactic antibiotics. Failure to correct reflux was defined as the persistence of VUR after endoscopic injection that was also documented on VCUG.

Patients in whom re-treatment failed were scheduled for open surgical correction of reflux.

At the 1-year follow-up each patient was further evaluated with the same investigations that were done for him before injection. Depending on the condition of the children, they were scheduled for a regular follow-up. If patients were cured on the basis of the VCUG after 1 year, and free of symptoms, they were considered cured and discharged from further follow-up visits.

In our study clinical cure was defined as reduction to grade 0 or reduction to grade I VUR that submitted to observation and further follow up visits until complete resolution.

RESULTS

Twenty patients (31 refluxing ureteral units), 6 males and 14 females were available for analysis at least 12 months after injection therapy. The grade of reflux was II, III, IV and V in 3, 7, 9 and 12 ureteral units, respectively [Table 1]. Reflux was unilateral and bilateral in 9 (45%) and 11 (55%) cases, respectively.

Overall correction at 3 months after a single endoscopic injection was 45% in 9 children with 11 (35.5%) refluxing ureters which increased to 55% in 11 children with

16 (51.6%) refluxing ureters in addition to improvement/downgrading of reflux in 2 (10%) child with 4 (12.9%) refluxing ureters "2 from grade IV to grade III and 2 from grade V to grade III" at 1 year after second endoscopic injection. Overall correction according to grades was 100% for grade II, 100% III, 9.7% IV and 9.7% V ($P < 0.001$), reflux grade did not change in 7 (35%) children with 11 (35.5%) refluxing ureters [Table 2]. The families of these children with improvement/downgrading did notdesire conservative follow up and they selected surgical intervention by ureteral reimplantation. Also patients who did not show any change in reflux grade, underwent ureteric reimplantation.

Ureteric reimplantation was necessary in 15 refluxing ureters. No intraoperative complications were noted. At 1 year follow up after injection, postoperative recurrent UTI was noticed in 12 patients. 9 with persistent reflux, 2 had bilateral reflux which resolved on one side and failed injection on other side, all of them treated according to culture then under went ureteric reimplantation and one patient had been cured but showed UTI because of uretheral catheterization as a result of total incontinence that due to meningocele. As shown on renal ultrasound asymptomatic denovo moderate hydronephrosis developed in 5 patients, in 25.8% (8/31) ureters that were of mild hydronephrosis preoperatively. All 5 had persistent reflux on reimaging and obstruction on diuretic renogram in 3 of them, all then submitted to surgical intervention by ureteral reimplantation. Six patients had evidence of renal scarring at the beginning of the study on the DMSA scan. Four of them had progressive "new" renal scarring during followup period. Those patients who experienced recurrent UTIs found to have persistent reflux. So they underwent ureteric reimplantation. However, postoperative contralateral reflux which occurs in unilateral cases was not observed in any case.

Table 1: Ureteral units according to reflux grade treated with subureteral Macroplastique® injection.

Reflux grade	No. of ureteral units	%
Grade II	3	9.7
Grade III	7	22.6
Grade IV	9	29
Grade V	12	38.7
Total	31	100

Table 2: Outcome of Macroplastique® treatment according to reflux grade.

Reflux grade	No. of ureteral units	Clinical cure (%)	Downgrading (%)	Persistence (%)
II	3	3 (100)	0	0
III	7	7 (100)	0	0
IV	9	3 (9.7)	2 (6.45)	4 (12.9)
V	12	3 (9.7)	2 (6.45)	7 (22.6)
Total	31	16 (51.6)	4 (12.9)	11 (35.5)

DISCUSSION

There is high association between VUR, UTI and renal damage. Reflux nephropathy is the cause of end stage renal failure in about 25% of children.[11] Conservative medical management in which patients are continued on prophylactic antibiotics to prevent the recurrence of infection, constitutes the standard initial management of VUR.

However, the international reflux study and Amercian Urological Association put forth absolute and relative indications for surgical interventions, break through UTIs is the leading cause of anti-reflux procedures. Endoscopic subureteral transurethral injection (STING) has become a first-line therapy for children with vesicoureteral reflux (VUR) because of its high success rates and few complication.[12]

Debate over the ideal bulking agent in endoscopic therapy for children with VUR remains controversial. However, the substance should be nontoxic, biocompatible, nonmigratory, and nonantigenic and should cause minimal local inflammation.[13] Many bulking agents have been used to treat reflux, among these agents,Macroplastique®. It is a nonbiodegradable substance, reabsorbed and exchanged with a reactive transudate containing fibroblasts that then facilitate its encapsulation.

We report on the results in 20 children with 31 refluxing ureters who have undergone a total 51 endoscopic subureteral injections as an alternative to open ureteral reimplantation. After a single injection reflux was corrected in 35.5% of ureters and 45% children, and after repeat injection when indicated 51.6% ureters and 55% children with success rate more in low grade than high grade reflux. In our analysis of the factors that predicted the success of Macroplastique® injection, we found that the grade of VUR was the only predictor of success, lower preoperative VUR grade results in higher success rate. Other studies have reported similar results with higher success rates observed in lower grades of reflux and in uncomplicated cases.[14,15] However, previously groups have reported success rates with PDMS injection of between 70 and 90%.[16-18] So another factors other than high grade may explain failure in our study such as, operator's technical failure/errors

when choosing the injection site or depth, incomplete achievement of the learning curve andshortage of operator's experience, preoperative bladder instability and voiding dysfunction which should be addressed and managed before endoscopic injection, old fashion technique where improvement in technique of injection offers greater success rate than usual technique such as modified STING technique showed high success rate in high grade reflux, preoperative recurrent UTIs with possibility of anatomical abnormality such as paraureteric diverticulum, trabeculated bladder or previous LUT reconstruction such as augmentation cystoplasty and specific co morbidity. These factors explained causes of failed injection in the previous mentioned studies.[17,18]

In 2004, Van Cpelle *et al.* reported that UTI recurred after treatment in 15% patients (n = 14/94) from *the Zwolle* group (11/14) with persistent VUR and in 17.8% patients (n = 18/101) from *the Glasgow* group (6/18) with persistent VUR.[19] However, Young Dae Bae *et al.* reported that incidence of asymptomatic UTIs during the follow-up period after successful Macroplastique® injection was low (9.6%) and concluded that the Macroplastique® procedure was effective not only in eliminating VUR on radiologic studies, but also in reducing the incidence of UTIs in children with VUR.[20] In our study, postoperative recurrent UTI was in 60% (n = 12/20) patients, 11/12 with persistent reflux on reimaging which may be related to sex because 70% of patients were females that at increased risk for recurrent UTIs, underlying condition as bladder/bowel dysfunction, high grade or bilateralism of reflux, stoppage of prophylactic antibiotics post injection because of drug intolerance or economic burden and antibiotic resistance.

Al-Hunayan *et al.* observed a single case of symptomatic obstruction following polydimethylsiloxane injection that treated with ureteral reimplantation. However, they noted that an "excess amount" of substrate was injected in this case, and the obstruction was attributedto this factor.[21] However, AbouTaleb *et al.* reported that incidence of *de novo* mild hydronephrosis after Macroplastique® injection was 3% which resolved with follow up.[22] In our series, we observed postoperative asymptomatic moderate de novo hydronephrosiswhich was of mild degree preoperatively in 25% (n = 5/20) patients, all with persistent reflux on reimaging. It may be related to underlying condition as neurogenic bladder "1 case" or dysfunctional voiding "3 cases", high grade of reflux, injection technical error "1 case" or radiologist opinion who was not constant where U/S is operator dependant.

As regard to renal scarring following Macroplastique® injection, this point was noted in observational study by El-Saied *et al.* who reported in series of 100 patients that 75% had renal scarring detected before correction of reflux and on follow up DMSA scan post injection, 6 (8%) patients showed progressive scarring. Those were found to have persistent reflux and required intervention by surgery.[23] In our study, we included 6 patients who had evidence of renal scarring, during follow up 4/6 had progressive or new scarring on DMSA scan. Those 4 patient sex perienced recurrent UTIs and were found to have persistent reflux for open surgery.

The most common complication that may be noticed after Macroplastique® injection was the occurrence of contralateral denovo reflux in the unilateral cases. In 2001 Herz *et al.* reported in their series*de novo* contralateral grades I and II reflux developed in (3%) children, after an ipsilateral injection, and both were observed.[17]

However, Abou Taleb *et al.* reported that postoperative contralateral reflux was not observed in any one of 74 (108 ureters) patients treated with Macroplastique®.[22]

In our study, we did not record such as this complication throughout the work and this is consistent with published data.

CONCLUSION

At our institution subureteral endoscopic injection of Macroplastique® is a reliable alternative to open ureteral reimplantation for treatment of VUR in children, with every expectation that the majority will be cured with this low morbidity outpatient endoscopic procedure.Further more, more than any other nonautologous bulking agent Macroplastique® fulfills many if not all criteria required for the ideal implantable bulking agent and has the advantage over autologous agents for being inherently stable. It offers major advantages to patients and parents, the procedure is performed generally in less than 20 minutes and is typically performed on an outpatient basis. It is simple, safe, minimally invasive, cost-effective, well tolerated by patients and associated with very low morbidity, which makes it more appealing to parents. It offers high success rate with minimal complications, this makes it a viable first line treatment option that can be offered to patients with low grade VUR (grade III or less) in whom medical management fails. Its success is as durable as open surgical repair, with a progress seen at 1 year of follow up.

To the best of our knowledge this report, Macroplastique® injection is an alternative initial approach to surgery if intervention were indicated in children with low grade primary VUR. As is true for all new modalities of surgical treatment, more studies with higher number of children undergoing Macroplastique® injection to treat reflux, and longer followup are required to confirm long-term safety and efficacy, and to determine at-risk patients necessitating intervention and to determine how patients benefit from injection therapy.

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Cite this article as: Mohamed EA, Shehata FH, Abdelbaset EA, Abdelkhalek MA, Abdelatif AH, Galal HA. Longterm outcome of Macroplatique injection for treatment of vesicoureteral reflux in children. Afr J Paediatr Surg 2014;11:174-8.

Source of Support: Urology department, al azhar university, Egypt, Cairo.
Conflict of Interest: Nil.