

Endoscopic treatment of vesicoureteral reflux with dextranomer/hyaluronic acid-our experience

Prasad Mylarappa*, Prathvi, Puvvada Sandeep, Kailash B. Banale and D. Ramesh

Department of Urology, M.S. Ramaiah Medical College and Hospital, MSRIT Post, New BEL Road, Bangalore-560054, Karnataka, India

Abstract: *Objectives:* We report our experience with subureteral submucosal injection therapy for vesicoureteral reflux and determine the safety and efficacy in patients treated with dextranomer/hyaluronic acid co-polymer. *Background:* Vesicoureteral reflux affects 1% of children and increases the chances of urinary tract infection, pyelonephritis, hypertension and chronic renal insufficiency. The aim of identifying and treating vesicoureteral reflux in children is to prevent occurrence of long term complications. *Method:* A total of sixty three patients aged between 1-21 years with grade III – V vesicoureteral reflux, who had failed on conservative treatment were considered for this study during February 2004 to May 2012. Vesicoureteral reflux was diagnosed by voiding cysto-urethrogram (VCUG). They underwent subureteral injection of dextranomer/hyaluronic acid co-polymer. *Results:* Among the sixty three patients treated, 51(81%) were cured with single injection while a second injection raised the cure rate to 60(95%). *Conclusion:* The minimally invasive treatment of vesicoureteral reflux with deflux (dextranomer/hyaluronic acid co-polymer) is an effective alternative procedure to open surgical technique requiring minimal operating time with low morbidity.

Keywords: Vesicoureteral reflux, Dextranomer/hyaluronic acid copolymer injection.

Introduction

Vesicoureteral reflux is one of the common problems encountered in urological practice. Vesicoureteral reflux affects 1% of children and increases the chances of urinary tract infection, pyelonephritis, hypertension and chronic renal insufficiency [1-2]. The aim of identifying and treating vesicoureteral reflux in children is to prevent occurrence of long term complications. Matouschek in 1981 first described an Endoscopic treatment of reflux by means of subureteral injection of bulking material which was further developed by Puri and O'Donnel [3-5].

Endoscopic treatment has gained popularity and has proved successful in high percentage of cases and it is considered as an alternative to open surgery or failed conservative treatment. In September 2001, the Food and drug administration approved dextranomer/hyaluronic acid (Dx/HA) copolymer (Deflux, Q-Med Scandinavia, Uppsala, Sweden) as an acceptable implant for subureteral injection for vesicoureteral reflux in children. Since then, various authors presented their reports with

success depending on grade of vesicoureteral reflux. We report our experience with subureteral submucosal injection therapy for vesicoureteral reflux and to determine the safety and efficacy in patients treated with dextranomer/hyaluronic acid co-polymer.

Material and Methods

A total of 63 patients aged between 1-21 years with grade III –V vesicoureteral reflux who had failed on conservative treatment were considered for this study. They underwent subureteral injection of dextranomer/hyaluronic acid co-polymer for vesicoureteral reflux (STING procedure = subureteric transurethral injection) at our institution during Feb 2004 to May 2012.

Technique: This procedure was done under general anesthesia with parenteral antibiotic prophylaxis. Patient is put in lithotomy position and cystoscopy was done with universal pediatric cystoscope. After identifying the appropriate ureteric orifice, needle is advanced through the operating channel of cystoscope to approach the ureteric

orifice at 6 o' clock position. The needle is advanced in plane between the bladder mucosa and the bladder muscle starting 4mm distal to the ureteric orifice and then travelling under the intravesical ureter for a distance of about 5mm (STING procedure). The injection was given until the appearance of the ureteric orifice resembling an inverted crescent. The needle remains in place for about one to two minutes to prevent any back leak of the injectable. Then instrument and the needle are removed simultaneously.

It is very important to make first needle placement accurately because multiple needle punctures under a given ureteric orifice would lead to back leak of the material with resultant failure. The volume of injection depends on the severity of the defect at the vesicoureteral reflux and the accuracy of needle placement. The volume of material injected generally ranges from 0.6-1.4ml. The patient is discharged on next day on oral antibiotic prophylaxis and advised to come for follow up after three weeks with renal ultrasound, micturating cystourethrogram, and urine culture sensitivity. Micturating cystourethrogram was done using standard protocol and resolution of reflux was defined as grade 0. If reflux is resolved and no further episodes of urinary tract infection, then patient is advised for follow up after one year with renal ultrasound. Repeat injections were given for patient with continuing reflux and later followed them with micturating cystourethrogram.

Results

Sixty three patients and eighty five ureters with a mean age of seven years (range 1-21 years) underwent dextranomer/ hyaluronic acid copolymer injection for vesicoureteral reflux from February 2004 to May 2012. There were thirty nine girls (62%) and twenty four boys (38%). In our study twenty-two patients (35%) had bilateral and forty-one patients (65%) had unilateral vesicoureteral reflux. All these patients were subsequently followed up with urine culture sensitivity, serum creatinine, renal ultrasound and micturating cystourethrogram with a mean follow up of two years (range 3 months to 48 months). The micturating cystourethrogram follow up showed that the overall cure rate was 81%. Among the sixty three patients treated 51(81%) were cured with single injection, while with second injection 60 were cured with the cure

rate of 95%. There were fifty-nine patients with primary vesicoureteral reflux and four patients (with five renal units) with secondary vesicoureteral reflux (due to neurogenic bladder). Renal scarring was documented in 33 renal units on DMSA scan (38.82%).

The mean operating time was sixteen minutes and the mean amount of Deflux injected per renal unit was 0.8 ml (0.6-1.4ml). One patient had complete duplex unit and the cure rate achieved was 100%. Dysfunctional voiding syndrome was diagnosed in nineteen children (mean age of eight years) and the cure rate was 18/19 (95%) with only one patient requiring second injection. Three patients were subjected for injection after failure of open reimplantation curing all three patients with 100% success rate. We injected two renal units associated with hutch diverticulum and one was cured (50%). Four patients had neurogenic bladder with a total of five refluxing renal units. Among those patients with neurogenic bladder, three patients had unilateral reflux and were cured after single injection; the other child with bilateral vesicoureteral reflux required two injections for cure. Contra lateral low grade de-novo vesicoureteral reflux was seen in two patients (4.8%) treated for unilateral vesicoureteral reflux. They were observed clinically and all of them resolved spontaneously on follow up micturating cystourethrogram. One patient developed calcification of deflux material after twenty four months with one episode of urinary infection. Ultrasound showed lower ureteric obstruction with mild hydroureteronephrosis. She was managed with balloon dilatation of lower ureter with double J stenting for two months. On follow up, patient is asymptomatic and no more episodes of urinary tract infections. Ultrasound and retrograde pyelography done on follow up study were normal.

Discussion

A minimally invasive alternative to open surgery or conservative treatment with antibiotic has been the "holy grail" of management. In our practice there has been paradigm shift in vesicoureteral reflux management. The Endoscopic correction of reflux has given a significant number of

patients a minimally invasive way of eliminating reflux and it allows immediate protection against further reflux associated with renal damage. The success rate of open surgery is reported to be close to 98% in most series [6]. Although endoscopic treatment has a little lower success rate, it has the advantage of being a daycare procedure, that is minimally invasive with a low morbidity and a low overall cost [7]. O'Donnell and Puri in 1980's introduced the technique of subureteral injection to create a less invasive treatment for vesicoureteral reflux [8]. The basic principle is to buttress beneath the ureteral orifice, thereby allowing the ureteral mucosa to coapt during bladder filling which will prevent reflux. The ideal substance should be durable, effective and safe. This substance needs to be inert, easily injectable and stable with time so that the volume is not lost and must not extrude or migrate. It should also be biocompatible, non-antigenic and non-carcinogenic. The success of subureteral injection in correcting vesicoureteral reflux appears to be dependent on correct surgical technique.

The procedure itself is technically easy and has a relatively short learning curve. The dextranomer microspheres are 80-120 microns in diameter. These microspheres are made up of a network of cross linked dextran polysaccharide molecules that prevent fragmentation and migration [9]. The suspension thus created causes neither allergic nor immunogenic reactions. The dextranomer/hyaluronic acid copolymer implant contracts minimally because of the in growth of fibroblast and the production of endogenous collagen between the microspheres. A clinical study has shown that this in growth of fibroblast and collagen limits volume reduction to 19% over the first three months after treatment [9]. Moreover, the volume reduction over twelve months has shown in an animal study to be only 23% and hence it is shown that injected gel is able to cure reflux for an extended period [10].

Christopher S Cooper et al suggests an increased susceptibility to infection in the developing kidney. The risk of renal scars is high in young children aged less than six years. There is a great reduction in the glomerular filtration rate, if a child develops pyelonephritis before three years of age [11]. Children with reflux and urinary tract infection are at increased risk of renal scarring.

Many studies have demonstrated a direct correlation between increased prevalence of scars and increased grades of reflux [12]. In the International Reflux study, 50% of children with grade III – V reflux had scars at diagnosis and the risk of parenchymal loss is higher with high grade reflux and intrarenal reflux [13]. In our study mean age of children was seven years and renal scarring was seen approximately in one third of patients, since all of our patients had high grade reflux (grade III – V). Capozza et al demonstrated that endoscopic treatment with dextranomer/hyaluronic acid copolymer proved to be effective and well tolerated during long term follow up (7.5 years) in children with vesicoureteral reflux [14]. In our study patients were followed up with mean duration of twenty four months.

Reoperation on a failed open reimplantation for vesicoureteral reflux may be difficult due to risk of devascularisation and endoscopic deflux injection is a simple procedure for these cases. In our study, all three patients who were failed on open reimplantation were cured with success rate of 100%. Marcos-Perez-Bray field et al reported a success rate of 88% in their series of seventeen patients [15]. Vesicoureteral reflux in neurogenic bladder results from high intravesical pressure created because of abnormal voiding pattern, unlikely to subside with conservative treatment. Four patients of neurogenic bladder with five refluxing units have undergone deflux injection in the current study curing three patients with single injection and other one requiring second injection. Similar results were reported in the reports of Marcos et al with the success rate of 78% [15].

Hutch diverticulum usually found lateral and cephalad to the ureteric orifice in patients with vesicoureteral reflux. If they are large, reflux unlikely to subside with conservative treatment. In a study by Marcos-Perez-Bray field et al six cases of Hutch diverticulum with vesicoureteral reflux were treated by endoscopic deflux with success rate of 67% [15], whereas in our current study we treated two renal units with Hutch diverticulum with success rate of 50%. Sternberg A et al reported overall success rate of 68-86%

following deflux injection for vesicoureteral reflux [9], whereas Luis A Guerra reported a success rate of 80% in his series [16]. A study by Richard N et al with a mean follow up duration of eighteen months showed resolution of reflux in 92.6% of cases following one to two injections using STING (subureteric transurethral injection) or HIT technique (Hydro distention-Implantation Technique) [17]. These results are similar to results of our study with the success rate of 95%. Lackgren G et al followed up his patients for five years following STING procedure for vesicoureteral reflux and observed a success rate of only 68% [18] as compared to the present study which demonstrated overall success rate of 81% following single injection and 95% following second injection.

There was no evidence of clinical deterioration in patients who responded positively to treatment and no adverse events seen in the postoperative period. Our study demonstrates dextranomer/hyaluronic acid co-polymer therapy is safe and highly successful. Our data strongly supports recommending this therapy as a first line treatment of vesicoureteral reflux.

Conclusion

The minimally invasive treatment of vesicoureteral reflux with deflux is an effective alternative procedure to open surgical technique requiring minimal operating time with low morbidity. 81% of the patients undergoing this treatment cured after one injection and the success rate increased to 95% with the second injection. Deflux promotes resolution of vesicoureteral reflux by providing adequate support to the posterior aspect of the ureter. Other associated problems like dysfunctional voiding and neurogenic bladder does not seem to adversely affect results. It is worthwhile considering this minimally invasive technique for cases like failed open reimplantation because of less morbidity than redo reimplantation. There is a short learning curve with injection therapy and further experience with this technique may improve our results and cure rate.

Acknowledgement

I thank Urology department of M.S. Ramaiah Medical College, the ethical committee and my family for their encouragement and support.

References

- Smellie JM, Barratt TM, Chantler C, Gordon I, Prescod NP, Ransley PG. Medical versus surgical treatment in children with severe bilateral vesicoureteral reflux and bilateral nephropathy: a randomized trial. *Lancet.*, 2001; 357(9265):1329-33.
- Jacobson SH, Hansson S, Jakobsson B. Vesico-ureteric reflux: occurrence and long-term risks. *Acta Paediatr Suppl.*, 1999; 88(431):22-30.
- Matouschek E. Die behandlung des vesikornalen refluxes durchtransurethraleinspritzung von Teflon paste. *Urologe A.* 1981; 20(5):263-4. [PubMed: 7197421].
- Puri P, O'Donnell B. correction of experimentally produced vesicoureteric reflux in the piglet by intravesical injection of Teflon. *Br Med J.* 1984; 289:5-7. [PMCID :PMC 1442059] [PubMed:6428663].
- O'donnell B. Correction of experimentally produced vesicoureteric reflux by endoscopic injection of Teflon. *Br Med J.* 1984; 289:7-9. [PMCID:PMC1442065] [PubMed:6428669].
- Medical versus surgical treatment of primary vesicoureteral reflux: report of the International Reflux Study Committee. *Pediatrics.* 1981; 67(3):392-400.
- Leonard MP, Decter A, Mix LW, Johnson HW, Coleman GU. Endoscopic treatment of vesicourteral reflux with collagen: preliminary report and cost analysis. *J Urol.* 1996; 155(5):1716-20.
- O'Donnell B, Puri P. Treatment of vesicoureteric reflux by endoscopic injection of Teflon. 1984. *J Urol.* 2002; 167(4):1808-9; discussion 1810.
- Stenberg A, Läckgren G. A new bioimplant for the endoscopic treatment of vesicoureteral reflux: experimental and short-term clinical results. *J Urol.* 1995; 154(2Pt2):800-3.
- Stenberg A, Larsson E, Lindholm A, Ronneus B, Stenberg A, Lackgren G. Injectable dextranomer-based implant: histopathology, volume changes and DNA-analysis. *Scand J Urol Nephrol.* 1999;33(6):355-61.
- Cooper CS, Austin JC. Vesicoureteral reflux: who benefits from surgery?. *Urol Clin North Am.* 2004; 31(3):535-41.
- Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med.* 2003; 348(3):195-202.
- Smellie JM. Commentary: management of children with severe vesicoureteral reflux. *J Urol.* 1992; 148(5Pt2):1676-8.

14. Capozza N, Caione P. Vesicouretral reflux: Surgical and endoscopic treatment. *Pediatr Nephrol.* 2007; 22(9):1261-5.
15. Perez-Brayfield M, Kirsch AJ, Hensle TW, Koyle MA, Furness P, Scherz HC. Endoscopic treatment with dextranomer/hyaluronic acid for complex cases of vesicoureteral reflux. *J Urol.* 2004; 172(4 Pt 2):1614-6.
16. Guerra LA, Khanna P, Levasseur M, Pike JG, LeonardMP. Endoscopic treatment of vesicoureteric reflux with Deflux: a Canadian experience. *Can UrolAssoc J.* 2007; 1(1): 41–45.
17. Yu RN, Roth DR. Treatment of vesicoureteral reflux using endoscopic injection of nonanimal stabilized hyaluronic acid/dextranomer gel: initial experience in pediatric patients by a single surgeon. *Pediatrics.* 2006; 118(2):698-703.
18. Lackgren G, Wahlin N, Skoldenberg E, Stenberg A. Long-term followup of children treated with dextranomer/hyaluronic acid copolymer for vesicoureteral reflux. *J Urol.* 2001; 166(5):1887-92.

*All correspondences to: Dr. Prasad Mylarappa, Associate Professor, Department of Urology, MS Ramaiah Medical College and Hospital, New BEL Road, Bangalore-560054 Karnataka, India. E-mail ID: prasadmyl@rediffmail.com