

Endoscopic Management of Complicated High-Grade Vesicoureteral Reflux in the First Year of Life

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Abstract

Purpose:

The treatment of high-grade vesicoureteral reflux in infants is controversial. Subureteric injection has been tried recently with its advantage of easy application and less invasiveness. In this study, we aimed to assess the efficacy of endoscopic sub-ureteric injection to correct high-grade reflux in infants with documented indications for anti-reflux surgery.

Materials and Methods:

Hospital records of high-grade (grade 4-5) VUR patients who had undergone endoscopic sub-ureteric injection in the first year of life with documented breakthrough infections, between 2009-2016 were reviewed. Radiologic success was defined as complete resolution of reflux in VCUG obtained at least three months after the injection and clinical success was defined as the downgrading of reflux degree below three and absence of urinary infection.

Results:

A total of 23 patients with 34 high-grade refluxing units were included in the study. The mean age at first injection was 6.3 ± 1.8 months (1-11 months). Radiologic success rate with initial injection was 61.7% and increased to 85.2% after repeated injections. The overall clinical success rate at first injection was 70.6% and 97.1% after repeated injections. Mean injected material volume was 0.34 ± 0.27 (0.1-1) ml per ureter.

Conclusion:

Endoscopic treatment is a successful alternative in infants with high-grade vesicoureteral reflux suffering breakthrough infections.

Introduction

Management of vesicoureteral reflux (VUR) in infants, whether diagnosed with antenatal hydronephrosis or urinary infections, remains controversial. In this specific group, there are factors that complicate decision making, such as demanding features of anti-reflux surgery in small babies and the possibility of spontaneous resolution even in high-grade reflux[1–3]. Subureteric injection for VUR gained worldwide popularity for its easy application, short hospital stay with superior patient comfort in children, including infants[4–6]. In this study, we reviewed our experience in an aim to evaluate the efficacy and safety of endoscopic sub-ureteric injection to correct high-grade reflux in infants with documented indications for anti-reflux surgery.

Patients And Methods

Hospital records of high-grade (grade 4–5) VUR patients who had undergone endoscopic sub-ureteric injection in the first year of life with documented breakthrough infections between 2009 and 2016 were reviewed. We defined breakthrough urinary tract infection (UTI) as a UTI with high fever ($> 38^{\circ}$ C) and with documented catheter collected urine culture positivity, that occurred during a course of antibiotic prophylaxis. Data including patient demographics, injected material volumes, VUR grades according to the pre and postoperative voiding cystourethrograms (VCUG), circumcision status of the boys, and success rates were recorded.

Reflux was classified according to the International Reflux Study Committee's Classification System. The procedure was performed under general anesthesia using 9.5 Fr 6° cystoscope (Storz, Tuttlingen Germany). Polyacrylate polyalcohol copolymer (PPC) (Vantris®, Promedon, Argentina) was administered submucosally at 6 o'clock position of the ureteral orifice until the creation of a prominent bulge using a Williams cystoscopic injection needle (Cook Medical®, Bloomington, USA). Radiologic success was defined as complete resolution of reflux in VCUG obtained at least three months after the injection, and clinical success was defined as downgrading of reflux degree below three and absence of urinary infection. The injection was repeated if persistent reflux above grade 2 was documented.

Ultrasonography was performed at the postoperative first, third, and sixth months, and then annually for the follow-up of obstructive findings such as new onset or increased hydroureteronephrosis.

This study was approved by the Institutional Review Board (IRB) under the number 20-1T/47.

Results

A total of 23 patients (5 girls, 18 boys) with 34 high-grade refluxing units were included in the study. The mean age at first injection was 6.3 ± 1.8 months (1–11 months). Four patients had contralateral low or moderate grade (1–3) refluxes. The mean duration of follow-up was 69.53 ± 24.65 months. Continuous antibiotic prophylaxis (CAP) was started with amoxicillin for babies under three months of age, and with co-trimoxazole after this period. Ten patients who were under prophylaxis had confirmed breakthrough UTI underwent endoscopic injection after the first breakthrough infection. In 13 patients, prophylaxis was changed to co-trimoxazole or cefixime and kept in observation due to questionable compliance of families to CAP regimens. The mean time interval from surgery to first postoperative VCUG was 5.63 ± 0.90 months. Radiologic success rate with initial injection was 61.7%, and it was 85.2% after repeated injections. Three refluxing units at first injection and one refluxing unit at second injection downgraded to grade 2 and grade 1. Including these patients, overall clinical success rate at first injection was 70.6% and 97.1% after repeated injections. Mean injected material volume was 0.34 ± 0.27 (0.1-1) ml per ureter. A flowchart depicting the steps of overall management for the study group is summarized in Fig. 1.

Eleven refluxing units of 9 infants with bilateral grade 5 reflux were successfully treated at the first injection, while 6 of them required a second attempt. The overall radiologic success rate for bilateral grade 5 refluxing units was 83.3% and the clinical success rate was 100%. In one patient whose reflux downgraded from 5 to 2, antibiotic prophylaxis was terminated with no subsequent UTI.

Most of the boys (16/18) were uncircumcised and 10 of them were circumcised during the general anesthesia given for endoscopic injection treatment. Children of parents who did not accept circumcision and one patient with megameatus were not circumcised. When patients were divided into two groups according to circumcision status, there was no statistical difference in clinical or radiological success rates between the groups (Chi-Square, p:0.478).

Eventually, only one patient required surgical correction for persistent VUR. In this case, ureteroneocystostomy was performed in line with the family's choice due to successive febrile urinary tract infections. During the open surgery a fibrous capsule surrounding the substance was noted and successfully removed. This did not complicate ureteric dissection. Any sign of obstruction such as increased hydronephrosis was not observed in any patients in a mean follow-up of five years.

Discussion

Controversy regarding management of vesicoureteral reflux in the first year of life continues. The majority of VUR diagnosed in this group belong to higher grades[7]. Increased risk of new scar formation in dysplastic kidneys and breakthrough infections during follow-up are strongly related to the higher reflux grade[8]. However, the rate of spontaneous resolution in this age group, even in high-grade reflux cases is impressive[9]. Ureteroneocystostomy is a demanding surgery in infancy with an increased risk of complications due to small anatomy and fragile mucosa of the bladder. However, for a small unique group of infants with breakthrough infections as in our study group, antireflux procedures may be indicated in certain conditions like urosepsis attacks, breakthrough infections, and severe kidney damage[10]. Reported series of endoscopic treatment were not promising except a few studies[5, 11]. We found that the success rate in our study is higher than those of most studies that published their endoscopic injection experience in infant high-grade reflux. This promising result was the major factor that motivated us to reassess the place of endoscopic treatment in this difficult group of patients.

Several studies draw attention to a higher risk of recurrent and complicated UTI with resistant microorganisms under prophylaxis[12–14]. Garin et al. presented resistant bacteria in all cases of recurrent pyelonephritis with VUR under prophylactic antibiotic treatment[12]. In a randomized controlled study, Hari et al. showed similar results[13]. In 2008, Pennesi et al. reported that prophylaxis had no effect on infection and renal damage, but caused recurrent UTI by resistant microorganisms in a case-control study[14]. In Swedish Reflux Trial, trimethoprim resistant infection rate in girls under prophylaxis was higher than the endoscopic treatment and surveillance groups[15]. Although the RIVUR study has shown that prophylactic antibiotics reduce the risk of UTI recurrence, the probability of resistant UTI has increased significantly[16]. Following successful endoscopic treatment, we did not observe any febrile UTI except one case who eventually required ureteroneocystostomy, and resistant bacterial infection was not documented.

In 2010, a prospective study in children between 1 and 2 years who had grade 3 or 4 VUR was conducted by the Swedish reflux group[17]. Three groups including endoscopic treatment, antibiotic prophylaxis, and

follow-up without treatment, were compared in terms of resolution of reflux, UTI, and renal scar development. The resolution rate was higher in the endoscopic treatment group than the two other groups in [18]. This study showed a success rate of 71% with endoscopic treatment, excluding grade 5 cases. Another branch of this study showed no difference in UTI frequency after endoscopic treatment; however, the difference between successful and unsuccessful cases was not stated [15]. The same group published another prospective study in 2016, including infants with grade 4 and 5 refluxes [19]. Endoscopic treatment and prophylaxis groups were compared, and reflux resolution was 59% in endoscopic treatment, and 21% in the prophylaxis group after 1 year follow up. The success rate after endoscopic treatment was 31% in bilateral grade 5 reflux cases. They revealed no statistical difference between endoscopic treatment and antibiotic prophylaxis group regarding recurrent UTI and new renal scar formation [19]. They also found that multiple recurrent infections were only seen in patients with persistent dilating reflux at follow-up. Our reflux resolution rates, including grade 5 reflux cases after first and repeat injections, were 63.1% and 89.4%, which were higher than similar studies in the literature. Besides, we achieved an unexpectedly high success rate of 85% in bilateral grade 5 refluxes, in a group with previously documented poor results with endoscopic treatment [6]. None of the cases in our series had UTI in the follow-up period.

Another study which published similar results with our study in infants with moderate and severe VUR, but with a smaller group of grade 5 reflux (3.6%) showed a minor recurrent infection rate of 1% [11]. We may speculate that the relatively low success rates of endoscopic treatment in two Swedish studies were the reason why they could not find significant difference between prophylaxis and endoscopic treatment groups regarding urinary infection and new scar formation rates [6, 18]. Thus, with higher success rates, endoscopic treatment could be superior to prophylaxis not only for reflux resolution but also for the prevention of recurrent UTI and new scar formation.

Long term reflux recurrence is another issue considered following endoscopic treatment, which is reported between 13.4–19% within 2 years. Since our current protocol does not include routine VCUG at long term follow-up except cases with febrile UTI, we can't give an overall long-term recurrence rate for this study. However, a recent review of our protocol revealed a 0.9% long term VUR recurrence in cases with recurrent febrile UTI that we obtained a VCUG [20].

Temporary vesicostomy is another method to manage high-grade vesicoureteric reflux in this age group. Podesta et al. showed that it is an effective method for infants with high-grade VUR and urosepsis [21]. Also, in the study of Sharifiaghdas et al., 15 infants younger than 6 months benefited from this treatment method [22]. However, temporary vesicostomy is a more invasive method than endoscopic injection therapy, and at least one additional anesthesia session is needed for vesicostomy closing and treating possible ongoing reflux. Our study showed that 70.6 % of the patients were treated permanently with a single session of endoscopy eliminating additional interventions. We believe that although temporary vesicostomy is a good treatment alternative, especially in cases with secondary reflux, it can be reserved for difficult cases in infants with primary reflux.

Our previous series of endoscopic VUR treatment in children of all ages showed a ureteric obstruction rate of 2.8%[23]. Despite being a smaller group, this study, with similar technique and material, revealed no obstruction in a mean follow-up period of 5.7 years.

Limitations of our study are its retrospective nature without a control group and the low number of cases. However, the high success rate in this special age group with severe reflux was noteworthy. Although the parents were informed and aware of febrile urinary tract infections, there may be infections treated elsewhere and forgotten to be reported. Prospective randomized studies are required to confirm our results.

Another limitation of our study was the difficulty of excluding the possible protective effect of circumcision due to the small number of patients. Elective circumcision 'might be,' but so far not proved to be a better first-line treatment in this specific, high-risk patient group. There is a unique feature of circumcision practice in our country. Although circumcision is routinely performed to almost all boys as a religious and cultural issue, the ratio of neonatal circumcision is very small. Considering circumcision in our study group as a first-line treatment would require an additional surgical intervention most probably under general anesthesia, since we do not support office circumcision. Furthermore, this would not have any effect on reflux resolution, but possibly would decrease UTI risk, according to available current literature. Although there is more than one publication which suggests that circumcision may prevent the development of febrile urinary tract infection in infants with antenatal hydronephrosis, there is no solid evidence that it should be the first-line treatment of breakthrough febrile urinary tract infection. We agree that our study group is too small to evaluate the effect of circumcision on the UTI rate and noted this within the limitations of our study. Although not directly related, and being aware of the low numbers in the groups, when patients were divided into two groups according to circumcision status, there was no statistical difference in clinical or radiological success rates between the groups (Chi-Square, $p:0.478$). As circumcision was done when performing the endoscopic treatment, it may be speculated that it helped to prevent UTI recurrence. In the study of Alsaywid et al., the rate of infection after the circumcision was lower than before circumcision[24]. However, a multivariate analysis evaluating other factors that could contribute, like age and the usage of prophylaxis, was missing in that study. Another study by Braga et al. also states that uncircumcised status is a risk factor for febrile UTI in babies with antenatal hydronephrosis [25]. However, they do not make any comment on circumcision as a first-line treatment for breakthrough UTI. On the other hand, in the study of Herz et al., circumcision status did not affect the UTI incidence in infants with antenatal hydronephrosis[26]. Although we practice in a country where routine religious circumcision is performed, we believe that larger prospective studies are needed to suggest circumcision as the first treatment option for febrile UTI in male infants with high-grade vesicoureteral reflux.

Conclusion

Endoscopic treatment is a successful alternative in infants with high-grade vesicoureteral reflux suffering breakthrough infections. Published studies comparing endoscopic treatment and antibiotic prophylaxis

have inconclusive results due to a wide range of success rates. Prospective randomized studies with larger numbers may support our findings.

Abbreviations

CAP: Continuous antibiotic prophylaxis

PPC: Polyacrylate polyalcohol copolymer

UTI: Urinary tract infection

VCUG: Voiding cystourethrogram

Declarations

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Conflict of Interest: The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent to Participant and Publication: Written informed consent has been obtained from the parents.

Availability of data and material: The data in an Excel file that support the findings of this study are available on request from the corresponding author.

Code availability: N/A

Author Contributions:

AT: Conceived and designed the analysis, performed the analysis, wrote the paper

ST: Contributed data or analysis tools, performed the analysis, wrote the paper

IY: Conceived and designed the analysis, wrote the paper

ÖK: Collected the data, performed the analysis

AA: Conceived and designed the analysis, served as scientific advisor

IU: Conceived and designed the analysis, wrote the paper, served as scientific advisor

Ethics approval: This study was approved by the Institutional Review Board (IRB) under the number 20-1T/47.

Bullet List:

What is Known: Endoscopic vesicoureteral reflux treatment is an effective method especially in selected cases.

What is New: Endoscopic vesicoureteral reflux treatment is an effective method in complicated high-grade vesicoureteral reflux in the first year of life as well.

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Figures

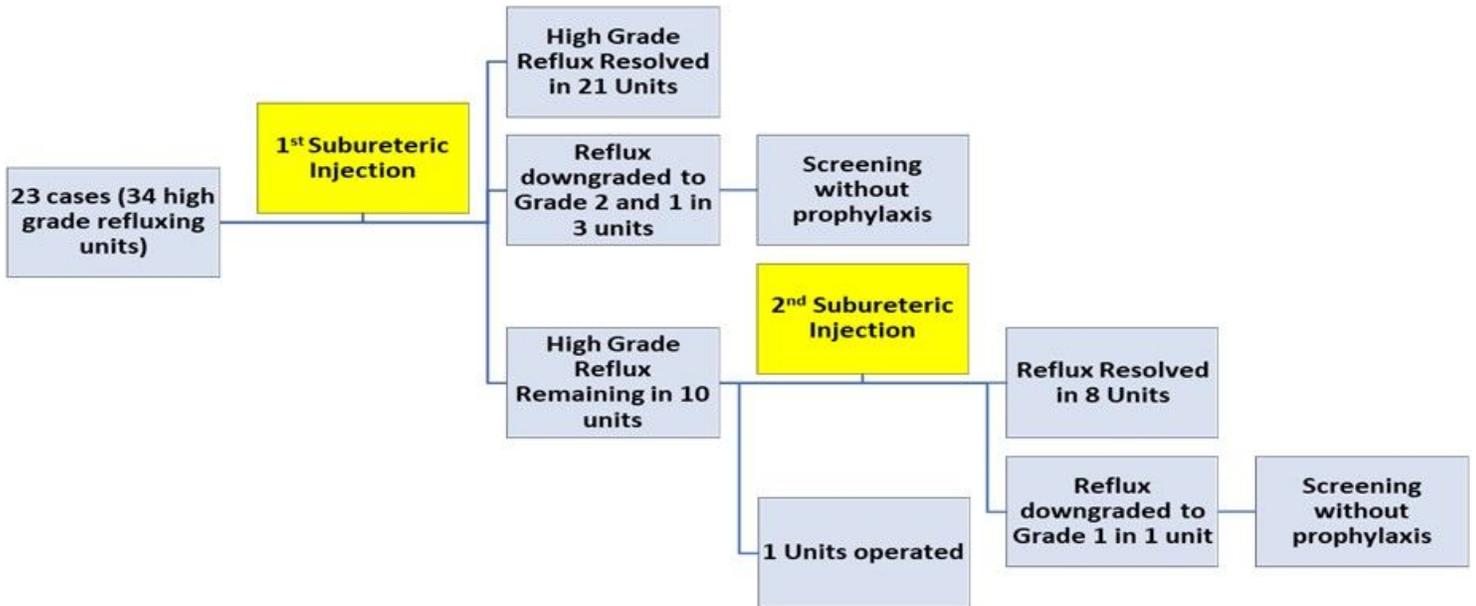


Figure 1

Flow-Chart of the overall management