SUBURETERAL MUCOSA INJECTION WITH DETRANOMER/HYALURONIC ACID FOR VESICOURETERAL REFLUX TREATMENT: SYSTEMATIC REVIEW

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ABSTRACT

Objective: *The aim of this study is to search the success rate of detranomer-hyaluronic acid (Dx/HA) used as injection through endoscopy approach and grades of vesicoureteral reflux (VUR) that could affect it success rate.* ***Material & methods:*** *We searched the literatures from MEDLINE database and PubMed from year 2001 until 2013. The data was analyzed using Random Effects Model with the method of Mantzel-Haenzel to analyze the success rates of dextranomer/hyaluronic acid and was determined by 95% Confidence of Interval (CI) disclosure. Meta-regression was performed to adjust the success rate compared with the grade of VUR as covariate. We assessed the heterogeneity by calculating the I2 statistic. All analyses were performed with Stata Statistical Software Version 12.0 (StataCorp).* ***Results:*** *We identified 9 literatures in full review. Of 1105 ureters that were injected with dextranomer/hyaluronic acid, 817 (72%; CI: 67-76%) were successfully treated according to author's definition. The success rates of Dx/HA for pediatric with grade 1 VUR reached 80% (95% CI: 66-89%), whereas in grade 5 VUR only 50% (95% CI: 34-66%; p<0.05).* ***Conclusion:*** *The overall success rate of dextranomer/hyaluronic acid injection treatment was 72% after 3 months, although success rates varied widely among studies. Preoperative grade of VUR was significantly associated with treatment outcome. Increased VUR grade negatively affected success rates.*

Keywords: *Vesicoureteral reflux, subureteral mucosa injection, dextranomer/hyaluronic acid, systematic review.*

ABSTRAK

Tujuan: *Tujuan penelitian ini adalah untuk meneliti tingkat sukses detranomer-hyaluronic acid (Dx/HA) yang digunakan sebagai injeksi melalui pendekatan endoskopi dan tingkat vesicoureteral reflux (VUR) yang dapat mempengaruhi tingkat keberhasilannya.* ***Bahan & cara:*** *Kami melakukan pencarian literatur dengan menggunakan database MEDLINE dan PubMed dari tahun 2001 sampai 2013. Data dianalisis menggunakan Random Effects Model dengan metode Mantzel-Haenzel untuk menganalisis hasil luaran dari keberhasilan postoperative injeksi dengan dextranomer/hyaluronic acid dan dipresentasikan dalam bentuk 95% Confidence of Interval (CI), serta dilakukan analisis meta-regresi yang membandingkan angka keberhasilan terapi dengan tingkatan derajat VUR sebagai covariate. Penilaian heterogeneity dilakukan dengan menggunakan I2 statistik. Keseluruhan data dianalisis dengan Stata Statistical Software, Version 12.0 (StataCorp).* ***Hasil:*** *Kami mendapatkan 9 literatur yang dapat ditelaah secara sistematik. Jumlah total sampel ureter yang didapat sebanyak 1105 ureter yang diinjeksikan dengan dextranomer/hyaluronic acid, 817 mencapai keberhasilan terapi (72%; CI: 67-76%) sesuai dengan definisi parameter yang digunakan. Tingkat keberhasilan terapi injeksi dextranomer/hyaluronic acid pada anak dengan VUR derajat 1 mencapai 80% (95% CI: 66-89%), sedangkan pada VUR derajat 5 hanya memiliki kemungkinan keberhasilan sebesar 50% (95% CI: 34-66%; p<0.05).* ***Simpulan:*** *Tingkat keberhasilan terapi injeksi subureteral dextranomer/hyaluronic acid pada VUR mencapai 72% setelah dilakukan follow-up 3 bulan pasca injeksi, meskipun success rate pada setiap studi bervariasi. Faktor preoperatif derajat VUR secara signifikan mempengaruhi keberhasilan terapi. Semakin tinggi derajat VUR preoperatif, semakin rendah tingkat keberhasilan terapi.*

Kata kunci: *Vesicoureteral reflux, injeksi mukosa subureteral, dextranomer/hyaluronic acid, telaah sistematik.*

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INTRODUCTION

Vesico Ureteral Reflux (VUR) is a condition when there is a retrograde flow of urine from vasica-urinaria (bladder) back to ureter and/or kidney. This condition is commonly seen in baby and children (1-3%). Baby and children of young age have tendency to get VUR due to its short of ureteral submucosal. In some cases, the occurrence of VUR could lead into several problems such as recurrent urinary tract infection, pyelonephrosis, hyper-tension, and permanent kidney damage.[1-3] The etiology of VUR could be classified into 2 categories, primary and secondary cause. Primary cause of VUR is the occurrence of congenital defect and alteration of ureterovesical junction (UVJ) function. Secondary cause of VUR is related to anatomical/functional obstruction or bladder inflammation disease, as well as direct damage to normal ureter orificium. Intravesica obstruction or bladder outlet obstruction (BOO), neurology abnormality, difficulty in micturition, and other cause of reflux related to gastrointestinal issue.[4,5]

There are two approach of VUR treatment; conservative and interventional therapy. The choice of treatment are based on the presence of renal scarring, disease progression, degree of reflux, renal function (bilateral and ipsilateral), bladder capacity and function, coexisting disease, patients' age and cooperation. Surgical intervention is preferred in the occurrence of fever caused by infection that non responsive to antibiotic.[1,2] In the past few years, treatment using suburetheral transurethral injection (STING)or through endoscopic approach became fist line treatment because of its high success rates and low complication rates. This treatment was firstly announced by Mathuschek in 1981 and serial clinical benefits already been published by)'Donnell and Puri in 1984.[3-5] In its early used, injectable drug that acts as a bulking agent were polytetra-fluoroethylene (Teflon®), Glutaraldehyde cross-linked bovine dermal collagen (Zyplast®), Calcium Hydroxyapatite (Coaptite®), Polydimethylsiloxane (Macroplastique®). However, because of the efficacy and safety of these drugs are still in doubt, its application are still limited. Polytetrafluoroethylene was already pulled from the market because the material could migrate into other tissue. The most widely used agent is dextranomer-hyaluronic acid/Dx/HA (Deflux®). The newest injection agent is PolyacrylatePolyalocoho; Copolymer (Vantris®). Chertin said that this agent is save and have high success rates as therapeutical approach but long term evaluation still need to be performed.[4,6-8]

OBJECTIVE

The aim of this study is to search the success rate of detranomer-hyaluronic acid (Dx/HA) used as injection through endoscopy approach and grades of VUR that could affect it success rate.

MATERIAL & METHODS

Literatures/Studies were search from database such as MEDLINE and Pubmed with limitation of time of publication from 2001 to 2013. The keywords used were “dextranomer”, “dextranomer hyaluronic acid”, and “deflux” with restriction to “vesicouretheral reflux”, and “reflux”. Only studies with subjects of patients age 0-18 years old with primary VUR that had injection of STING using dextranomer-hyaluronic acid)Dx/HA) were included in this study. We only analyzed the success rate form single injection. Success condition was defined as recovery state into VUR grade 0 or 1 after single injection. Patients follow up were taken after 3 months after injection.

Data were analyzed using random effects model with the method of Mantel-Haenszel in order to calculate risk ratios (RRs) and 95% confidence interval (CI) to analyze the success rate of postoperative injection with Deflux in pediatric patients with VUR. Meta-regression analysis was used to compare success rate and severity of VUR as covariate. Rate heterogeneity is evaluated using the I2 statistic. The level of heterogeneity divided into 3 categories; low (25-50%), moderate (50-75%), and high (>75%). All data were analyzed with Stata Statistical Software, Version 12.0 (StataCorp).

RESULTS

There were 343 studies were found from the database but 219 studies were excluded from this study because did not related to research topic. There were 124 literature underwent detail assessment regarding the severity of VUR as well as its success rate of therapy. Finally, there were 9 studies included in this study.

The 9 studies had data about total sample size. Success rate of therapy was defined as success rate of recovery to VUR grade 0 or 1 after the 3 months from first injection given to patients.

Table 1. Studies characteristics.

Study	Study Design	Success Parameter	Total Sample Size	Success Rate
Biocic, et al. 2012	Prospective Cohort	Grade 0	396	76%
Kim, et al. 2011	Prospective Cohort	Grade 1	51	84%
Chung, et al. 2009	Prospective Cohort	Grade 0	64	67%
Alkan, et al. 2008	Prospective Cohort	Grade 0	81	56%
Bajpai, et al. 2013	Prospective Cohort	Grade 0	99	82%
Seibold, et al. 2011	Prospective Cohort	Grade 0	30	83%
Chen, et al. 2010	Prospective Cohort	Grade 0	239	45%
Bae, et al. 2010	Prospective Cohort	Grade 0	84	79%
Molitierno et al. 2008	Prospective Cohort	Grade 0	61	73%

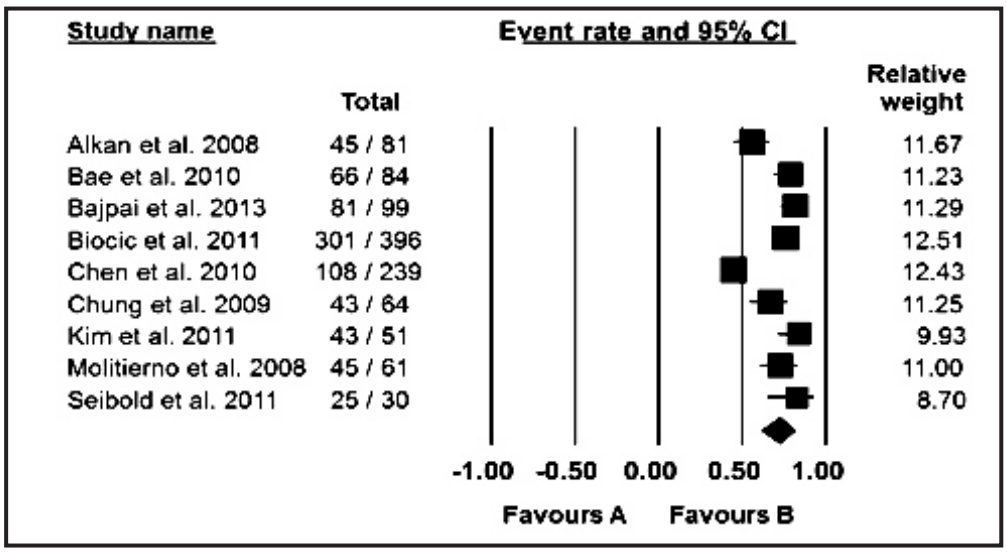

Figure 1. Forest plot of Dx/HA success rate.

Table 2. Success rates of Dx/HA injection according to severity of VUR.

Severity of Preoperative VUR	Total Samples	Success Rate (95% CI)	I^2(95% CI)
1	52	80% (66-89%)	0.000
2	270	86% (73-93%)	66.730
3	426	72% (65-78%)	45.731
4	238	69% (60-72%	40.616
5	119	50% (34-66%)	57.878

Total sample taken from 9 studies were 1105 and 817 were reach success recovery condition (72%; CI 67-76%). Heterogeneity evaluation from those studies based on I2 methods results in moderate heterogeneity (62%).

In each of these studies also reported in detail the number of patients divided according to the severity of preoperative BUR (Table 2) and based meta-regression analysis, it was showed that the severity of VUR was related to the success rate of therapy.

The success rate of Dx/HA injection therapy in children with grade 1 VUR was around 80% (95% CI: 66-89%), whereas in grade 5 VUR the chance of

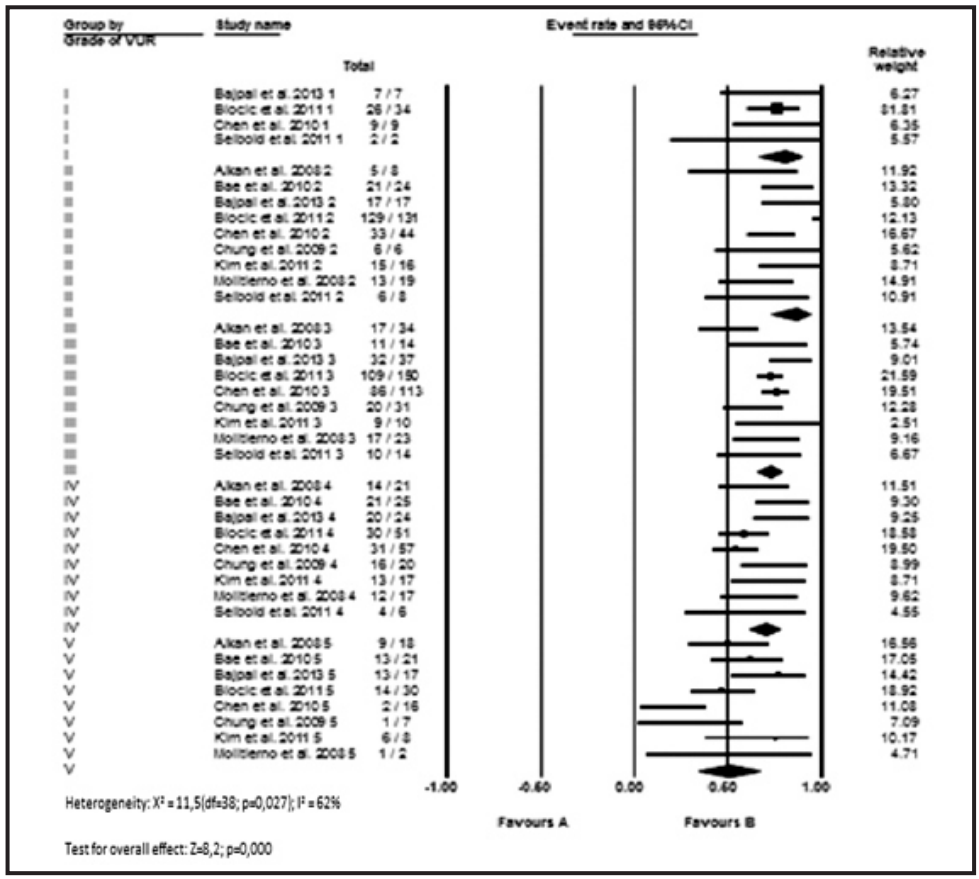

Figure 2. Forest plot of success rate of Dx/HA injection according to severity of VUR.

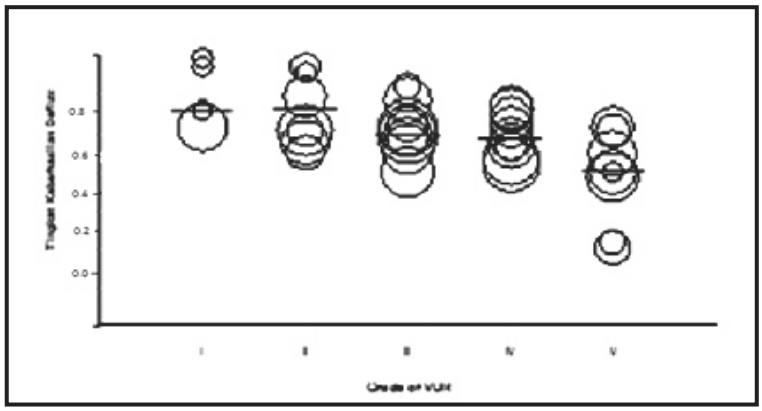

Figure 3. Bubble plot of success rate of Dx/HA injection according to severity of VUR.

successful treatment was only 50% (95% CI: 34-66%; p<0.05). The success rate of Dx/HA injection therapy decreased as the severity of preoperative VUR increased. Sequentially the success rate of Dx/HA therapy according to the severity of pre-operative VUR were 80%, 86%, 72%, 69%, 50%, respectively from grade 1 to 5.

However, there was something interesting regarding the success rate of therapy and severity of VUR. Grade 1 VUR had lower success rate if compared with grade 2 VUR (80% vs 86%). This circumstance could be caused by different in term of subject. Grade 1 VUR had lower subjects that could be related to conservative therapy

DISCUSSION

Since it was recognized by Food and Drug Administration in 2001, the used of Dx/HA injections as treatment of VUR are increase word widely. Dx/HA fulfilled ideal criteria as tissue-augmenting agent since its clinically proven efficacy and safety compared with previous agents. Dx/HA injection is a minimally invasive approach as an alternative treatment of open surgical intervention. Several authors recommend Dx/HA injection as the first line treatment of VUR.[4,6,7]

In this study, authors analyzed the success rate of Dx/HA injection and evaluated the severity of preoperative VUR to success rate of therapy. Success rate is determined by the recovery of VUR into grade 0-1 after Dx/HA injection.

The results of this study showed that the success rates of Dx/HA injection as treatment of VUR was around 72% after 3 month follow up of single injection. The severity of preoperative VUR was significantly affecting the success rate. However, Bajpai et al showed that success rate of Dx/HA injection as treatment of VUR could be increased following the second and third injection.[8]

Others studies showed some factors that can affect the success rate of Dx/HA injection as treatment of VUR, including the patient's age, injection volume factor, and operator experience. Routh et al. said that increase in the volume of Dx/HA injection was not significantly improve the success rate.[9,10]

Previous studies also revealed that the role of pharmaceutical companies in terms of production procurement could affect the continuity of this therapy and the continuity of further research in this field. Authors hope that this injection agent can be sold in various countries.[10]

CONCLUSION

The success rate of suburethral Dx/HA injection as treatment of VUR was around 72% after 3 months of follow up. The severity of VUR is an important factor in determining the success of therapy. In general, as the VUR become more severe, the success rate of therapy becomes lower.

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