
Article:
Pang, K.H., Chapple, C.R. orcid.org/0000-0002-2960-9931, Chatters, R. et al. (5 more authors) (2021) A systematic review and meta-analysis of adjuncts to minimally invasive treatment of urethral stricture in men. European Urology, 80 (4). pp. 467-479. ISSN 0302-2838

https://doi.org/10.1016/j.eururo.2021.06.022

A systematic review and meta-analysis of adjuncts to the minimally-invasive treatment of urethral stricture in men

Karl H. Pang [a], Christopher R. Chapple [b], Robin Chatters [c], Alison P. Downey [d] Christopher K. Harding [e], Daniel Hind [c], Nick Watkin [f], Nadir I. Osman [b*]

[a] Academic Urology Unit, University of Sheffield, Sheffield, UK

[b] Section of Reconstruction, Department of Urology, Royal Hallamshire Hospital, Sheffield, UK

[c] School of Health and Related Research, University of Sheffield, Sheffield, UK

[d] Department of Urology, Pinderfields General Hospital, Wakefield, UK

[e] Department of Urology, Freeman Hospital, Newcastle, UK and Translational and Clinical Research Institute, Newcastle University, Newcastle, UK.

[f] Department of Urology, St George's Hospital, London, UK

***Correspondence**

Nadir I. Osman

Section of Reconstruction

Department of Urology

Royal Hallamshire Hospital

Sheffield, UK

nadir.osman@nhs.net

Abstract

Context: Urethral strictures (USD) are initially managed with minimally-invasive techniques such as urethrotomy and urethral dilatation. Minimally-invasive techniques are associated with a high recurrence rate especially in recurrent USD. Adjunctive measures, such as local drug injection have been used in an attempt to reduce recurrence rates.

Objective: To systematically review evidence for the efficacy and safety of adjuncts used alongside minimally-invasive treatment of USD.

Evidence acquisition: A systematic review of the published literature between 1990 and 2020 in accordance with the PRISMA checklist.

Evidence synthesis: A total of 26 studies were included in the systematic review and 13 different adjuncts were identified which included, intralesional injection (triamcinolone, number of patients in the adjunct group, n=135; prednisolone, n=58; mitomycin C, n=142; steroid-mitomycin-hyaluronidase, n=103, triamcinolone-mitomycin-N-acetyl cyteine, n=50; platelet-rich plasma, n=44), intraluminal instillation (mitomycin, n=20; hyaluronic acid and carboxymethylcellulose, n=70; captopril, n=37; 192-iridium bracytherapy, n=10), application via a lubricated catheter (triamcinolone, n=124), application via a coated balloon (paclitaxel, n=106) and enteral (tamoxifen, n=30; deflazacort, n=36). Overall, 13 randomised-controlled trials were included in the meta-analysis. The use of any adjunct was associated with a lower rate of USD recurrence (OR 0.37, CI 95% 0.27-0.50, $p<0.001$) compared to no adjunct use. Of all adjuncts mitomycin C was associated with the lowest rate of USD recurrence (intralesional injection: OR 0.23, 95% CI 0.11-0.48, $p<0.001$; intraluminal injection: OR 0.11, 95% CI 0.02-0.61, $p=0.01$). Urinary tract infection (2.9-14%), bleeding (8.8%), extravasation (5.8%) was associated with steroid injection; pruritis of urethra (61%) occurred at the instillation of captopril; mild gynaecomastia (6.7%) and gastrointestinal side effects (6.7%) were associated with oral tamoxifen.

Conclusions: Adjuncts to minimally-invasive treatment of USD appear to lower recurrence rate and are associated with a low adjunct-specific complication rate. However, the included were studies were at high risk of bias. Mitomycin C is the adjunct supported by the highest level of evidence

Patient summary: In this work, we looked at adjuncts to minimally-invasive treatments for urethral narrowing in men. Adjuncts such as mitomycin injection result in a lower recurrence rate compared to no adjunct use. The use of adjuncts appeared to be safe and complications are uncommon, however the studies were small and of low quality.

Keywords

Urethral stricture, urethrotomy, urethral dilatation, adjuncts, mitomycin, steroid, triamcinolone, brachytherapy

1.0 Introduction

Male urethral stricture (USD) disease is a significant healthcare burden. In the United States, the incidence is estimated to be in the range of 229-627 per 100,000 males (0.6% of male population) with a sharp increase in incidence observed after the age of 55 years (1,2). The anterior urethra is most frequently affected by USD (92.2%), in particular the bulbar urethra (46.9%) (2). The aetiology of USD varies by geographical region, in well-resourced countries typically iatrogenic, whereas in less well-resourced countries, infective and traumatic (3). Regardless of aetiology, the pathological finding is of ischaemic spongiofibrosis (4). USD have a significant health economic impact, in the United Kingdom USD affects around 62,000 men, in England this corresponds to 16,000 National Health Service hospital admissions annually, 16,000 bed-days and 13,000 operations at a cost of >£10 million per year (5).

The management of USD depends on the stricture site, length, aetiology and whether it is primary or recurrent. For a primary bulbar urethral stricture the recommended initial treatment in the recent EAU Guidelines on USD is a urethral dilatation (UD) or a direct vision internal urethrotomy (DVIU) (6). An earlier randomised-controlled trial demonstrated that UD and DVIU to be to be equally effective as a first line treatment for USD (7), with a stricture recurrence rate of 50% at 12 months for strictures 2-4cm in length. However, the long term success rate following the initial DVIU is 32% with success decreasing with repeat minimally-invasive treatment (8).

To overcome the high recurrence rate following minimally-invasive treatment of USD, several adjuncts have been investigated, including intralesional injection with steroids, mitomycin, captopril, platelet-rich plasma and hyaluronidase; drug-coated (e.g. steroids) catheters; drug (paclitaxel) coated balloon dilatation; brachytherapy; oral steroids and tamoxifen (9,10). The recurrence rate and treatment-specific complications are variable amongst different adjuncts. Spurred on by claims of strong efficacy signals, some adjuncts are being adopted without systematic appraisal of the evidence. Our objective is to systematically review the literature to assess the efficacy and safety of adjuncts to the minimally-invasive treatment of USD.

2.0 Evidence acquisition

2.1 Protocol and registration

Our systematic review was registered with the PROSPERO database (CRD42021226906) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA, Supplementary Table 1) guidelines (11).

2.2 Study eligibility

A specific population (P), intervention (I), comparator (C), outcome (O) and study design (S) (PICOS) framework defined study eligibility. Studies were considered eligible for this review if they fulfilled the following criteria: (P): Adult men ≥18 years with primary or recurrent USD of any aetiology; (I): Urethrotomy (direct visual or laser) or urethral dilatation with any form of adjuncts; (C): Any standard minimally-invasive treatment; (O): USD recurrence and reintervention rate, and secondary outcomes included time to recurrence and adjunct-specific complications; (S): Randomised controlled trials (RCTs), non-randomised controlled studies (NRS), retrospective and prospective cohort studies including ≥5 men.

Case reports, conference abstracts, reviews, letters, editorials were excluded. In addition, animal studies, studies with samples size <5 patients and articles in languages other than English were excluded.

2.3 Search and study selection

A systematic search for original articles was performed using PubMed and the Cochrane Library on 22 November 2020. The search terms used included: (urethral OR bulbar OR bulbomembranous OR penile) AND (stricture OR stenosis) AND (urethrotomy OR balloon dilatation OR dilatation OR laser) AND (adjuncts OR steroids OR mitomycin OR drug OR injection OR brachytherapy). The search was filtered for male and human.

Studies published between January 1st 1990 and November 22nd 2020 were included. Articles were screened by two reviewers (KHP and APD) using *a priori*

inclusion/exclusion criteria and Covidence software (Covidence™; Veritas Health Innovation, Melbourne, VIC, Australia). Any conflicts were resolved between the two reviewers and any disagreements were resolved by a senior author (NIO). The reference lists of included manuscripts were also searched and screened for eligibility. Studies fulfiling our PICOS criteria were included for analysis (12).

2.4 Data extraction and analysis

Data extraction and risk of bias (RoB) assessment of inculded studies were performed by the same two abstract and full-text article reviewers. Data extracted included study design, USD aetiology, site and length of USD, type of adjuncts used, change in International Prostate Symptom Score (IPSS) and flow rate, recurrence rate, reintervention rate and adjunct-specific complications.

The Cochrane RoB tool (13) was used for assessing RCTs (Supplementary Table 2a) and the Risk of Bias in non-randomised studies of interventions (ROBINS-I (14)) was used to assess NRS (Supplementary Table 2b).

The meta-analysis was performed using Review Manager 5.4 (The Cochrane Collaboration, Oxford, UK), and included RCTs only. We pooled estimates of clinical effect using odds ratios (OR) and their 95% Confidence Intervals (95% CI). Trials were combined using the Mantel-Haenszel (M-H) fixed effects model (15). We used I^2 to assess statistical heterogeneity. Convention I^2 measurements of 25%, 50%, and 75% suggesting inconsistency at low, moderate, and high levels respectively (16).

3.0 Evidence synthesis

Our search identified 141 articles of which 26 studies (17–42) were included for analysis (Figure 1). Overall 13 RCTs and 13 NRS were retrieved. There were 972 participants in the adjunct group and 581 participants in the control group. The follow up ranged between 3 and 47.2 months (Table 1).

3.1 Adjuncts

A total of 13 adjuncts were identified (Table 1). Adjuncts were grouped into methods of delivery which included intralesional injection (triamcinolone, n=4 (17,18,29,36);

prednisolone, n=2 (37,38); mitomycin, n=3 (20–22); triamcinolone, mitomycin and hyaluronidase n=1 (25); triamcinolone, mitomycin, hyaluronidase and N-acetyl cysteine n=1 (24); autologous platelet-rich plasma injection (PRP) n=1 (31)), intraluminal instillation (mitomycin n=1 (23); hyaluronic acid and carboxymethylcellulose n=2 (26,27); captopril n=1 (30); 192-iridium bracytherapy, n=1 (28)), application via a lubricated catheter (triamcinolone n=5 (19,39–42)), application via a coated balloon (n=2 (32,33)), and enteral (tamoxifen, n=1 (34); deflazacort, n=1 (35)).

The regimen varied amongst the studies, triamcinolone injection dose ranged between 5mg and 320mg, mitomycin injection dose ranged between 0.1 mg and 4mg, and the duration of intermittent self-catheterisation (ISC) with triamcinolone ranged between 2 weeks and 4 months (Table 1).

3.2 Aetiology and site of stricture

The included studies analysed primary and/or recurrent USD, anterior and/or posterior urethra of a range of aetiology including iatrogenic, traumatic, inflammatory/infective and idiopathic. The length of stricture analysed ranged between under 1cm and over 4cm (Table 1).

3.3 Recurrence and reintervention rate

The assessment of pre and post treatment varied, but included one or more of the following; symptoms (assessed via IPSS, flowmetry, post-void residual (PVR), cystourethroscopy, retrograde urethrogram (RUG) and micturating cystourethrogram (MCUG). The definition of recurrence/failure rate varied amongst the studies analysed, which included recurrent symptoms following treatment, maximum flow rate (Qmax) below 10, 12 or 15mL/s, stricture on RUG, inability to pass a catheter or cystoscope of size 14, 16, 17 or 19Fr, or the need for reintervention (Table 2). The recurrence rate was 4.9-100% in the adjunct group and 15-81% in the control group and reintervention rate was 7-70.6% in the adjunct group and 44.1-61.9% in the control group (Table 2). The mean time to recurrence was 3-12 months (Table 2).

A total of 13 RCTs were included in the meta-analysis: steroid-coated catheter, n=5; steroid injection, n=2; mitomycin injection, n=2; intraluminal mitomycin, n=1;

hyaluronic acid, n=1; PRP, n=1; oral tamoxifen, n=1. A total of 426 men in the adjunct group and 433 men in the control group. Any form of adjunct is associated with a lower rate of USD recurrence (OR 0.37, CI 95% 0.27-0.50, p<0.001) compared with no adjunct. Mitomycin C was associated with the lowest rate of USD recurrence (intralesional injection: OR 0.23, 95% CI 0.11-0.48, p<0.001; intraluminal injection: OR 0.11, 95% CI 0.02-0.61, p=0.01) (Figure 2).

3.4 Adjunct-specific complications

Adjunct-specific complications were expereinced in four studies. Urinary tract infection (UTI, 2.9-14%)), bleeding (8.8%), extravasation (5.8%) was associated with steroid injection (17,29); pruritis of urethra (61%) occurred at the instillation of captopril (30); mild gynaecomastia (6.7%) and gastrointestinal side effects (6.7%) were associated with oral tamoxifen (34) (Table 2). Complications in the control arms were not reported.

3.5 Risk of bias within studies

The results of the RoB assessment are shown in Supplementary Table 2. The Cochrane RoB tool was used to assess 13 RCTs (Supplementary Table 2a), and the domain showing the highest proportion of studies with a 'high' risk of bias was the 'blinding of participants and personnel' domain (53.9%). The ROBINS-I tool was used to assess 15 NRS (Supplementary Table 2b), and the domain showing the highest proportion of studies with a 'high' risk of bias was the 'bias due to confounding' domain (84.6%).

4.0 Discussion

We report the first systematic review and meta-analysis of adjuncts to minimally-invasive treatment for USD. A total of 14 adjuncts were identified. These can be classified according to the mode of delivery; injection into urethral wall, topical via instillation, topical by application via a lubricated catheter, topical via application of coated balloon or enteral. The most well studied adjuncts are local steroids either injected locally (17,18,29,36–38) or used via coated-catheters (19,39–42) and mitomycin C (20–23). Only mitomycin C and local steroids have been studied in more than one RCT. Intraurethral instillation with hyaluronic acid and carboxymethylcellulose (26), PRP (31) and oral tamoxifen (34) have each been

studied in single RCTs and the other adjuncts such as brachytherapy (28), captopril (30), paclitaxel-coated balloons (32,33) and oral deflazacort (35) have been evaluated in prospective or retrospective cohort studies.

Our pooled analysis of RCTs showed that any form of adjuncts is superior to no adjunct use with regards to reducing recurrence, and mitomycin C injection appears to be the most effective. These findings are in keeping with a previous meta-analysis addressing mitomycin which demonstrated reduced recurrence compared DVIU alone (Risk ratio 0.41, 95% CI 0.25-0.68, $p<0.001$) (43). The finding of the analysis of steroids is consistent with a previous meta-analysis, that steroids prolonged time to recurrence but did not reduce recurrence rate following DVIU (44). All other agents, such as oral tamoxifen included in the analysis were studied in single RCTs.

This review has several limitations. Firstly, the studies included were in general small and of variable quality. We have attempted to mitigate for this in the pooled analysis by only including RCTs. A further limitation relates to the variable inclusion criteria in terms of USD location as well as previous interventions, all factors known to impact upon success of minimally-invasive intervention (8). Moreover, there was heterogeneity in the definition of recurrence or failure, postoperative assessment and follow up protocols. The wide variation in recurrence rates in the control groups (15-81%) may be attributable to variability in the inclusion criteria and definition of recurrence. Only four studies experienced adjunct-specific complications and none reported complications in the control group, thus making it difficult to evaluate if the adjuncts are safe compared to usual care**.**

Definition of recurrence is particularly important, in the pooled analysis 11 (39.3%) studies used objective outcomes (reintervention, RUG, FR, inability to pass a catheter or cystoscope), 13 (46.4%) studies used a composite outcome (objective and symptoms), and four studies did not define a criterion for recurrence or failure. It is well recognised that the most accurate means of following up patients after stricture surgery is direct visualization by the use of endoscopy or urethrography (45). Both symptomatic improvement and flow rate can be misleading in terms of whether a stricture has recurred as with normal detrusor contractility, the flow rate does not diminish until the calibre of the urethra falls below 11Fr (46). Meanwhile 're-

intervention' rates lack sensitivity as some patients may have a recurrence but not yet require or want surgery.

Minimally-invasive treatment of USD although relatively simple and associated with low morbidity is associated with high recurrence and reintervention rates. The seminal trial by Steenkamp et al showed that the recurrence rate at 12 months was approximately 40% for USD <2cm, 50% for strictures 2-4cm and 80% for USD longer >4cm. The recurrence rate for USD between 2 and 4 cm increased to 75% at 48 months. For each 1cm increase in USD length the risk of recurrence increased 1.22 (7). In the setting of recurrent USD the results of minimally-invasive intervention are even worse with recurrences rate after a second DVIU/UD, for a USD recurring by 3 months, was 50-70% at 24 months and 60-100% at 48 months (8). Hence, further minimally-invasive intervention for recurrent USD is palliative and is usually followed by a need to perform intermittent self-dilatation.

Several authors have sought to improve upon the success of minimally-invasive interventions by using a variety of adjuncts. The rationale for this is largely centred around the effect of recurrent USD prejudicing outcomes of subsequent surgery: recurrent minimally-invasive intervention is undesirable as it is associated with increased costs (8,47) and more scarring thereby increasing stricture complexity (48) and risk of failure of a urethroplasty (49). Urethroplasty is the recommended intervention treatment paradigm for recurrent USD due to the poor recurrence rate with repeat minimally-invasive treatments, unless the patients to follow up the latter with a prolonged period of intermittent self-dilatation. Although urethroplasty offers high success rates it is a more invasive procedure requiring longer recovery and is associated with more significant risks including sexual dysfunction. Consequently, men are often reluctant to undergo urethroplasty (50,51). Urethroplasty is also associated with greater costs than DVIU, the OPEN trial reported a procedure cost of £4893 versus £1541 and also showed that over 24 months urethroplasty is likely to remain more costly and result in similar quality-adjusted life years (QALYs) (52,53).

The principle of DVIU is to incise the scarred epithelium and allow the wound to heal by secondary intention. The process is successful if re-epithelialization occurs before significant wound contraction that narrows the lumen and thereby a recurrent stricture.

An indwelling catheter is left in place for 3-5 days post-operatively to splint the wound open whilst re-epithelialisation completes. Adjuncts aim to modulate the wound healing process by reducing collagen production and/or deposition which results it less fibrosis and thereby a lower risk that the stricture returns. Most of these adjuncts have been used for similar indications in other areas of medicine, e.g. mitomycin C in glaucoma surgery (54), steroids in keloid scarring (55), tamoxifen in Peyronie's disease (56).

Several factors are likely to influence the success of adjuncts, including mode of drug delivery, local concentration achievable, reliability of achieving a therapeutic dose, mechanism of action of the drug and drug pharmacokinetics. Patient factors are also likely to be important, particularly the degree of spongiofibrosis. Very dense strictures where severe local ischaemia exists are unlikely to respond to anything but reconstructive surgery. Likely favourable pre-operative factors are a lower number of previous interventions and shorter stricture length. It is apparent that there is wide variation in doses used for the most commonly studied adjuncts (steroids and mitomycin C) and no standardised administration protocols, indeed descriptions of techniques are often poorly reported. Consequently, no treatment recommendation can be made based on the current literature.

A novel method of drug delivery was recently introduced in the form of a propriety Paclitaxel-coated balloon device (Laborie), which combines balloon dilatation and drug delivery. Paclitaxel is a chemotherapeutic and inhibitor of mitosis and has been widely used in percutaneous vascular interventions (57). In the included observational study it resulted in 70% of patients remaining free of USD with no serious adverse events at 2 years follow up (33). The patient population all had had 1-4 previous minimally-invasive interventions. A large phase 3 industry sponsored RCT (NCT03499964) is ongoing in North America with 1-year outcomes expected to be reported later in 2021.

Another novel approach which is being considered is the injection of stem cells in to the anterior urethra. Thus far this has been studied in animal models only where it is difficult to recreate the disease process of ischaemic spongiofibrosis in urethral stricture disease (58,59). Given that USD form consequent to ischaemia, the main

challenge to the clinical application of stem cells for USD will be the requirement of a good local vascular supply for the survival of the cells and promotion of a constructive remodelling process (10).

Most studies in the current analysis did not report any significant adjunct-specific complications. Tamoxifen resulted in two (6.7%) patients having mild gynaecomastia (34). Although no significant side effects were reported with mitomycin C in this study, one retrospective study reported two cases of osteitis pubis and one case of rectourethral fistula when injecting mitomycin at the bladder neck for recalcitrant bladder neck stenosis (60). It is also important to note that chemotherapeutic agents such as mitomycin and paclitaxel are associated with potential systemic toxicities if used at high enough doses. Plasma concentration of paclitaxel following use of a paclitaxel coated balloon was shown to be very low (approaching limit of quantification) and no systemic problems were reported with use in the urethra (33). Similarly, no problems attributable to systemic toxicity were reported with mitomycin use for urethral stricture.

Futher research is needed to evaluate adjuncts and determine efficacy, safety and cost effectiveness in a more specifically defined popultaion. This population should include men with short bulbar USD which would be expected to be more amenable to minimally invasive treatment than long USD (>3cm). Given the reasonable success of endoscopic treatment in primary bublar USD, it would seem more appropriate to study those with recurrent bulbar USD. Such studies should be randomised and multicentric and should compare adjuncts to standard minimally invasive treatments i.e, UD or DVIU, depending on how the adjunct is delivered. These studies should include both subjective (PROMs) and objective outcome measures (ideally including anatomical assessment with cystoscopy or urethrogram). There should be a a more robust assessment of adverse events in both the intervention and control groups. In addition a health economic evaluation to assess cost effectiveness will help determine real world applicability. Without such RCTs introduction of adjuncts may be limited by lack of reimbursement in insurance based health care systems.

5.0 Conclusion

Any form of adjuncts to DVIU or UD for USD appear to lower recurrence rate compared to no adjunct use, however the majority of studies were at high risk of bias. Intralesional injection with mitomycin appears to be most effective studied adjunct. Available adjuncts appear to be safe and associated with a low adjunct-specific complication rate, however the reporting of complications was poor across studies. There is a now a need for high quality RCTs using both subjective and objective outcome measures to robustly evaluate the safety, efficacy and cost effectiveness of adjuncts, especially those adjuncts that have only been studied in NRS. This is particularly important where adjuncts are associated with potential risks and significant expense. Further studies should powered to detect clinically meaningful differences, in ideally assess recurrent bulbar USD with standardised and easily reproducible methods of drug delivery.

Take home message

Adjuncts to the minimally invasive treatment urethral strictures may reduce recurrence rates thereby avoiding the need for urethroplasty. Further adequately powered studies are needed to establish safety, efficacy and cost effectiveness and optimal drug dosing and delivery protocols.

Author contribution

KHP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: NIO

Acquisition of data: KHP, APD

Analysis and interpretation: KHP, NIO

Drafting of the manuscript: KHP, NIO

Critical revision of the manuscript: KHP, APD, NIO, CRC, CKH, RC, DH, NW

Statistical analysis: KHP

Obtaining funding: None

Administrative, technical or material support: None

Supervision: NIO

Financial disclosures

Karl H. Pang certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g. employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/support and role of the sponsor

None

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