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Effect of local steroids on urethral strictures: A systematic review and meta-analysis

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Purpose: Urethral stricture disease is common and has high associated morbidity and impact on quality-of-life. This systematic review and meta-analysis aims to summarise current evidence on the efficacy of local urethral steroids post-direct vision internal urethrotomy (DVIU) for the treatment of urethral strictures in males.

Materials and Methods: A comprehensive search was performed using reputable databases and registries, up to 22 February 2022. Only randomised control trials in which participants were randomised to DVIU plus local urethral steroids versus DVIU only were included. Statistical analyses were performed using a random-effects model. Quality of evidence was rated according to the GRADE approach.

Results: The search identified seven studies in which 365 participants were randomised to DVIU plus local urethral steroids versus DVIU only. The application of local steroids appeared to reduce recurrence rates (risk ratio, 0.67; 95% confidence interval [CI], 0.49–0.90) and time-to-recurrence (hazard ratio, 0.58; 95% CI, 0.39–0.85). Qmax also improved following steroid application (mean difference, 0.82; 95% CI, -1.02–2.66); however, this was not statistically significant. No heterogeneity was identified between included studies for all outcomes. The certainty of evidence was downgraded due to study limitations with a small sample size and unclear risk-of-bias related to insufficient trial information.

Conclusions: Compared to DVIU alone, adjuvant steroids applied to the urethra may reduce risk of recurrence and time-to-recurrence. These findings were statistically significant and likely also clinically significant given low associated costs and risk. However, more robust randomised trials are necessary to enhance the validity of these outcomes.

Keywords: Male; Steroids; Urethral stricture

INTRODUCTION

A urethral stricture, in males, refers to a narrowed segment of the anterior urethra which occurs secondary to the process of spongiofibrosis. Urethral strictures are one of the most common causes of obstructive lower urinary tract symptoms in males, with a mean age of 45.1 and an estimated overall incidence of 229 to 627 per 100,000 males [1,2]. The anterior urethra is most frequently affected (92.2%), with most strictures occurring at the bulbar urethra (46.9%) [2]. In high-income countries, iatrogenic urethral injury accounts for majority of stricture aetiology at 32% to 79% [2,3]. Other leading causes of urethral strictures include sexually transmitted infections [3], external urethral trauma [3] and

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inflammation associated with lichen sclerosis [4]. Urethral stricture disease not only has a high associated morbidity and impact on patient quality of life (QoL) [5], but due to its recurrent nature, the cost of treatment and burden on healthcare should not be underestimated [6].

After proper clinical assessment and diagnostic evaluation, various techniques have been well-described for the treatment of urethral strictures, depending on disease factors (i.e., stricture aetiology, length, location, calibre, and previous interventions) and patient factors (i.e., age, comorbidities, and functionality) [7-9]. In contemporary practice, urethral dilatation, and direct vision internal urethrotomy (DVIU) have long been recommended for the initial treatment of urethral strictures shorter than 1.5 cm but have been associated with high recurrence rates up to 65% to 90% [6,8,10]. Median time to recurrence post DVIU is less than twelve months in most studies [8,11-13]. The introduction of open urethroplasty revolutionised the treatment of recurrent stricture disease and remains the gold standard for urethral reconstruction [14]. Nevertheless, urethroplasty is not always viable and requires care in a specialised tertiary centre. As such, endoscopic management of urethral strictures is still necessary due to its wide availability, cost effectiveness, and ability to be performed under non-general anaesthesia. Although many complementary strategies have been recommended to optimise endoscopic therapy and reduce recurrence, such as indwelling catheters (IDCs), clean intermittent self-catheterisation (CISC), intraurethral antifibrinolytics and corticosteroids, definitive evidence is still lacking in the literature.

The objective of this systematic review and meta-analysis is to summarise current available evidence on the efficacy of local urethral steroids (topical or injectable) versus no steroids, post-DVIU, for the treatment of urethral stricture disease in males.

MATERIALS AND METHODS

1. Protocol and registration

A review protocol was completed using the PROSPERO registry (PROSPERO-ID CRD42021251456).

2. Eligibility criteria

The following eligibility criteria were used to identify relevant studies:

- Types of studies: We included only randomised control trial (RCT), regardless of their publication status, date of publication, or language of publication.
- Types of participants: We included studies that enrolled male individuals with urethral stricture disease undergoing DVIU, with a cold knife or laser, regardless of the stricture aetiology, location, length, or history of previous interventions.
- Types of interventions: We considered studies that involved application of local steroid to the urethral stricture site (versus no steroid application), either through injection or lubricated catheter, regardless of the use of other adjunctive therapies (i.e., IDC or CISC) provided these were consistent in both groups.

Types of outcome measures planned included:

- Primary outcomes
  - o Recurrence rates – defined by the recurrence of symptoms, reduced Qmax, visualised stricture disease and/or need for re-intervention at 12- and 24-months.
  - o Adverse events – defined by the occurrence of infection, bleeding, extravasation, or local and/or systemic complications of steroid administration at 12- and 24-months.
  - o QoL – at 12- and 24-months post DVIU measured using a validated QoL tool (i.e., International Prostate Symptom Score [IPSS]).
- Secondary outcomes
  - o Qmax – defined as the peak urinary flow rate as measured using uroflowmetry at 12- and 24-months.
  - o Time to recurrence – defined as the duration of time post DVIU until the recurrence of symptoms, reduced Qmax, visualised stricture disease and/or need for re-intervention.

3. Search method for identification and selection of studies

We performed a comprehensive literature search, up to 22 February 2022, using a range of established scientific databases (PubMed [MEDLINE], Cochrane Libraries, Embase [Ovid], and Web of Science) and trial registries (ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform). Our search included the MeSH terms "urethral-stricture" AND "steroids", and non-MeSH terms "urethrotomy AND steroid", and "urethra AND steroid." No restrictions on language or date of publication were applied. Furthermore, we also searched grey literature, and major international general urological meetings and guidelines (i.e., European Association of Urology, Société Internationale d'Urologie, American Urological Association) for relevant abstracts or references. Reference lists of identified studies were checked for further relevant studies to ensure other publications of interest were not missed. Finally, citation

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alerts were placed on included studies to identify any recent articles.

4. Data selection and extraction

Two review authors (CS and HYCP) independently searched all databases and used other search strategies as listed above. Titles and abstracts were identified and screened. Irrelevant and repeated titles and abstracts were excluded. A consensus was obtained through discussion to resolve disagreements between the two reviewers.

For studies that fulfilled the inclusion criteria, two review authors (CS and HYCP) then independently investigated all potentially relevant records as full text and extracted relevant information. Disagreement between the reviewers, if unable to be resolved by discussion, was resolved by consultation with a senior third author (NJS). No additional information was required beyond published data.

Relevant outcome data was extracted as needed for calculation of summary statistics and measures of variance.

- For dichotomous outcomes (e.g., recurrence rates, adverse events), the numbers of events and totals for population were obtained, and summary statistics with corresponding measures of variance.
- For continuous outcomes (e.g., QoL scores, time to re-intervention, Qmax), mean and standard deviations were obtained to calculate this information.
- For time-to-event outcomes, we extracted the hazard ratio (HR) from published data according to published guidance, with corresponding measures of variance or data necessary to calculate this information.

5. Risk of bias quality assessment

Two review authors (CS and HYCP) independently assessed the risk of bias in each eligible study using the set framework outlined in the Cochrane's 'Risk of bias (RoB)' assessment tool (Higgins and Green, 2011) [15]. The following domains were included:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other sources of bias

We judged risk of bias domains as 'low risk', 'high risk', or 'unclear risk' and evaluated individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011) [15]. We have presented a RoB summary figure to illustrate these findings. Funding for individual studies was not reported by authors.

1) Funnel plot analysis

Cochrane Handbook [15] recommends use of funnel plots to assess small study effects only if there are 10 studies or more investigating a particular outcome. As such we were unable to perform formal funnel plots assessment for publication bias as intended due to the insufficient number of studies (n=7).

However, upon informal funnel plot assessment there was an equal distribution of positive and negative studies to suggest that publication bias was not concerning in this review.

6. Data synthesis and analysis

1) Strategy for data synthesis

For dichotomous outcomes, the Mantel–Haenszel method was used. For continuous outcomes, the inverse variance method was used. For time-to-event outcomes, the generic inverse variance method was used. We used random-effects models for all analyses. Statistical significance was set at p-value <0.05. All analyses were performed using R version 3.4 (R Foundation for Statistical Computing, Vienna, Austria).

2) Analysis of subgroups or subsets

We attempted to perform multiple subgroup analyses as per protocol. However, no subgroup analyses were possible due to insufficient available data from the included trials.

Proposed subgroup analyses a priori included:

- Stricture location
- Duration of IDC insertion post DVIU
- Timing of onset of CISC post DVIU
- Frequency of CISC post DVIU
- Dosage of steroid injection used post DVIU

3) 'Summary of findings' table

We have presented a 'Summary of findings' table (Table 1), reporting the following available outcomes listed according to priority.

- Recurrence rates
- Qmax (short-term data)
- Time to stricture recurrence

We present the overall certainty of the evidence for each outcome according to the GRADE approach, which considers five criteria relating to internal validity (i.e., risk of bias, inconsistency, imprecision, and publication bias), and external validity (i.e., indirectness) [16]. For each comparison, two review authors (CS and HYCP) independently rated

Table 1. Summary of findings

Certainty assessment							Summary of finding		
								Anticipated absolute effect	
No of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence (GRADE)[a]	Relative effect (95% CI)[b]	Risk with DVIU	Risk difference with DVIU+local urethral steroids
Recurrence rate									
365 (7 RCTs)	Very serious[c]	Not serious	Not serious	Not serious	None	⨁⨁◯◯ Low	Risk ratio 0.67 (0.49–0.90)	402 per 1,000	133 fewer per 1,000 (from 205 fewer to 40 fewer)
Qmax									
0 (3 RCTs)	Very serious[c]	Not serious	Not serious	Serious[d]	None	⨁◯◯◯ Very low	N/A	N/A	N/A
Time to recurrence									
1,084 (3 RCTs)	Very serious[c]	Not serious	Not serious	Not serious	None	⨁⨁◯◯ Low	Hazard ratio 0.58 (0.39–0.85)	441 per 1,000[e]	155 fewer per 1,000 (from 238 fewer to 51 fewer)

DVIU+local urethral steroids compared to DVIU for urethral strictures in men.

Patient or population: Urethral strictures in men. Intervention: DVIU+local urethral steroids. Comparison: DVIU.

DVIU, direct vision internal urethrotomy; CI, confidence interval; RCT, randomised control trial; N/A, not applicable/estimable.

[a]:GRADE Working Group grades of evidence: (1) High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. (2) Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. (3) Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. (4) Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[b]:The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[c]:Marked down 2 levels due to multiple risk of bias domains scoring an unclear level of uncertainty due to insufficient information.

[d]:Very wide confidence interval which crossed 0 (null).

[e]:Baseline risk of stricture recurrence following DVIU (control) estimated at 44.1% using median rate of stricture recurrence across all 7 included studies.

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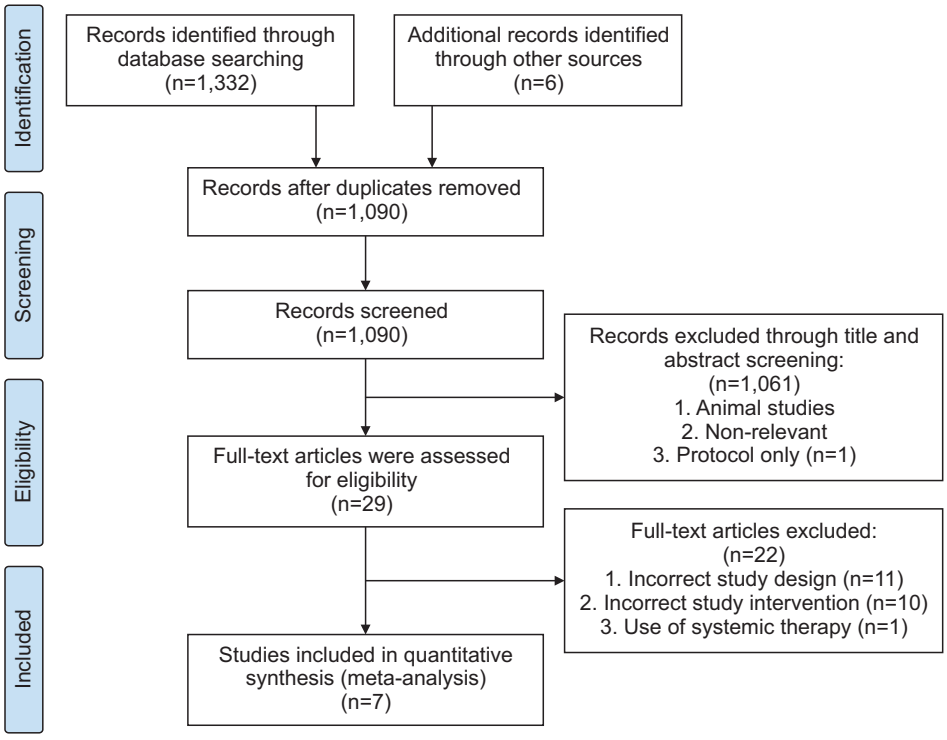

Fig. 1. Flowchart depicting the incorporation of included articles according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very-low' using GRADEpro GDT (McMaster University, Hamilton, ON, Canada; Evidence Prime, Kraków, Poland). Any discrepancies were resolved by consensus, or, if needed, by arbitration with a third review author (NJS). For each comparison, a summary of the evidence for the main outcomes were presented in a 'Summary of findings' table, which provides key information about the best estimate of relative and absolute effects for each outcome [17].

RESULTS

1. Study search, selection, and flow

We identified 1,332 records through search of electronic databases and 6 additional records through search of trial registries (Supplementary Table 1). After removal of duplicates, we screened the titles and abstracts of 1,090 records of which we excluded 1,061. We screened 29 full-text articles and excluded 22 that did not meet the inclusion criteria (Supplementary Table 2). We included a total of seven trials in this review.

We identified one relevant randomised trial via ClinicalTrials.gov that was performed by Ain Shams University in Egypt (ClinicalTrials.gov Identifier: NCT05078788). The 124-participant trial assessing the efficacy of Holmium laser in combination with intra-lesional steroid injection in the treatment of bulbar urethral strictures is listed as completed as of 10 September, 2021; however, no study results are listed, no manuscript is available online, and no details are available to allow direct contact with the authors. As such, this review may need to be updated in the future once this clinical trial data becomes freely available.

The flowchart depicting the incorporation of included articles through the assessment process is shown in the PRISMA flowchart (Fig. 1).

2. Study characteristics

All seven included trials were identified through the literature search [18-24]. All trials were randomised and included the administration of steroids (triamcinolone) via a coated catheter or submucosal injection. A total of 365 randomised male patients with urethral strictures (181 participants in the intervention group, 184 participants in the control group) were included in the review. The mean follow-up of all studies in the review was 17.54 weeks (ranging from 8.68 to 36 weeks). Details of the included trials are presented in Table 2.

3. Risk of bias of included studies

All seven included studies [18-24] were assessed for a range of risk of bias domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other bias'. A vast majority of domains across all included trials were assessed

Table 2. Baseline characteristics of the seven included studies

Study	Design	Participant[a]		Age (y)[a]		Aetiology	Site	Length (mm)[a]		Intervention	Duration of post-op IDC (d)	Follow-up (mo)
Regmi et al. 2018 [18]	RCT	27	28	37.2±1.6	36±1.7	Traumatic 26 (47.2), inflammatory 12 (21.9), others 17 (30.9)	N/S	9.3±3.3	10.7±3.2	Catheter coated with triamcinolone for 6 months (weaning)	7	12
Ergün et al. 2015 [19]	RCT	30	30	61.2	60.7	Iatrogenic 74 (82.2), idiopathic 16 (17.8)	N/S	N/S	N/S	Catheter coated with triamcinolone weekly for 6 weeks	3	24
Yeşil et al. 2013 [20]	RCT	22	19	45.1±8.0	47±8.8	Urethral instrumentation 12 (29), trauma 3 (7), urinary infection 7 (17), idiopathic 19 (46)	Bulbar	7.4±4.0	7.8±4.3	Catheter coated with triamcinolone for 2 weeks	N/A	36
Tavakkoli Tabassi et al. 2011 [21]	RCT	34	36	42.38	42	Trauma (17.64), catheter (16.17), infection (5.88), unknown/other (60.31)	Bulbar, penile	8.07±1.40	8.4±1.38	Submucosal triamcinolone injection (5 cc)	3–5	8.68±5.36
Gücük et al. 2010 [22]	RCT	15	15	31.2±8.3	35.2±7.9	Trauma 13 (28.9), infectious 5 (11.1), instrumentation 11 (24.4), unknown 16 (35.6)	Bulbar	8.3±2.7	8.3±1.9	Catheter coated with triamcinolone nightly for 2 weeks	3	16.4±2.97
Mazdak et al. 2010 [23]	RCT	23	22	37.1±20.9	34±19.9	Traumatic 21 (46.8), Inflammatory 7 (15.5), unknown 17 (37.8)	Bulbar	9.5±1.7	8.8±2.3	Submucosal triamcinolone injection (40 mg)	5	13.7±5.4
Hosseini et al. 2008 [24]	RCT	30	34	37.7±17.1	34.5±13.3	Urethral distraction 29 (45.6), straddle Injury 12 (18.4), catheter 10 (15.7), other 13 (20.3)	N/S	8.5±4.0	9±3	Catheter coated with triamcinolone for 6 months (weaning)	N/A	12

Values are presented as number only, mean±standard deviation or number (%).
IDC, indwelling foley catheter; RCT, randomised control trial; N/S, not specified; N/A, not applicable.
[a]:Intervention control.

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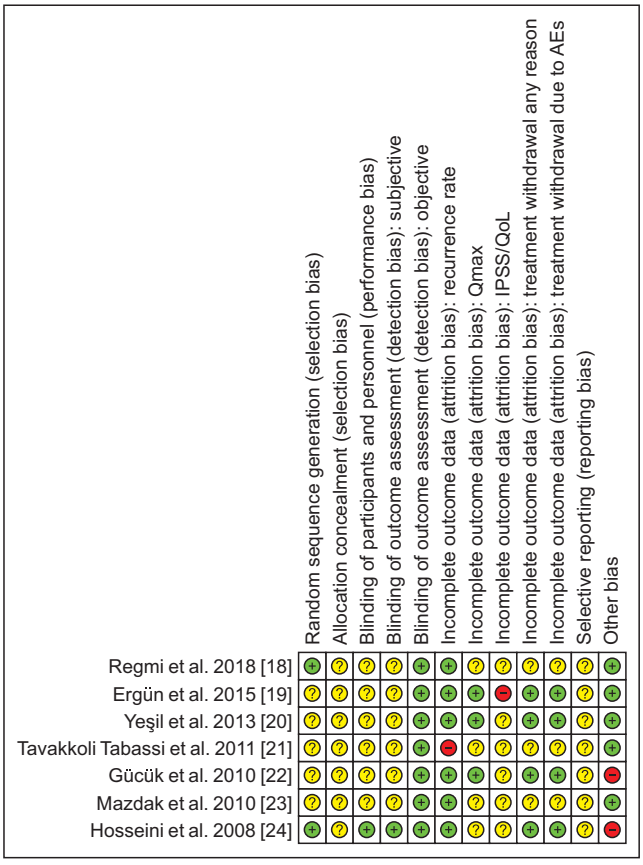

Fig. 2. Risk of bias of the seven included studies summary. IPSS, international prostate symptom score; QoL, quality of life; AE, adverse event.

to be of unclear risk of bias due to insufficient information. Detailed results of the RoB assessment are provided in Fig. 2.

4. Synthesis of results

1) Primary outcomes

(1) Recurrence rates

We included seven randomised trials [18-24] with 365 participants in total. Recurrence of urethral stricture was defined by either symptomatic or endoscopic recurrence, or the need for repeat procedure in the follow-up period. Steroids (triamcinolone) applied to the urethra (via a coated catheter or submucosal injection route) appear to reduce the recurrence rates of urethral strictures, compared to control, post DVIU (risk ratio, 0.67; 95% confidence interval [CI], 0.49–0.90) (Fig. 3A). These findings were both statistically and likely clinically significant. No heterogeneity was identified between included studies (p=0.75, I^2=0%). This corresponds to 133 fewer stricture recurrences per 1,000 in patients receiving DVIU plus steroids compared to DVIU alone. We rated the certainty of this evidence as low.

(2) Adverse events

Only Tavakkoli Tabassi et al. [21] appropriately reported adverse events in their trial. Of the 13 patients with recorded adverse effects, 3 contracted infections, 6 experienced bleeding, and 4 had extravasation. Regmi et al. [18], Ergün et al. [19], Yeşil et al. [20], and Hosseini et al. [24] all reported no adverse events at all in their follow-up periods, while Gücük et al. [22] and Mazdak et al. [23] did not assess adverse event outcomes. As such, there was insufficient data to perform a meta-analysis.

(3) Quality of Life (IPSS)

Only Ergün et al. [19] reported on quality-of-life in the form of IPSS at 1, 3, and 24 months. None of the six other included trials reported any quality-of-life measure. As such, there was insufficient data to perform a meta-analysis on short (<12 months) or long-term (>12 months) data.

2) Secondary outcomes

(1) Qmax

Short-term data (≤12 months): We included three randomised trials [19,20,22] with 131 participants in total. At 12 months, steroids (triamcinolone) applied to the urethra via a coated catheter appear to improve the Qmax, compared to control, post DVIU, although these findings were not statistically significant (mean difference [MD], 0.82; 95% CI, -1.02–2.66) (Fig. 3B). Furthermore, these findings were likely also not clinically significant; however, this information would be difficult to ascertain given the nature of Qmax. No heterogeneity was identified between included studies (p=0.82, I^2=0%). Estimation of the associated risk difference was not statistically possible. We rated the certainty of this evidence as very low.

Long-term data (>12 months): Variable long-term data (>12 months) is available for all three trials; however, only Yeşil et al. [20] and Ergün et al. [19] provide data at the same timepoint (i.e., 24 months). As such, only 101 participants in total were available for long-term data analysis.

At 24 months, steroids (triamcinolone) applied to the urethra via a coated catheter appear to improve the Qmax, compared to control, post DVIU, although these findings were not statistically or clinically significant (MD, 0.87; 95% CI, -1.11–2.84) (Fig. 3C). No heterogeneity was identified between included studies (p=0.88, I^2=0%).

(2) Time to recurrence

We included three randomised trials [18,21,23] with 170 participants in total. Steroids (triamcinolone) applied to the urethra (via a coated catheter or submucosal injection

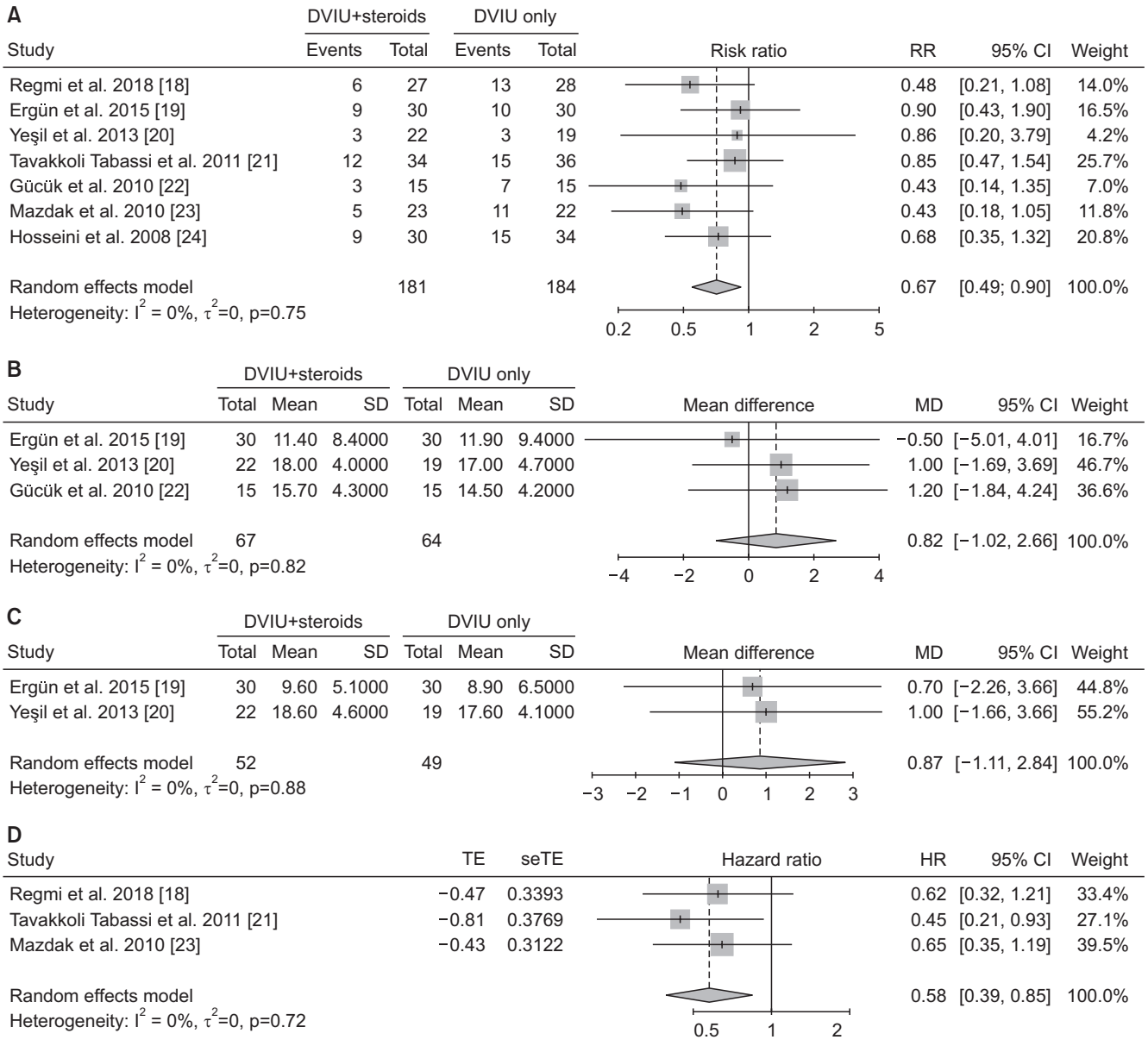

Fig. 3. Forest plots of outcome comparisons. (A) Stricture recurrence rates. (B) Qmax – short-term data (≤12 months). (C) Qmax – long-term data (>12 months). (D) Time to recurrence. DVIU, direct vision internal urethrotomy; CI, confidence interval; SD, standard deviation; TE, estimated treatment effect; seTE, standard error of treatment estimate.

route) appear to reduce the time to recurrence of urethral strictures, compared to control, post DVIU (HR, 0.58; 95% CI, 0.39–0.85) (Fig. 3D). These findings were both statistically and likely clinically significant. No heterogeneity was identified between included studies (p=0.72, I^2=0%). This corresponds to 155 stricture recurrences per 1,000 that occur later in patients receiving DVIU plus steroids compared to DVIU alone. We rated the certainty of this evidence as low.

DISCUSSION

Our review and meta-analysis of the currently available literature indicates that local steroid administration, both topical and injectable, is a viable adjuvant therapy for treatment of urethral stricture disease. Although local steroid use appeared to improve Qmax, these results were not significant; however, it may reduce overall recurrence rates and significantly delay the time to recurrence in patients undergoing DVIU for urethral strictures. Additionally, while application of local steroids is likely benign, safety data was poorly recorded in the included studies and thus the risk-benefit of urethral steroid application remains unclear. As such, incorporation of a structured reproducible complication reporting system in future trials may improve the accuracy

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and comparability of urethral steroids and other DVIU adjuncts.

DVIU has played an important role in the management of urethral stricture disease since its introduction in the 1980s [25]. In today's practice, DVIU is commonly performed as a first line treatment of primary strictures with a length shorter than 1.5 cm [26]. Urethral dilatation also plays a significant role in this management; however, both forms of endoscopic management are hindered by the same pitfalls of high recurrence rates and limited outcomes in longer strictures. Steenkamp et al. in 1997 [7] evidenced these drawbacks, in a trial of 210 patients randomised to filiform dilatation versus DVIU with local anaesthesia in the outpatient setting, demonstrating that urethral dilatation is equally effective as DVIU but both procedure modalities become less effective with increasing stricture length. Additionally, recurrence rates after DVIU have been reported at 60% to 65% by Pansadoro and Emiliozzi in 1996 [8] and, of even more concern, up to 90% by Santucci et al. in 2007 [6] – although this dramatic increase in recurrence rate may be related to an increased number of re-treatments. Regardless of the treatment and condition being treated, failure rates of this extent in developed countries with accessible healthcare are unacceptable, and the need to develop improved adjuvant techniques are long overdue.

DVIU alone aims to separate scarred epithelium to promote effective secondary wound healing, but it does not provide epithelial approximation. Thus, DVIU will only be successful in the long-term if epithelialisation progresses before wound contraction, or else stricture recurrence is inevitable [27]. As previously mentioned, a number of complementary adjuvant procedures, including CISC, have been proposed to minimise stricture recurrence rates. Likewise, topical or injectable steroid application decreases scar formation by reducing collagen and glycosaminoglycan synthesis and expression of inflammatory mediators [28], and has been shown in animal models to reduce up to 30% of wound contraction occurring by day 28 [29]. Local steroid injections were first described in the 1960s by Göthlin and Akerlund [30] and Ekström and Hultengren [31], and later again in the 1970s by Hebert [32], and finally Sharpe and Finney [33] who suggested that this monotherapy treatment was especially helpful in cases with strictures in the distal urethra or the meatus, and in those occurring post-radical prostatectomy.

In recent years, the focus on local steroid use at urethral stricture sites has been adjuvant in nature following endoscopic stricture treatment. A systematic review and meta-analysis by Zhang et al. [34] in 2014 aimed to summarise the available evidence on efficacy and safety of local steroids for urethral strictures. The review included eight randomised and non-randomised trials with a total of 203 patients post DVIU who were treated with steroid injection or catheter lubrication. The authors reported that time to recurrence was statistically significant (mean: 10.14 and 5.07 months, $p<0.01$), while the number of patients with recurrent stricture formation significantly decreased at different follow-up time points ($p=0.05$), with no statistically significant differences found between the recurrence rates, adverse effects, and success rates of second internal urethrotomy in patients with applied local steroids and those without. In conclusion, authors derived that use of local steroids with DVIU seems to prolong time to stricture recurrence but does not affect the high stricture recurrence rate. Of note, the meta-analysis was severely limited by the small number of participants in each study. Furthermore, the analysis was hampered by relevant differences in the literature. Hosseini et al. [24] included 35 patients after urethroplasty, which has a drastically different risk profile to a primary urethral stricture, while Tavakkoli Tabassi et al. [21] had only a mean follow-up of 8.68 months, which is insufficient time given that stricture recurrence occurs often up to 12 months post intervention. Ultimately, further robust comparative effectiveness studies were still recommended [34].

Since the 2014 review by Zhang et al. [34], only two RCTs have been completed – Ergün et al. in 2015 [19] and Regmi et al. in 2018 [18]. Zhang illustrated that adjuvant steroid use post DVIU reduced the time to recurrence (weighted mean difference, 4.43; 95% CI, 2.77–6.09, $p<0.00001$), though did not statistically improve recurrence rates or Qmax. Although the inclusion of these two new trials added limited participants (n=115 collectively), this meta-analysis suggests that not only did adjuvant steroid use prolong time to recurrence, in keeping with Zhang et al.'s conclusion [34], but it also improves recurrence rates and potentially Qmax. Furthermore, we consistently downgraded our assessments of the certainty of the evidence by one or two steps due to study limitations with a small sample size and unclear risk of bias related to insufficient trial information as described. The overall low-to-very low certainty of evidence is the predominate major limitation of this meta-analysis. Moreover, the risk of bias from Ergün et al. [19] was lower compared to other studies and may contribute to these outcomes. Additionally, in both studies the duration of post-operative catheterisation was concerning. Ergün et al. [19] discharged patients with an IDC for 2 weeks, while Regmi et al. [18] for 1 week. The influence of this must be considered in the context of the Albers et al. [35] retrospective analysis of 937 patients post DVIU, which concluded that a post-operative catheter will increase this

risk of recurrence if left for more than 3 days.

In 2021, several updated and partly overlapping reviews have been published in the literature. A thorough review by Jacobs et al. [36] of both preclinical and clinical studies focused on various local therapies in preventing urethral strictures after endoscopic procedures. Mitomycin-C (MMC) and hyaluronic acid/carboxymethylcellulose outcomes were of most interest, but the review also highlighted a potential decrease in steroid success rate with an increase in follow-up time which is consistent with previous literature. While a review by Xu et al. [37] primary discussed the controversial effectiveness of MMC in reducing the recurrence rate of a urethral stricture after first urethrotomy.

Of most significance is a systematic review and meta-analysis, performed by Pang et al. [38], on adjuncts to minimally invasive treatment of urethral stricture disease in men. The review scope was very broad in its assessment of available adjuncts; although, steroids were included in subgroup analysis. Outcomes suggested that any form of adjunct to DVIU for urethral stricture disease appeared to lower recurrence rates compared to no adjunct use; however, majority of studies included were at high risk of bias. Importantly, Pang et al. [38] found that steroids prolonged the time to recurrence but did not reduce the recurrence rate following DVIU. Given these conflicting outcomes as compared to our findings, we will discuss the various scientific and methodological differences between Pang et al.'s recent review [38] and our current review and ensure that potential benefits to both the scientific community and patients suffering from urethral stricture disease are highlighted.

In contrast to Pang et al.'s review [38], our review was targeted specifically to local steroid administration which is easily accessible compared to other adjuncts and has a good safety profile. In addition, we provide a more in-depth analysis of associated outcomes (e.g., QoL measure with short and long-term results) with conflicting results. As previously discussed, our analysis suggests that in addition to rate of recurrence, recurrence rates post DVIU were in fact reduced. Findings were statistically, and likely clinically, significant, and no heterogeneity was identified between included studies – this is a novel finding in contrast to pre-existing reviews. Moreover, we highlight variations in post-op IDC duration between included studies and discuss the potential significant impact on recurrence rates.

Furthermore, we believe our review was performed according to strict methodological guidelines in line with Cochrane Handbook recommendations, as well as AMSTAR 2 and PRISMA 2009 checklists. The difference in the details of the protocol highlight the methodological differences and the robustness of our review. For example, our PICO used for the search was very specific and detailed. Our review searched multiple databases, trial registries (Supplementary Table 1), and meeting abstracts. We placed no restriction on language of studies. We had clear and detailed description of the screening, full-text review, and data extraction process. This was performed by two independent reviews. As a result, we successfully identified a further trial (ClinicalTrials.gov Identifier: NCT05078788) that was not previously identified and may impact future updates reviews once clinical trial data is available. In addition, we had planned subgroup and sensitivity analyses to investigate any heterogeneity which may have been found. Additionally, as per AMSTAR 2 recommendations, we provide a list of the excluded studies and the reasons for exclusions (Supplementary Table 2). Finally, we provide an assessment of the overall certainty of evidence for each outcome according to the GRADE approach with a summary of findings table (Table 1) which strengthens the quality of our evidence.

CONCLUSIONS

In conclusion, the use of adjuvant steroids (triamcinolone) applied to the urethra (via a coated catheter or submucosal injection route) may reduce the risk of recurrence and time to recurrence. These findings were statistically significant and likely also clinically significant given the associated low cost and minimal risk of steroid administration. However, certainty of evidence was downgraded due to study limitations with a small sample size and unclear risk of bias related to insufficient trial information. More robust randomised trials with higher patient populations would be beneficial to enhance the validity of these outcomes.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Christopher Soliman, Henry Y.C. Pan, and Niranjan J. Sathianathen. Data acquisition: Christopher Soliman and Henry Y.C. Pan. Statistical analysis: Niranjan J. Sathianathen. Data analysis and interpretation: Christopher Soliman and Niranjan J. Sathiana-

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20210391.

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