

REVIEW

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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Summary *Introduction: Urethral stricture, characterized by urethral narrowing due to fibrosis and scar tissue, is a common urological condition. It occurs in about 200 per 100,000 people, with increasing incidence over the past 50 years. Internal urethrotomy is commonly performed for short strictures, but its high recurrence rate has led to the exploration of adjunctive treatments like adjunct of triamcinolone application. This study aimed to analyze the effect of triamcinolone as adjunctive therapy for internal urethrotomy on reducing urethral stricture recurrence in urethral stricture patients.*

Methods: A systematic search was conducted in PUBMED, ScienceDirect, and Google Scholar. This review was conducted according to the PRISMA guideline, and the protocol has been registered in the PROSPERO database (CRD420202254).

Results: Six RCTs, including 373 urethral stricture patients, were eligible for this study. Pooled results of the included studies showed a significant difference between the triamcinolone and control groups, indicating a lower recurrence rate in the triamcinolone group (OR = 0.49 95% CI 0.31-0.77, p = 0.002). A 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 in the submucosal injection subgroup (p > 0.05). The treatment and control groups had similar maximum urinary flow rate (Q_{max}) at six and twelve months (p > 0.05).

Conclusions: Triamcinolone ointment with CIC reduced urethral stricture recurrence following internal urethrotomy, whereas submucosal injection did not. Both treatments do not increase the maximum urinary flow rate.

KEY WORDS: Urethral stricture; Triamcinolone; Internal urethrotomy; Systematic review.

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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. It can occur in

many patients with various etiologies as trauma, infection, ischemia, inflammation, instrumentation, or other unknown causes (1).

Studies reported that it occurs in 200 in 100,000 people, with an increasing incidence rate in the last 50 years (2). The treatments recommended for patients with urethral strictures include urethrotomy, dilatation, and urethroplasty (3).

Internal urethrotomy is used for urethral stricture with a length of less than 1.5 cm. However, the efficacy of internal urethrotomy is still being questioned because of its high stricture recurrence rate (4). A case-control study regarding urethral stricture in Indonesia by Gede *et al.* in 2017 stated that the urethral stricture recurrence after internal urethrotomy was as high as 92.5% (5). Many treatment alternatives after internal urethrotomy have been widely studied to reduce the urethral stricture recurrence rate. Corticosteroid is one of the most commonly used drugs studied. It has been widely used in many centers to reduce scar formation. It is able to decrease collagen, glycosaminoglycan synthesis, and the expression of inflammatory mediators (6). Among corticosteroids, triamcinolone is regularly reported. However, results of this approach are conflicting.

Many studies investigating the role of corticosteroids have been published (7-10). Therefore, we aimed to assess the efficacy of triamcinolone following internal urethrotomy in preventing urethral stricture recurrence.

MATERIALS AND METHODS

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 CRD420202254.

Eligibility criteria

We used the following inclusion criteria to determine the eligibility of studies:

(1) *Randomized Controlled Trial* (RCT) study design, (2) studies comparing Triamcinolone with internal urethrotomy alone, (3) men with urethral stricture treated with internal urethrotomy.

Studies with the following criteria were excluded: (1) non-English articles, (2) animal studies, (3) unpublished articles, and (4) abstract-only articles.

Search strategy, study selection and data extraction

We performed a systematic search in the *MEDLINE*, *PubMed*, *ScienceDirect* and *Google Scholar* databases. 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 were 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.

Outcome measurement and data analysis

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 effect model would be used. For statistical analysis RevMan version 5.4 (*The Cochrane Collaboration, 2020*) for Windows was used, presenting results in the form of Forest plots and narrative description.

Risk of bias assessment

Risk of bias was assessed using Cochrane Risk of Bias Tools for Randomized Trials 2 (9). Two reviewers conducted an independent bias assessment, with the results of the risk of bias being low risk, some concerns, and high risk.

RESULTS

In the initial search, as shown in Figure 1, 458 studies were obtained from the *PubMed*, *Science-Direct*, and *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 fit the inclu-

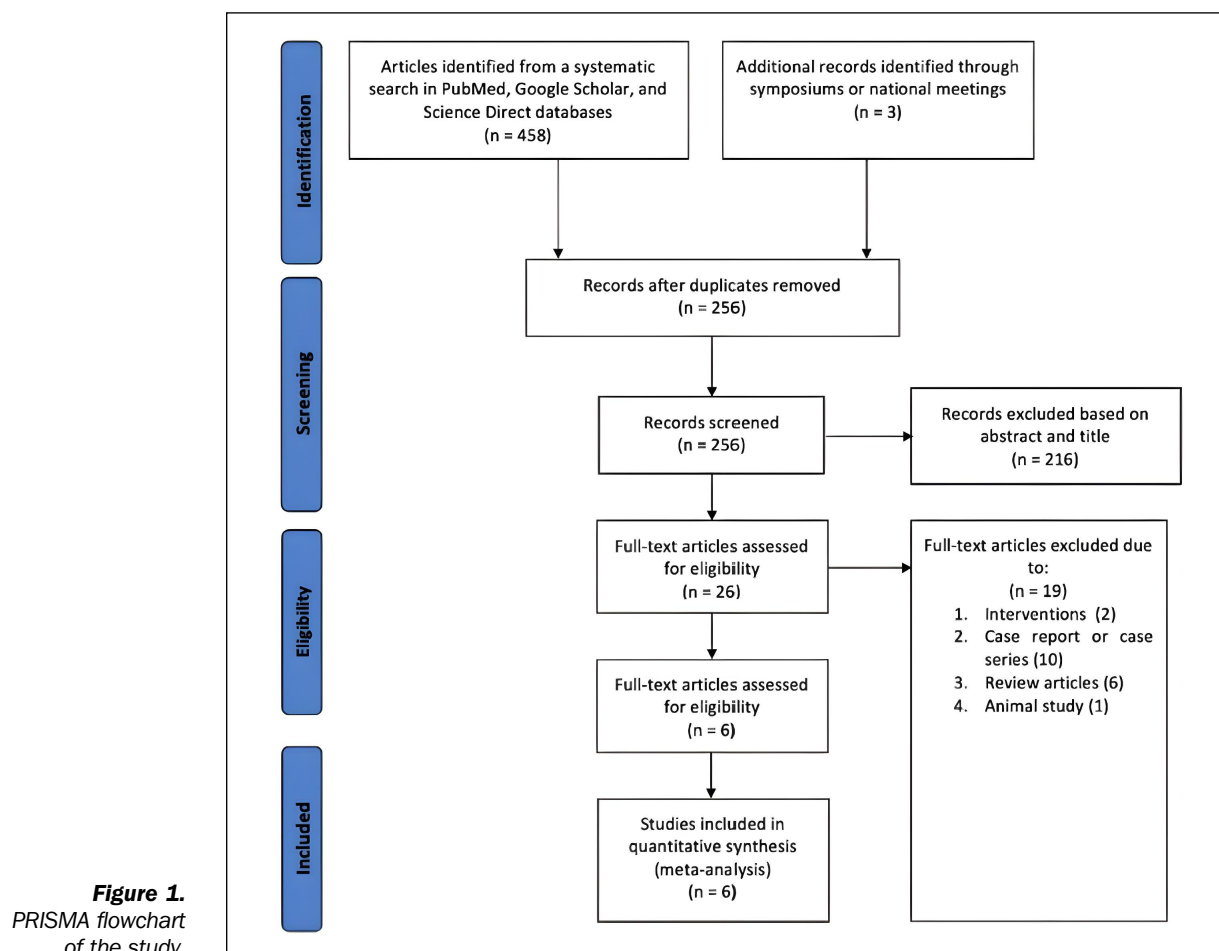


Table 1.
Baseline characteristics of studies.

Author (Year)	Group	Sample	Age	Action (mean + SD) year	Operator	Intervention	Previous urethroplasty (n)	Location (number of strictures)	Length of stricture	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 urethroplasty	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 urethroplasty	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 urethroplasty	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 urethroplasty	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 urethroplasty	Bulbo-membranous (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						

*DVIU: Direct Vision Internal Urethrotomy; CIC: Clean Intermittent Catheterisation; SD: Standard Deviation; Fr: French; NR: Not Reported.

sion and exclusion criteria for this review. There were six articles that could be analyzed qualitatively and quantitatively in this study. 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. Four studies evaluated the application of triamcinolone ointment with *clean intermit-*

tent catheterization (CIC), whereas two studies administered submucosal triamcinolone injection. 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 of urethroplasty, except for *Hosseini et al.* (11). Complications were only found in the study by *Tabassi et al.* (12).

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Mazdak 2010	⊖	⊕	⊕	⊕	⊖	⊕
Regmi 2018	⊕	⊕	⊕	⊕	⊕	⊕
Tabassi 2011	⊖	⊕	⊕	⊕	⊕	⊕
Gucuk 2010	⊕	⊕	⊕	⊕	⊕	⊕
Hosseini 2008	⊕	⊕	⊕	⊕	⊕	⊕
Ergun 2015	⊕	⊕	⊕	⊕	⊕	⊕

Domains:
 D1: Bias arising from the randomization process.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgement
 ⊖ Some concerns
 ⊕ Low

Figure 2.
Risk of bias assessment using Cochrane RoB Tool 2.

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 (13), as shown in Figure 2. In this study, four studies had a low risk of bias. The studies conducted by *Mazdak et al.* (14) and *Tabassi et al.* (12) were at risk for randomization bias since the studies did not clearly explain the randomization process and whether the allocation process was blinded.

Urethral stricture recurrence rate after triamcinolone application (ointment lubrication and injection)

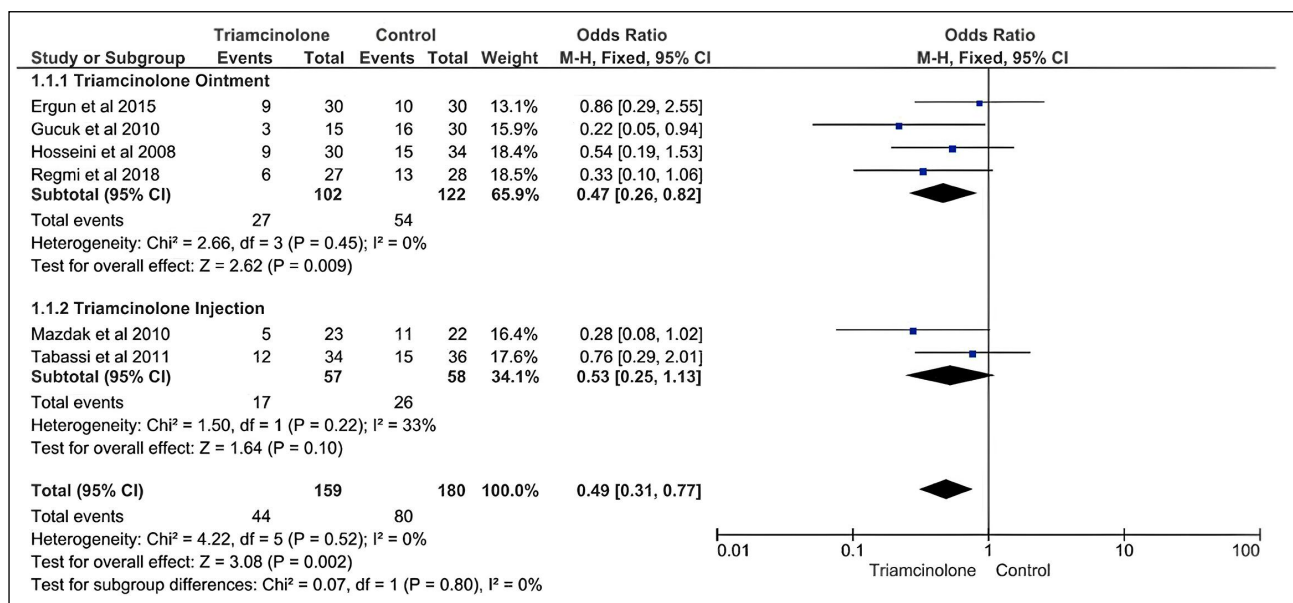
All six studies evaluated the application of triamcinolone after urethrotomy, as shown in Figure 3. The data of the studies were considered homogenous ($I^2 = 0\%$, $p = 0.45$).

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 of triamcinolone ointment lubrication 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 3 showed that there is a significant difference in urethral stricture incidence between the treatment and control groups (OR = 0.47 CI 95% 0.26-0.82, $p = 0.009$).

Figure 3.
Urethral stricture recurrence rate after triamcinolone application.



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, $p = 0.10$).

Urethral recurrence rate and follow-up duration

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

Maximum urinary flow rate (Q_{max}) in 6 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 effect model analysis in Figure 5 showed that there was no difference in Q_{max} between groups (MD = 0.91 CI 95% -0.82-2.63, $p = 0.30$).

Maximum urinary flow rate (Q_{max}) in 12 months

There were two studies describing the mean maximum urinary flow rate after 12 months as shown 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

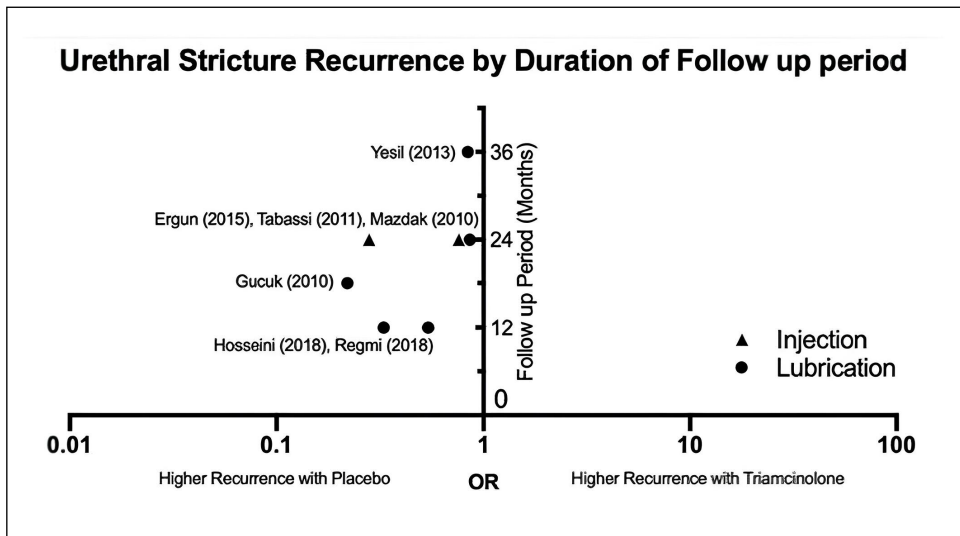


Figure 4. Recurrence rate probability of the studies with different durations of follow-up.

Figure 5. Maximum urinary flow rate (Q_{max}) at 6 months.

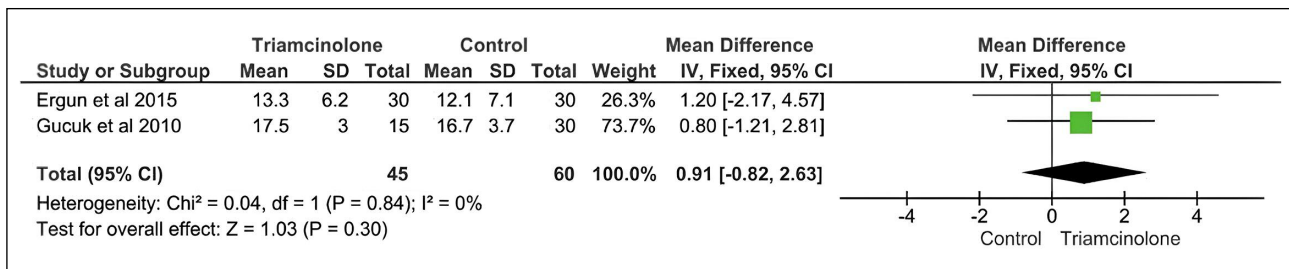
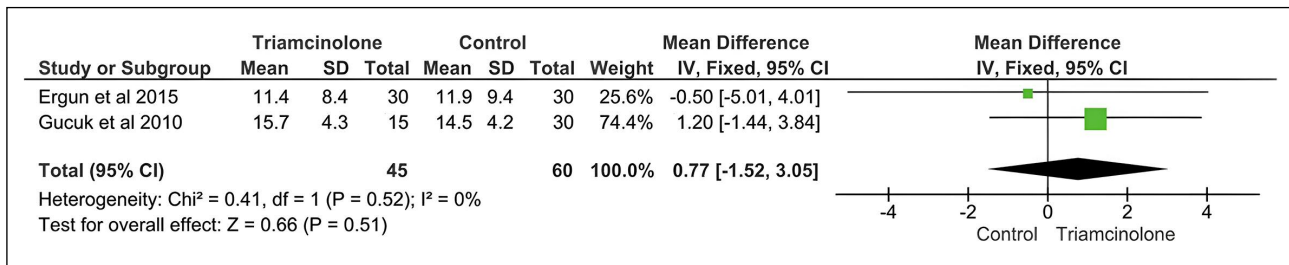


Figure 6. Maximum urinary flow rate (Q_{max}) at 12 months.



effects model, showing no difference in Q_{max} between groups (MD = 0.77 CI 95%-1.52-3.05, $p = 0.51$).

DISCUSSION

Symptomatic urethral strictures impede voiding function and may significantly impact patient's quality of life (15). The role of corticosteroids for urethral strictures and stenoses has been studied for decades (16-18).

Triamcinolone is a long-acting synthetic glucocorticoid with anti-inflammatory and vasoconstricting properties. It is commonly used in many urological disorders as it is inexpensive and well-tolerated (19). Many studies have been exploring the possibilities of corticosteroids after internal urethrotomy, as the procedure does not provide an epithelial approximation, but only separates the scar tissues while relying on secondary healing (20).

Triamcinolone is believed to be able to reduce scar formation by reducing collagen, glycosaminoglycan synthesis, and the expression of inflammatory mediators (21). A previously published meta-analysis evaluated the application of triamcinolone after internal urethrotomy (22). 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 (ointment lubrication and injection)

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 by 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, 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 the route of administration, *Korhonen et al.* reported that administering intralesional injections of steroids generated poor results compared to self-dilatation (24). Self-dilatation using CIC following internal urethrotomy is considered 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

Studies evaluating triamcinolone injection in urethral stricture are still limited. Only two trials examined submucosal triamcinolone injection and found similar stricture probabilities (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 (26, 27). 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. *Tabassi et al.* (28) believed that the insignificant findings in their study were because their subjects were not instructed to use CIC apart from given injections. Even though they could not demonstrate a decrease in recurrence rate, they claimed that the recurrence of stricture after internal urethrotomy was postponed due to the injection (28). However, the other study included in this meta-analysis by *Mazdak et al.* (14) 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 (16). The difference in findings between the studies. Another evaluation in the future with more studies evaluating triamcinolone injection is warranted.

Maximum urinary flow rate (Q_{max})

Uroflowmetry helps diagnose stricture and monitor its recurrence. 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 Q_{max} 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. In this paper the flow rate evaluation may suffer from selection bias since patients not treated with triamcinolone had earlier and more frequent recurrences (53% in the control group compared to 20% group) and subjects where recurrence has occurred were excluded from the evaluation of maximum urinary flow rate.

The 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 direct vision internal urethrotomy, which limit 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 clean intermittent catheterization. The study by *Hosseini et al.* also included patients with a history of urethroplasty which could affect the outcome of the urethrotomy *al.* (11) 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. As more clinical trials will become available in the future, an updated systematic review which overcome these limitations should be performed.

CONCLUSIONS

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

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DECLARATIONS

Ethical approval and consent for participate: No ethical review needed for this type of article.

Availability of data and material: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interest: No Conflict of interest was declared by the authors.

Conference presentation: This article was never presented in any conference before.

Authors' contributions: DPA: Led the conceptualization of the systematic review, designed the methodology, performed the data synthesis, and drafted the manuscript, and ensured all revisions were addressed. MAS: Conducted the literature search, screened studies for inclusion, and contributed to data extraction and analysis. Assisted in drafting and critically revising the manuscript. TD: Performed the data extraction, contributed to the quality assessment of included studies, and participated in manuscript writing and revisions. FH: Assisted in the systematic literature search, data analysis, and contributed to manuscript drafting and revisions. ZAR: Supported the data analysis, assisted in reviewing the included studies, and contributed to manuscript revisions. IAR: Contributed to the literature search, data extraction, and performed statistical analysis. Also provided input on the manuscript's structure and revisions. PAS: Assisted in the data extraction process, contributed to the quality assessment of studies, and helped in revising the manuscript. All of the authors read and approved the final manuscript.

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