

Outcome of salvage ureteral reimplantation after endoscopic treatment failure for high-grade vesicoureteral reflux compared to primary ureteral reimplantation

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Abstract

Introduction: Surgical treatment of vesicoureteral reflux is required after conservative treatment has failed. However, there is a controversy if fibrosis related to previous attempts of dextranomer/hyaluronic acid (Dx/Ha) injection increases the risk of surgical difficulty and postoperative complications. Therefore, the purpose of our study was to compare the outcome of salvage ureteral reimplantation (SUR), after failed endoscopic therapy, to that of primary ureteral reimplantation in patients with high-grade primary vesicoureteral reflux (VUR).

Materials and Methods: We conducted a retrospective analysis of children, <14 years old, treated for Grade IV or V VUR, between 1998 and 2014. Cases were classified into the SUR or the PUR group. Cases of secondary VUR were excluded. All patients were treated using a cross-trigonal ureteral reimplantation technique by two surgeons. The following demographic and clinical variables were included in the analysis: presentation, reflux severity, scarring on imaging, age at endoscopic injection, total amount of Dx/Ha injected, operative time, postoperative hospital stay, operative complications, incidence of febrile urinary tract infections (UTIs) after surgery, and persistent VUR. Between the groups, differences were evaluated using Fisher's exact test.

Results: Twenty-six patients were included, 19 in the SUR and 7 in the primary ureteral reimplantation (PUR) group. In the SUR group, 12 cases had a bilateral VUR and 7 had a unilateral VUR, with 4 bilateral and 3 unilateral VUR cases in the PUR group. In the SUR group, 13 patients had received one Dx/Ha injections, with the other 6 receiving two injections, of 0.5 ml of Dx/Ha (range, 0.5–2.0 ml). A bilateral reimplantation was performed in 14/19 patients in the SUR group and 4/7 in the PUR group. The median age at surgery was 4 years in the SUR group and 3 years in the PUR group ($P < 0.02$). The median operative time was comparable between the groups (120 and 140 min for the SUR and PUR groups, respectively, $P = 0.73$), with

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Received: 01.05.2019, **Accepted:** 13.10.2019, **Published:** 23.12.2019.

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/UA.UA_58_19

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How to cite this article: Burki T, Howeiti MS, Almadhi MK, Al Modhen FM, Alhazmi H, Vallasciani SA, *et al*. Outcome of salvage ureteral reimplantation after endoscopic treatment failure for high-grade vesicoureteral reflux compared to primary ureteral reimplantation. *Urol Ann* 2020;12:49-53.

a comparable length of hospital stay (5 and 6 days, respectively, $P = 0.061$). Blood loss was generally < 10 ml, except in three cases in the SUR group, due to difficult dissection. Over the median follow-up of 1 year, persistent Grade III SUR was identified in only one patient in the SUR group, with no occurrence of febrile UTIs postoperatively.

Conclusion: SUR for high-grade primary VUR after failed Dx/Ha injection has the same success rate as PUR, with no significant complication rate, although the necessary dissection may be more difficult.

Keywords: Failed endoscopic treatment, ureteral reimplantation, vesicoureteral reflux

INTRODUCTION

Vesicoureteral reflux (VUR) is one of the most common urological entities in pediatric urology, affecting 1%–3% of children.^[1] If left untreated, VUR can lead to recurrent urinary tract infections (UTIs), renal scarring, and/or hypertension, with a possible serious consequence of end-stage renal disease.^[2-4] Before popularization of the endoscopic management of VUR by O' Donnell and Puri, ureteral reimplantation was the gold standard to treat VUR.^[5] Currently, dextranomer hyaluronic acid (Dx/Ha), which is a combination of dextranomer and hyaluronic acid,^[6] is the most popular agent used for endoscopic treatment of VUR, due to its efficacy and safety profile.^[7,8] The hyaluronic acid component acts as a vehicle which is absorbed within a few weeks. The dextranomer component causes an inflammatory foreign body reaction with ingrowth of host vessels and fibroblasts and ultimately deposition of autologous collagen with some fibrosis.^[9]

The outcome of Dx/Ha treatment varies for the different grades of VUR, with different success rates having been reported by different centers for the same grade of VUR. A meta-analysis by *et al.* reported a success rate of 78.5% for VUR Grades I and II, 72% for Grade III, 63% for Grade IV, and 51% for Grade V.^[10] Surgery is usually recommended when medical management fails. In cases of treatment failure, when salvage ureteral reimplantation (SUR) is required, concern has been raised regarding increased difficulty with the surgical procedure and operative complications due to the fibrosis caused by Dx/Ha.^[11-13]

The aim of our study was to compare the outcome of SUR performed after failure of endoscopic injection, in terms of complications during and after surgery and success rate, to that of primary ureteric reimplantation (PUR) for patients with high-grade VUR. To our knowledge, this is the first study to compare the outcomes of SUR and PUR exclusively for cases of Grade IV–V primary VUR.

MATERIALS AND METHODS

After approval by our institutional review board, we retrospectively reviewed the medical records of all patients < 14 years of age who underwent surgical treatment for primary high-grade VUR (Grade IV–V, according to international VUR grading system) by two pediatric urologists in two tertiary care institutions, between 1998 and 2014. Patients were classified to the SUR or PUR group according to treatment received. In the SUR group, we included cases where ureteral reimplantation was performed after failed initial Dx/Ha. These patients were treated between 2004 and 2014, when Dx/Ha was available. In the PUR group, we included all cases where ureteral reimplantation was performed without prior injection of Dx/Ha. These patients were treated between 1998 and 2004. Patients with low-grade reflux and secondary VUR were excluded. In cases of bilateral reflux, we only included cases that had a Grade IV or V VUR at least on one side. The indications for intervention were breakthrough UTI while on antibiotic prophylactic and/or formation of new renal scars with persistent VUR.

The following variables were extracted from the medical records for analysis: age; sex; presentation; severity of reflux before surgery, assessed by a voiding cystourethrogram (VCUG); presence/absence of scarring on ^{99m}Tc -dimercaptosuccinic acid (DMSA) nuclear scans; age at injection of Dx/Ha, when performed; total amount and number of times Dx/Ha was injected, when performed; operative time for salvage reimplantation; length of postoperative hospital stay; and intraoperative and postoperative complications, such as bleeding, injury to surrounding tissues, and any further UTI.

Intraoperatively, in cases of SUR, the injected Dx/HA was either drained if it was distant from the ureter or excised along with only the adjacent part of the ureter before reimplantation. A cross-trigonal ureteral reimplantation was performed in all cases. The use of ureteral stenting was left to the discretion of the surgeon. A Foley catheter was placed for bladder drainage at the end of the procedure in

all cases. The catheter and stent if used were removed on postoperative day 5, and patients were discharged on the same day after passing urine.

Over the postoperative follow-up, all patients underwent ultrasound (US) examination at 6–12 weeks and a VCUg to rule out persistent VUR. Any incidences of further febrile UTI were recorded. DMSA was only performed postoperatively in cases of febrile UTI after surgery to assess further renal damage. Patients were discharged after 1 year if VCUg and US examinations were normal and the patient had no further UTIs. All data were expressed as a median, range, and percentile values (as appropriate for the variable type), with Fisher's exact test used to evaluate between-group differences, with $P < 0.05$ (statistically significant).

RESULTS

Our study group was formed of 26 patients, 19 in the SUR group and 7 in the PUR group. In the SUR group, 12 had a bilateral high-grade VUR and 7 had a unilateral presentation, with 11 cases of Grade IV VUR and 8 of Grade V. Among the 12 patients with a bilateral VUR, three presented with a Grade V VUR bilaterally, whereas three had a Grade IV VUR bilaterally, three had a combination of Grade V and Grades I–III, and three had a combination of Grade IV and Grades I–III. In the PUR group, four had a bilateral VUR and three had a unilateral high-grade VUR. Among these, one patient presented with bilateral Grade V, one with bilateral Grade IV, and two with a combination of Grade IV and Grade II VUR.

Relevant preoperative demographic and clinical variables are summarized in Table 1. In the SUR group, 13 children had received one Dx/Ha injection and six had received two injections. The median volume of Dx/Ha injected in each ureter was 0.5 ml (range, 0.5–2 ml), with a median time between the first endoscopic injection and reimplantation of 14 months (range, 4–41 months). All the children in both the groups had breakthrough UTI with or without formation of new scars despite antibiotic prophylaxis. A bilateral ureteral reimplantation was performed in 14 children in the SUR group, including two children with a unilateral VUR but with evidence of bilateral scarring on DMSA, and in four children in the PUR group. The median age at surgery for the SUR group was 75 months (range, 10–161 months) and 26 months (range, 12–79 months) for the PUR group ($P < 0.02$).

Surgical results are summarized in Table 2. The median duration of surgery for SUR was 120 min (range, 74–360 min), 90 min (range, 74–180 min) for

Table 1: Preoperative demographic and clinical variables

	SUR group	PUR
Age at reimplantation (months)		
Median (range)	75 (10-161)	26 (12-79)
<i>P</i>		<0.02
Side of reflux		
Bilateral	12	4
Left	3	2
Right	4	1
Maximum grade of reflux (<i>n</i>)		
Grade IV	11	6
Grade V	8	1
Scars on DMSA after UTI		
Bilateral	6	1
Unilateral	2	1
Nil	11	5
Endoscopic injection		NA
Once	13	-
Twice	6	-

NA: Not applicable, DMSA: 99mTc-Dimercaptosuccinic acid nuclear scans, SUR: Salvage ureteral reimplantation, PUR: Primary ureteric reimplantation, UTI: Urinary tract infection

Table 2: Results of surgery

	SUR	PUR	<i>P</i>
Side of surgical treatment (<i>n</i>)			
Bilateral	14	4	
Unilateral	5	3	
Surgery duration (min), median (range)			
Combined	120 (74-360)	140 (90-120)	0.73
Unilateral	90 (74-180)	120 (90-140)	
Bilateral	133 (115-360)	140 (120-180)	
Hospital stay (days), median (range)	5 (4-7)	6 (5-10)	0.09
Blood loss (ml), median (range)			
Total	<10 (<10-150)	<10 (<10-<10)	0.38
Unilateral	<10 (<10-<10)	<10 (<10-<10)	
Bilateral	<10 (<10-150)	<10 (<10-<10)	
Persistent VUR (<i>n</i>)	1 (grade III)	0	0.73
Further UTIs (<i>n</i>)	0	0	

SUR: Salvage ureteral reimplantation, PUR: Primary ureteric reimplantation, VUR: Vesicoureteric reflux, UTIs: Urinary tract infections

unilateral cases, and 133 min (range, 115–360 min) for bilateral cases. In the PUR group, the median duration of surgery was 140 min (range, 90–180 min), 120 min (range, 90–140 min) for unilateral cases, and 140 min (range, 120–180 min) for bilateral cases. It took longer than usual operative time in three patients of the SUR group. Among these, two had bilateral reimplantation (360 and 236 min) and one had unilateral reimplantation (180 min). Despite that statistically, the operative time was not significant ($P = 0.703$) between the two groups. In these three cases of reimplantation in the SUR group, the surgeon documented subjective “significant” difficulty in dissection due to fibrosis.

The median volume of blood loss was <10 ml in both the groups. In two cases of bilateral ureteric reimplantation in the SUR group, there was a larger volume of blood loss (100 ml and 150 ml; >2 standard deviation [SD]) due to difficult dissection, but these volumes were not significantly

greater than the median for the group ($P = 0.38$). There were no major intraoperative complications in either group, and the median duration of hospital stay was comparable for both the groups ($P = 0.09$), 5 days (range, 4–7 days) in the SUR group and 6 days (range, 5–10 days) in the PUR group.

The median duration of follow-up was 1 year (range, 1–5 years) for both the groups, with only one patient in the SUR group experiencing a persistent unilateral Grade III VUR at the 1-year follow-up. There were no cases of symptomatic UTI over the follow-up period.

DISCUSSION

Many types of bulking agents have been used for endoscopic treatment of VUR, including Tefl on® (polytetrafl uoroethylene), collagen and fat. Each of these may induce some degree of inflammatory reaction with a potential to form a scar.^[9,11] In cases of treatment failure, during subsequent reimplantation, this scarring can lead to increased operative difficulty and complications, particularly persistence of VUR.^[9,11,14] Dx/Ha which causes mainly a foreign body giant cell reaction seems to cause less inflammation compared to other agents that have been used in the past.^[9,15] However, only a few studies to date have evaluated if the inflammatory reaction to Dx/Ha is sufficiently severe to cause similar complications as with other bulking agents, with mixed findings having been reported so far.^[11,12] Our study is different from these previous studies as we have only included primary high-grade VUR.

Our indications for SUR were breakthrough infections and/or formation of new scars, which are similar to the indications reported by other authors.^[9,16,17] We also limited our attempts of Dx/Ha to two injections before SUR, compared to three attempts which have previously been reported.^[9,16-18] As we only included cases of high-grade (IV and V) VUR, we considered that if VUR remained unchanged after the second injection of Dx/Ha, then the third injection was not likely to succeed.

We routinely perform a Cohen ureteral reimplantation as it is a very reliable approach for all grades of VUR and provides several advantages, including the possibility of treating associated structural anomalies, avoids nerve injury, and has a high success rate.^[12] Of note, patients in the SUR group were older at the time of surgery than those in the PUR group ($P < 0.02$), with a median age of 75 months (range, 101–161 months) compared to 26 months (range, 12–79 months), respectively. The higher

median age in the SUR group reflects the additional time due to the first endoscopic treatment and the associated necessary follow-up. This lapse of time, however, did not cause further damage to the kidneys.

Our median duration of surgery was comparable for the SUR and PUR groups ($P = 0.73$) and is similar to previously reported durations.^[12,17] However, we did encounter significant subjective difficulty with dissection due to fibrosis in three cases in the SUR group which extended the operative time to 360 min for one bilateral case, with the median time being extended by 20–30 min for two unilateral cases. Sencan *et al.* reported that although previous endoscopic injection with Dx/Ha caused some difficulty in dissection, the treatment did not alter the success rate of open ureteric reimplantation.^[11] Moreira-Pinto *et al.* and Vallasciani *et al.* have reported that although SUR is not free of complications and is technically difficult, it is still feasible and highly successful.^[12,13]

The intraoperative volume of blood loss was comparable for the SUR and PUR groups ($P = 0.38$). Moreover, the volume of blood loss was typically <10 ml, with the exception of two cases in the SUR group, with a volume of 100 ml and 150 ml (both >2 SD of the overall median for the study group). None of our patients required a blood transfusion. These larger volumes of blood loss resulted from the more difficult dissection due to fibrosis. It was not possible to determine if the amount of scarring in cases of difficult dissection was caused by Dx/Ha or recurrent UTI. There were no major intraoperative complications, such as injury to the vas, major vessels, ureter, bladder, or other surrounding structures. Major complications have not been previously reported in the literature.

Over the follow-up period, we routinely performed VCUg to rule out recurrent/persistent VUR. Although this practice has been questioned, the majority of institutions still do recommend repeated screening to avoid missing cases of persistent VUR.^[19] With regard to the resolution of VUR, we achieved a success rate of 93% in the SUR group (with one case of persistent Grade III VUR) and 100% in the PUR group, rates which are comparable to previously reported studies.^[9,11,16] None of our patients developed further UTIs.

The generalization of our findings is limited by the retrospective design of our study and our inability to match the number of patients in both the groups. We also included only patients with a high-grade VUR, which resulted in a relatively small sample size, with further research needed to confirm our findings.

CONCLUSION

For patients with high-grade VUR, SUR after failed Dx/Ha injection has the same success rate as PUR, with no additional risk of complications. However, fibrosis, due to previous treatment and/or longer duration of VUR, resulted in difficulty in dissection in three cases in the SUR group, with a longer operative time and greater volume of blood loss.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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