Sapporo Medical Journal
Volume 55, Issue 07, July 2021

Triamcinolone Application following Internal Urethrotomy for Reducing Urethral Stricture Recurrence Rate: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract—Internal urethrotomy is one of the most commonly performed urethral stricture surgeries. However, the efficacy of urethrotomy is still being questioned due to its high stricture recurrence rate. Several adjunctive treatments for internal urethrotomy have been widely studied to reduce the recurrence of urethral strictures, one of which is triamcinolone. We aimed to analyze the effect of triamcinolone in reducing urethral stricture recurrence rate.A systematic search was conducted in PUBMED, Science Direct, and Google Scholar databases to identify relevant randomized controlled trials (RCTs) of triamcinolone in patients with urethral stricture undergoing urethrotomy. This review has been conducted according to the PRISMA guideline and the protocol has been registered to the PROSPERO database (CRD42020202254).Six RCTs were eligible for this study. A total of 373 urethral stricture patients were included in this review. Pooled results of the included studies showed a significant difference between the triamcinolone and control group, indicating a lower recurrence rate in the triamcinolone group(OR = 0.49 95% CI 0.31-0.77, p = 0.002). Significant difference was seen in the ointment with clean intermittent catheterization (CIC) intervention subgroup (OR = 0.47 CI 95% 0.26-0.82, p=0.009), but not the submucosal injection subgroup (p>0.05). The maximum urinary flow rate (Qmax) was similar between the treatment and control groups (p>0.05) during the sixth- and twelfth-month follow-ups.Triamcinolone ointment administration with clean intermittent catheterization (CIC) could reduce urethral stricture recurrence rate after internal urethrotomy, whereas sole triamcinolone submucosal injection could not. It also does not improve maximum urinary flow rate.
Keywords: *Triamcinolone, Urethral Stricture, Internal Urethrotomy*

1. Introduction

Urethral stricture is one of the most commonly found urological problems, in which there is a narrowing of the urethra caused by fibrosis and scar tissue.[1] It can occur in many patients with various etiologies. It can be caused by trauma, infection, ischemia, inflammation, instrumentation, or other unknown causes.[2] Studies reported that it occurs in 200 in 100,000 people, with an increasing incidence rate in the last 50 years.[3] The treatments recommended to urethral stricture patients include urethrotomy, dilatation, and urethroplasty.[4] Internal urethrotomy is routinely used amidst the development of urethroplasty technique.[5]

Internal urethrotomy is used for urethral stricture with a length of less than 1.5cm. However, the efficacy of internal urethrotomy is still being questioned because of its high stricture recurrence rate.[6] A case control study regarding urethral stricture in Indonesia by Gede et al.[7] in 2017 stated that the urethral stricture recurrence after internal urethrotomy was as high as 92.5%. Many treatment alternatives after internal urethrotomy have been widely studied to reduce the urethral stricture recurrence rate. Corticosteroid is one of the commonly used drugs studied. It has been widely used in centers to reduce scar formation. It is able to decrease collagen, glycosaminoglycan synthesis, and the expression of inflammatory mediators.[8] Among those regularly reported is triamcinolone.[9] However, results surrounding the subject vary. As of the conduction of this review, many studies investigating the role of corticosteroids have been published.[10–13] Therefore, we aimed to evaluate several studies reporting on the effects of triamcinolone after internal

urethrotomy to reduce urethral stricture recurrence.

2. Materials and Methods

This This study was a systematic review and meta-analysis performed and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline. The protocol is registered in the PROSPERO database with the registration number CRD42020202254.We used the following inclusion criteria to determine the eligibility of studies:(1) Randomized Controlled Trial(RCT) study design, (2) Studies comparing Triamcinolone with sole internal urethrotomy or no adjunctive treatments, and (3) Men with urethral stricture treated with internal urethrotomy as subjects. Studies with the following criteria were excluded: (1) non-English articles, (2) Animal studies, (3) Unpublished articles, and (4) Abstract-only articles. We performed a systematic search in the MEDLINE, PubMed, ScienceDirect and Google Scholar databases on February 28th, 2021. We used the keyword "Triamcinolone AND urethra OR Stricture". We used Mendeley to combine the results from the databases and evaluate possible duplicates. The primary screening of the studies was performed by reading the titles and abstracts. The studies that fit the inclusion criteria based on the title and abstract would be evaluated in their full-text forms during the secondary review. Both the primary and secondary screenings in this systematic review were performed by three investigators. Any disputes between the investigators would have been resolved in a discussion. In the screening process of this review, there weren't any inter-rater disagreements.The primary outcome was urethral stricture recurrence rate, whereas the secondary outcomes were maximum urinary flow rates examined in the 6th and 12th month after urethrotomy. The analyzed primary outcome was dichotomous and presented in an odds ratio(OR) with a confidence interval (CI) of 95%. The secondary outcomes were continuous and analyzed using a mean difference (MD). The heterogeneity between studies was calculated using I^2. It was assumed that heterogeneity between studies was statistically high if the $I^2 > 50\%$, then the random effects model analysis would be used. Otherwise, a fixed effects model would be used. The statistical analysis used RevMan version 5.4 (Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020) for Windows, which would be presented in the form of forest plots and descriptive narrative.The research bias risk analysis was assessed using CochraneRisk of Bias Tools for Randomized Trials 2.[14]Two reviewers conducted an independent bias assessment, with the results of the risk of bias being low risk, some concerns, and high risk.

3. Results

There In the initial search as shown in figure 1, 458 studies were obtained from the PubMed, Science-direct, Google scholar databases and three studies were obtained from the references of previous meta-analysis. A total of 26 studies were extracted from the primary screen. The full paper version of the articles was evaluated in the secondary screening to determine which studies fitted the inclusion and exclusion criteria for this review. There were seven articles that could be analyzed qualitatively and quantitatively in this study.

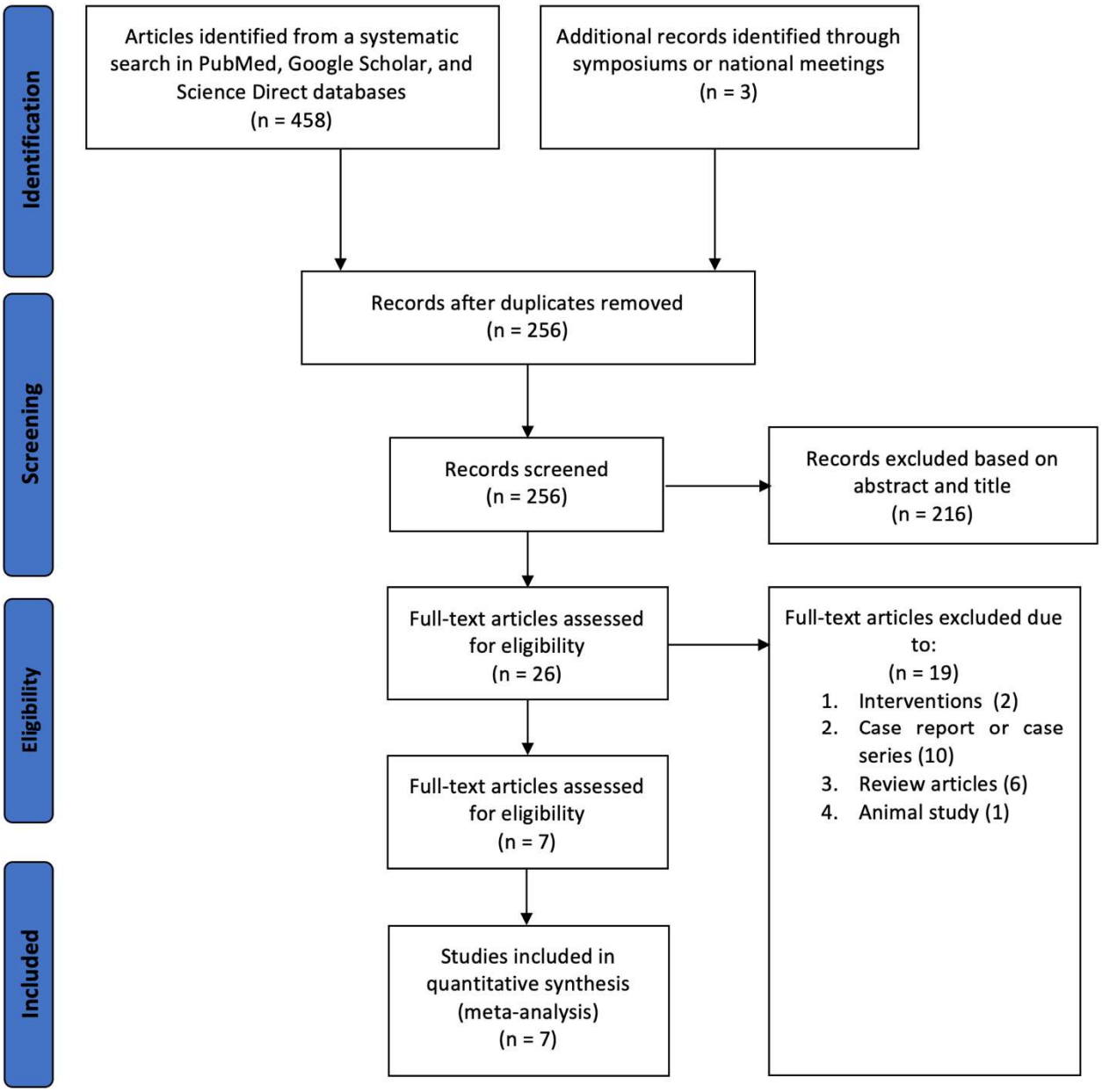

Figure 1.PRISMA flow diagram

Study Characteristics

All studies were presented in the baseline characteristics table in table 1. A total of 373 patients were included in this review. There were six RCT studies that met the inclusion criteria for this study. Overall, each study limited the length of the stricture to below 2 or 1.5 cm. Five studies evaluated the application of triamcinolone ointment with clean intermittent catheterization (CIC), whereas two studies administered submucosal triamcinolone injection. Triamcinolone was given alongside clean intermittent catheterization (CIC) in five studies and dilatation in one study. The etiologies of the strictures consisted mostly of infections and traumas. The strictures mostly occurred in the bulbar area, with a few studies reporting both bulbar and penile, as well as multiple strictures. Most studies excluded patients with a history ofurethroplasty, except for Hosseini et al.[15] Complications were only found in the study by Tabassi et

Table 1. Studies'Baseline Characteristics

Author (Year)	Group	Sample	Age (Mean ± SD) year	Action	Operator	Intervention	Previous Urethroplasty (n)	Location (Number of strictures)	Length of Stricture (cm)	Stricture Etiology	Complication Rate (n)	Follow up (Months)
Mazdak, (2010)	Triamcinolone	23	37,1 ± 20,9	20fr DVIU (cold knife)	Single operator	Submucosal triamcinolone injection	No previous urehtroplasty	Bulbar (NR)	<1,5	Trauma, inflammatory, unknown	No complications	24
	Without triamcinolone	22	34 ± 19,9			none						
Regmi (2018)	Triamcinolone	27	37,2 ± 1,6	21fr DVIU (cold knife)	Single operator	16 fr CIC + triamcinolone ointment 1%	No previous urehtroplasty	Bulbar or penile or both (NR)	<1,5	Trauma, inflammatory, unknown	No complications	12
	Without triamcinolone	28	36 ± 1,7			16 fr CIC						
Tabassi (2011)	Triamcinolone	34	42,38	DVIU (cold knife)	NR	submucosal triamcinolone injection	No previous urehtroplasty	Bulbar or penile or both (NR)	<1,5	Trauma, catheterization, infection, unknown	Infection (1), bleeding (3), extravasation (2)	24
	Without triamcinolone	36	42			None					Infection (2), bleeding (3), extravasation (2)	
Gucuk (2010)	Triamcinolone	15	33,4 ± 7,6	21fr DVIU (cold knife)	NR	18fr CIC + triamcinolone ointment 1%	No previous urehtroplasty	Bulbar (NR)	<1,5	Trauma, infection, instrumentation, unknown	No complications	18
	Without triamcinolone	15				18fr CIC						
Hosseini (2008)	Triamcinolone	30	37,7 ± 17,1	DVIU (cold knife)	Multi operators	18fr CIC + triamcinolone ointment 1%	18	Multiple (NR)	<1,5	Urethral distraction disease, straddle injury, urethral catheterization	No complications	12
	Without triamcinolone	34	34,5 ± 13,3			18fr CIC	17					
Ergun (2015)	Triamcinolone	30	60,7	DVIU (cold knife)	Single operator	14fr until 20fr CIC + triamcinolone ointment	No previous urehtroplasty	Bulbomembranous (NR)	<2	Iatrogenic (endoscopic Urologic surgery, urethral catheterization), trauma, idiopathic	No complications	24
	Contratubex	30	57,8			14fr until 20fr CIC + contratubex ointment						
	Without triamcinolone	30	61,2			14fr until 20fr CIC						
	Without triamcinolone	19	47 ± 8,8			18fr CIC						

Research Bias Risk Analysis

All studies included in the qualitative and quantitative analysis in this review were randomized controlled trial (RCT) studies, thus the Cochrane Risk of Bias Tools for Randomized Trials 2 was used, as shown in figure 2.[14] In this study, four studies had a low risk of bias. The studies conducted by Mazdak et al.[17] and Tabassi et al.[16] had the possibility of randomization bias since the studies did not clearly explain the randomization process and whether the allocation process was blinded.

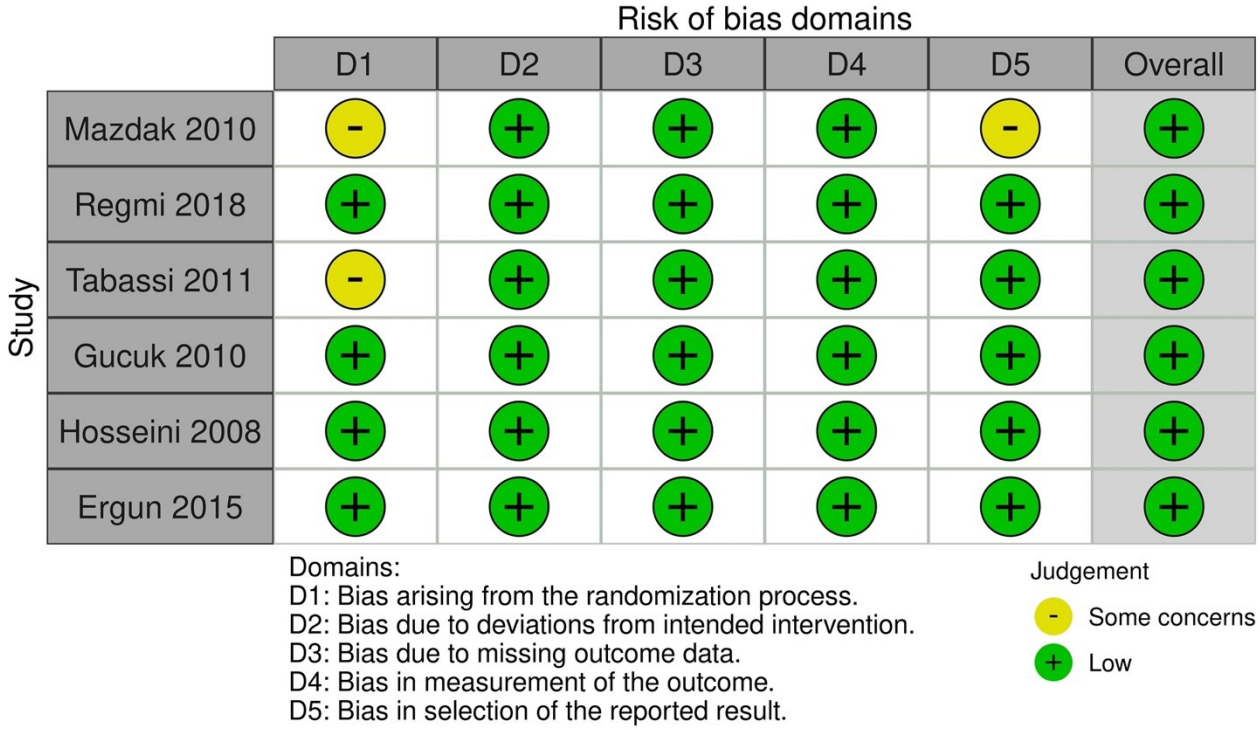

Figure 2. Risk of Bias Assesment (using Cochrane Risk of Bias Tools for Randomized Trials 2**)**

Urethral stricture recurrence rate after triamcinolone application

All six studies evaluated the application of triamcinolone after urethrotomy, as shown in figure 3. The data of the studies were considered homogenous ($I^2 = 0\%$, $p = 0.45$). The fixed model analysis in the forest plot showed a lower urethral stricture incidence of the triamcinolone group (OR = 0.49 95% CI 0.31-0.77, p = 0.002). Further subgroup analyses were performed based on the methods of application, injection, and ointment.

Urethral stricture recurrence rate after triamcinolone ointment lubrication

There were four studies evaluating the application triamcinolone ointment in figure 3. The combined data obtained in each study was homogeneous ($I^2=0$ %, $p = 0.45$). The fixed effects model analysis in figure showed that there is a significant difference of urethral stricture incidence between the treatment and control groups (OR = 0.47 CI 95% 0.26-0.82, p=0.009).

Urethral stricture recurrence rate after submucosal triamcinolone injection

There were two studies evaluating submucosal triamcinolone injection. The pooled odds ratio analysis in the subgroup of figure 3 showed that the combined data obtained from each study were homogeneous ($I^2 = 33\%$, $p = 0.22$). The analysis was carried out using a fixed effect models, showing an insignificant difference

(OR = 0.53 CI 95% 0.25-1.13, p=0.10).

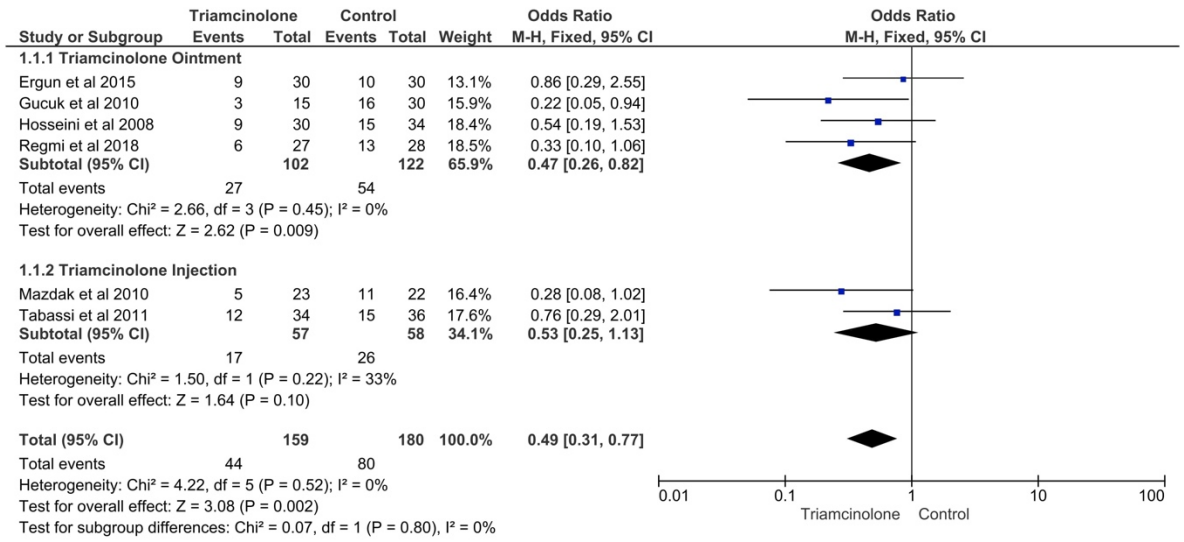

Figure 3. Forest plot of Urethral stricture recurrence rate after triamcinolone application

Urethral Recurrence Rate and Follow-up Duration

Figure 4 showed the visualization of the recurrence rate probability of the studies with different durations of follow-up.

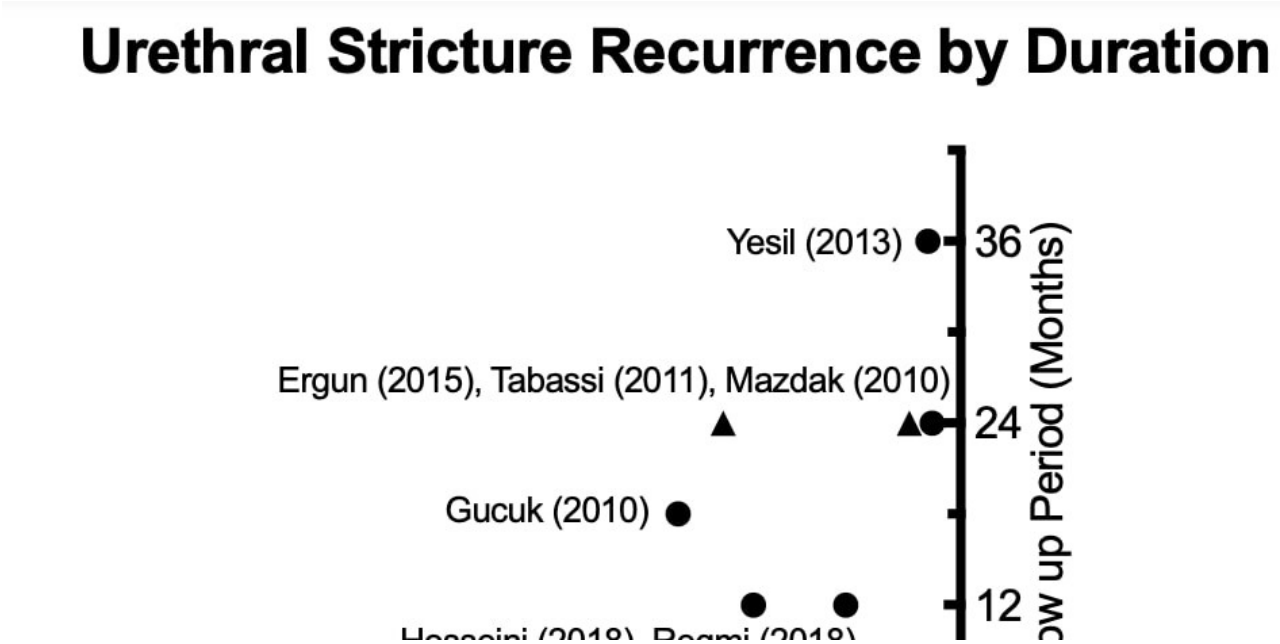

Figure 4. Urethral Recurrence Rate and Follow-up Duration

Maximum Urinary Flow Rate (Qmax) in six months

There were two studies reporting the mean maximum urinary flow rate after six months. The data of the studies were homogeneous with the value of (I^2=0%, p = 0.84). The fixed effects model analysis in figure 5 showed that there was no difference in Qmax between groups (OR = 0.91 CI 95% -0.82-2.63, p=0.30).

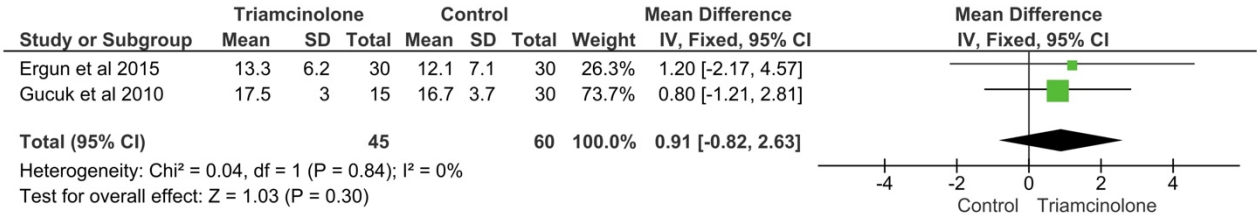

Figure 5. Forest plot of Q max after 6 months

Maximum Urinary Flow Rate (Qmax) in 12 months

There were three studies describing the mean maximum urinary flow rate after 12 months in figure 6. The combined data obtained in each study were homogeneous
(I^2=0%, p = 0.52). The analysis was carried out by a fixed effects model, showing that there was no difference in Qmax between groups (OR = 0.77 CI 95% -1.52-3.05, p=0.51).

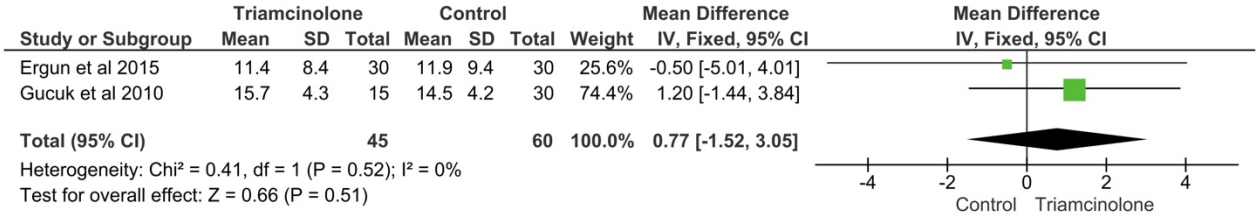

Figure 6. Forest plot of Q max after 12 months

4. Discussion

The role of corticosteroids for urethral strictures and stenoses has been studied for decades.[18–20] Triamcinolone is a long-acting synthetic glucocorticoid with anti-inflammatory and vasoconstricting effects. It is commonly used in many urological disorders as it is inexpensive and well-tolerated locally.[21] It has also been used as an adjunctive treatment to internal urethrotomy. Many studies have been exploring the possibilities of corticosteroids after internal urethrotomy, as the procedure does not provide epithelial approximation, but only separates the scar tissues while relying on secondary healing.[22] Triamcinolone is believed to be able to reduce scar formation by reducing collagen, glycosaminoglycan synthesis, and the expression of inflammatory mediators.[8] A previously published meta-analysis evaluated the application of triamcinolone after internal urethrotomy.[9] However, the review also evaluated a variety of other corticosteroids. This review, on the other hand focused only on clinical trials evaluating triamcinolone as an adjunctive treatment for internal urethrotomy.

Urethral stricture recurrence rate after triamcinolone application

The pooled results of all published RCTs evaluating the application of triamcinolone as an adjunctive treatment showed a lower probability of urethral stricture recurrence (OR = 0.49 95% CI 0.31-0.77, p = 0.002). In early animal studies, the application of a single dose of steroid on a wound site was shown to decrease wound contraction up to 30% by the 28th day.[23]

The promising effects of corticosteroid on preventing scar tissues formation were what led to investigations regarding its effect on strictures. In this review, we discovered that there are two routes of administration used among the studies, in which four studies evaluated triamcinolone ointment with CIC and two studies administered the steroid through a submucosal injection. Dividing the analysis into two subgroups provided interesting results.

Urethral stricture recurrence rate after triamcinolone ointment lubrication

There were four studies evaluating the use of triamcinolone ointment following internal urethrotomy, which indicated the protective effect of topical triamcinolone (OR = 0.47 CI 95% 0.26-0.82, p=0.009). Regarding route of administration, Korhonen et al. reported that administering intralesional injection of steroids generated poor results compared to self-dilatation.[24] Self-dilatation using CIC following internal urethrotomy is considered as an acceptable procedure to reduce treatment failure and had been recommended in the past to be performed within three to six months following the procedure.[25] The studies included in this review showed the addition of triamcinolone to CIC significantly decreases the rate of stricture recurrence.

Urethral stricture recurrence rate after submucosal triamcinolone injection

Triamcinolone injections have been widely used in recent years for skin scars and mucosal strictures.[26, 27] However, studies evaluating its use in urethral stricture are still limited. There were only two studies evaluating submucosal triamcinolone injection with similar probabilities for stricture occurrence seen between the groups (OR = 0.53 CI 95% 0.25-1.13, p=0.10). These studies also included patients with multiple urethral strictures in the bulbar and pendular areas.[17, 28] These findings are similar to a study by Korhonen et al.[24] who reported a higher rate of stricture recurrence in the triamcinolone injection group compared to the control group. Tabasssi et al.[28] believed that the insignificant findings in their study was because their subjects were not instructed to use CIC apart from given injections. Even though they couldn't demonstrate a decrease in recurrence rate, they claimed that recurrence of stricture after internal urethrotomy was postponed due to the injection. The study was also the only study in this review who reported infection, bleeding, and extravasation complications in the study subjects. The rate of complications could be due to the route of triamcinolone administration, as other studies in this review evaluating topical triamcinolone ointment did not find any complications among the patients.[28] However, the other study included in this meta-analysis by Mazdak et al.[17] reported favorable outcomes of triamcinolone injection. A previous study also reported the beneficial effects of circular steroid injections as opposed to applying them directly into the structure.[18] The difference in findings between the studies warranted another evaluation in the future as more studies evaluating triamcinolone injection are published.

Maximum Urinary Flow Rate (Qmax)

Uroflowmetry is commonly used to help diagnose strictures and evaluating its recurrence during patient follow-up. If the symptoms and uroflowmetry findings suggested urethral stricture, retrograde urethrography would be performed to make a definitive diagnosis of the stricture as it can reveal the full length of the urethra to the stricture, passing through the urethral sphincter and prostatic urethra.[29] There were two studies reporting the mean maximum urinary flow rate in six and twelve months. However, the

findings of both follow-up periods were insignificant (p>0.05). Gucuk et al.[30] reported that when the groups were compared with respect to Qmax values, the patients undergoing self-dilatation combined with triamcinolone showed improvements, even though the difference with the patients of the control group was not statistically significant. The flow rate may suffer from selection bias since patients not treated with triamcinolone in this paper had earlier and more frequent recurrences (53% in the control group compared to 20% group).

Therefore, the average maximum urinary flow rate in the groups might be overestimated, as they excluded subjects where recurrence have occurred.This review has several limitations. Three studies evaluated multiple strictures and diverse etiologies, even though they were still within the anterior urethra. Furthermore, the studies analyzed have included patients beyond the contemporary indications for DVIU, which limits its use to bulbar strictures. The different catheter sizes used by the patients were also a potential bias regarding the actual effects of the ointment combined with the dilatation caused by the CIC. The study by Hosseini et al. also included patients with a history of urethroplasty which could affect the outcome of the urethrotomy. Studies evaluating submucosal injection were only a few with contrasting results, indicating a possible biased result. The differences in time to urethral stricture recurrence were also different among studies. An updated systematic review taking these limitations into account should be performed in the future.

5. Conclusion

The administration of submucosal triamcinolone injection did not improve the urethral stricture recurrence rate after internal urethrotomy, whereas the administration of triamcinolone ointment with CIC could decrease urethral stricture recurrence. However, the administration of both triamcinolone ointment and injection did not improve maximum urinary flow rate.

6. References

[1] Anger JT, Buckley JC, Santucci RA, et al. Trends in stricture management among male medicare beneficiaries: Underuse of urethroplasty? *Urology* 2011; 77: 481–485.
[2] Latini JM. Minimally invasive treatment of urethral strictures in men. *Curr Bladder Dysfunct Rep* 2008; 3: 111–116.
[3] Hampson LA, McAninch JW, Breyer BN. Male urethral strictures and their management. *Nat Rev Urol* 2014; 11: 43–50.
[4] McDougal W, J. WA, Kavoussi LR, et al. *Campbell-Walsh Urology eleven Edition Review : Urethral stricture disease.* 2016.
[5] Bullock TL, Brandes SB. Adult Anterior Urethral Strictures: A National Practice Patterns Survey of Board Certified Urologists in the United States. *J Urol* 2007; 177: 685–690.
[6] Naudé AM, Heyns CF. What is the place of internal urethrotomy in the treatment of urethral stricture disease? *Nat Clin Pract Urol* 2005; 2: 538–545.
[7] Gede ID, Sanjaya R, Rizaldi F, et al. Journal of Global Pharma Technology The Recurrence of Stricture in Postoperative Patients at Dr . Soetomo Hospital from 2013-2017 : A Case-Control Study. 2017; 711–716.
[8] Koc E, Arca E, Surucu B, et al. An open, randomized, controlled, comparative study of the combined effect of intralesional triamcinolone acetonide and onion extract gel and intralesional triamcinolone acetonide alone in the treatment of hypertrophic scars and keloids. *Dermatologic Surg* 2008; 34: 1507–1514.
[9] Zhang K, Qi E, Zhang Y, et al. Efficacy and safety of local steroids for urethra strictures: A systematic review and meta-analysis. *J Endourol* 2014; 28: 962–968.
[10] Gupta S, Roy S, Pal DK. Efficacy of oral steroids after optical internal urethrotomy in reducing recurrence of urethral strictures. *Turkish J Urol* 2018; 44: 42.

[11] Ahmed M, Hossain SM, Islam MT, et al. Use of intra-urethral steroid clobetasol cream to prevent the recurrence of urethral stricture after optical urethrotomy: Randomized clinical trial. *Mediscope* 2019; 6: 59–63.
[12] Bhuiyun MHK, Al Mamun AM, Belal T, et al. Treatment of Short Segment Anterior Urethral Stricture: Optical Internal Urethrotomy (OIU) Alone and OIU with Triamcinolone. *Bangladesh Med J* 2019; 48: 31–38.
[13] Abdallah HM, Abuelnaga M, Rasmy AG. Intraurethral Steroid Injection Following Visual Internal Uerthrotomy in the Management of Anterior Urethral Strictures. *QJM An Int J Med* 2020; 113: hcaa070-002.
[14] Higgins J, Savović J, Page MJ, et al. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. *Br Med J* 2019; 1–24.
[15] Hosseini J, Kaviani A, Golshan AR. Clean intermittent catheterization with triamcinolone ointment following internal urethrotomy. *Urol J* 2008; 5: 265–268.
[16] Tabassi KT, Yarmohamadi A, Mohammadi S. Triamcinolone injection following internal urethrotomy for treatment of urethral stricture. *Urol J* 2011; 8: 132.
[17] Mazdak H, Izadpanahi MH, Ghalamkari A, et al. Internal urethrotomy and intraurethral submucosal injection of triamcinolone in short bulbar urethral strictures. *Int Urol Nephrol* 2010; 42: 565–568.
[18] Sharpe JR, Finney RP. Urethral strictures: treatment with intralesional steroids. *J Urol* 1976; 116: 440–443.
[19] Uemura S, Hutson JM, Woodward AA, et al. Balanitis xerotica obliterans with urethral stricture after hypospadias repair. *Pediatr Surg Int* 2000; 16: 144–145.
[20] ME MF. Treatment with triamcinolone cetonide (trigon-depot) for stenosis after surgery of severe hypospadias. *Actas Urol Esp* 2000; 24: 347–350.
[21] Jiang T, Zhou X, Chen Z, et al. Clinical efficacy of submucosal injection of triamcinolone acetonide in the treatment of type II/III interstitial cystitis/bladder pain syndrome. *BMC Urol* 2020; 20: 1–6.
[22] Partin AW, Wein AJ, Kavoussi LR, et al. *Campbell Walsh Wein Urology, E-Book*. Elsevier Health Sciences, 2020.
[23] Richters CD, Paauw NJ, Mayen I, et al. Administration of prednisolone phosphate–liposomes reduces wound contraction in a rat partial-thickness wound model. *Wound repair Regen* 2006; 14: 602–607.
[24] Korhonen P, Talja M, Ruutu M, et al. Intralesional corticosteroid injections in combination with internal urethrotomy in the treatment of urethral strictures. *Int Urol Nephrol* 1990; 22: 263–269.
[25] Lawrence WT, MacDonagh RP. Treatment of urethral stricture disease by internal urethrotomy followed by intermittent 'low-friction'self-catheterization: preliminary communication. *J R Soc Med* 1988; 81: 136–139.
[26] Ramage Jr JI, Rumalla A, Baron TH, et al. A prospective, randomized, double-blind, placebo-controlled trial of endoscopic steroid injection therapy for recalcitrant esophageal peptic strictures. *Am J Gastroenterol* 2005; 100: 2419–2425.
[27] SNODGRASS W. Triamcinolone to prevent stenosis in Mitrofanoff stomas. *J Urol* 1999; 161: 928.
[28] Tavakkoli Tabassi K, Mansourian E, Yarmohamadi A. One-stage transperineal repair of pan-urethral stricture with dorsally placed buccal mucosal grafts: results, complications, and surgical technique. *Urol J* 2011; 8: 307–312.
[29] Mundy AR, Andrich DE. Urethral strictures. *BJU Int* 2011; 107: 6–26.
[30] Gücük A, Tuygun C, Burgu B, et al. The short-term efficacy of dilatation therapy combined with steroid after internal urethrotomy in the management of urethral stenoses. *J Endourol* 2010; 24: 1017–1021.