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ORIGINAL ARTICLE

Comparison between cold knife and laser urethrotomy for urethral stricture: a systematic review and meta-analysis of comparative trials

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Abstract

Background Previous study compared limited number of parameters post the treatment of cold knife and laser urethrotomy for urethral stricture and controversy about the superiority of those two techniques still remains. This study aims to update the evidence and provide better clinical guidance.

Method We systematically searched Pubmed, Embase, ClinicalTrial.gov, and Cochrane Library Central Register of Controlled Trials for articles comparing cold knife and laser urethrotomy for urethral stricture. Parameters including maximum urinary flow (Q_{max}), recurrence, reoperation, complications, operation time, and Visual Analog Scale (VAS) pain score were compared using RevMan 5.3.

Results Seven articles involving 453 patients were eventually included. The cold-knife group had better 6-month Q_{max} (MD – 0.95, 95% CI – 1.49 to – 0.41) and similar 3-month and 12-month Q_{max} compared with the laser group. No significance was observed regarding the comparison of recurrence rate. The laser group had lower risk of bleeding (OR 0.08, 95% CI 0.01–0.43), lower rate of reoperation (OR 0.39, 95% CI 0.19–0.81) and longer operation time (MD 4.09, 95% CI 3.35–4.82). There was no significant difference in terms of other complications and VAS pain score.

Conclusion Cold knife and laser urethrotomy had similar efficacy regarding short-term and long-term recurrence rate and Q_{max}, except that the cold-knife group had slightly better 6-month Q_{max}. However, the laser group had less risk of bleeding and lower rate of reoperation but also longer operation time.

Keywords Urethral Stricture · Cold knife urethrotomy · Laser urethrotomy · Maximum urinary flow · Recurrence · Complications

Introduction

Urethral stricture is the narrowing of urethral lumen because of fibrosis due to congenital or acquired pathological changes, whose prevalence is estimated to be 0.6% in developed countries and even higher in developing countries [1]. The occurrence of obstructive urinary symptoms secondary to urethral stricture can cause potential urinary infection and renal disease, and lead to decline of life quality [2].

Internal urethrotomy is widely operated among patients with urethral stricture [3], of which cold knife and laser are two common options [4]. Controversies have remained despite Castellanos performing a meta-analysis to investigate the superiority of those two treatments [5]. However, they included only four studies and a very limited number of parameters (stricture recurrence rate and maximum urinary flow rate) were discussed in their analysis.

Xiaonan Zheng, Xin Han and Dehong Cao authors have contributed equally to this work.

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Hence, the current study aims to include more relevant clinical trials and analyze more intraoperative and postoperative parameters to compare the efficacy and safety of cold knife and laser treatment for urethral stricture, and provide updated evidence for clinical practice.

Methods

Search strategy and inclusion criteria

Terms including "urethral stricture", "Urethral stenosis", "laser", "urethrotomy" and "cold knife" were used to systematically search Pubmed, Embase, ClinicalTrial.gov and Cochrane Library Central Register of Controlled Trials date to January 2019 for articles that compared cold knife with laser urethrotomy for urethral stricture. Inclusion criteria were defined as following:

1. comparative studies between Holmium laser and cold knife for urethral stricture;

2. data for either efficacy or safety (or both) must be provided;

3. studies must be published in English. Non-comparative studies and non-English publications were excluded.

Data extraction and analysis

Two investigators independently extracted data from the included articles and all the members of our team resolved the discrepancies by consensus. All the analyses were performed using Review Manager (version 5.3).

The primary outcomes of the current study were maximum urinary flow rate (Q_{max}) and recurrence of stricture after intervention regarding efficacy, and complications (bleeding, fluid extravasation, complication rate, and re-operation) regarding safety. The secondary outcomes were other perioperative parameters including operation time and Visual Analog Scale (VAS) pain score. Odds ratio (OR) and mean difference (MD) with 95% confidential interval (CI) were calculated for dichotomous and continuous outcomes, respectively. Heterogeneity among trials was tested using both I^2 test or Q test. An $I^2 > 50\%$ or Q test reporting P values < 0.1 were considered to denote heterogeneity. Sensitivity analyses were performed through the exclusion of one or more studies suspected of causing heterogeneity.

Quality assessment of included studies was performed by two independent reviewers using Jadad score for randomized controlled trials (RCT) and Newcastle−Ottawa Scale (NOS) for non-RCT [6, 7]. Cochrane risk of bias tool was also used to assess those studies. When the two reviewers encountered discrepancies in the outcomes, they resolved those through discussion.

Results

Study characteristics

Figure 1 showed that a total of 42 articles were identified and seven studies involving 453 patients (cohort size 42–107 patients) were eventually selected (Table 1) [8–14]. Four of those studies were RCTs and other three were prospective or retrospective. The follow-up varied from 6 months to 1 year. Recurrence or Q_{max} were measured 1, 3, 6 or 12 month(s) after intervention in some studies. All of the patients were adults except that Waseem conducted the study focused on children [13]. The cause of stricture was specified as iatrogenic, traumatic, urethritis, and idiopathic but the reporting standard of stricture location varied. The mean stricture length was shorter than 2 cm in all studies. Quality assessment showed that all studies were ranked as high quality (Table 2) and risk of bias is displayed in Supplementary Table S1.

Q_{max} and stricture recurrence

Five studies including 352 patients reported Q_{max} after intervention (Fig. 2). There was no significant difference of short-term Q_{max} (1–3 days: MD 0.65, 95% CI – 0.24 to 1.55; 3 months: MD – 0.02, 95% CI – 0.58 to 0.55) between after laser and cold knife. However, patients treated with Holmium laser had worse 6-month Q_{max} (MD -0.95, 95% CI – 1.49 to – 0.41). Even at 12 months after therapy, the laser group also approached to have a worse performance of Q_{max} (MD – 0.64, 95% CI – 1.63 to 0.35).

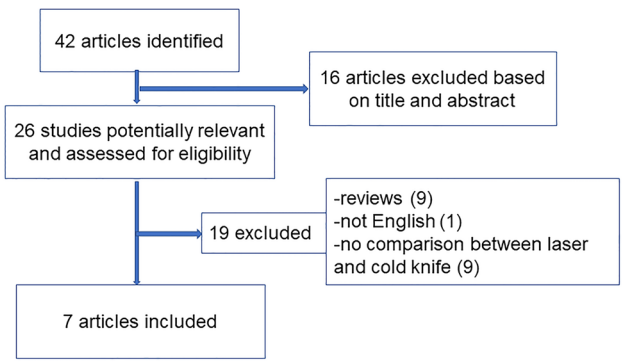

Fig. 1 PRISMA flowchart of study selection

Table 1 Baseline characteristics of included studies

Study	Design	Size (laser vs. cold knife)	Intervention	Follow-up (Months)	Age (laser vs. cold knife)	Stricture length (laser vs. cold knife)	Etiology of stricture (laser vs. cold knife)	Location (laser vs. cold knife)
Jablonowski [8]	RCT	50 (30 vs. 20)	Nd:YAG vs. cold knife	12	59.8 (22–83) vs. 66.9 (49–83)	1.24 (0.4–2) vs. 1.77 (0.3–2.4)	Iatrogenic: 30 (17 vs. 13); Traumatic: 5 (4 vs. 1) Urethritis: 1 (0 vs. 1); Idiopathic: 14 (9 vs. 5)	Spongy urethra: 12 (6 vs. 6) Spongy and bulbar Urethra: 3 (0 vs. 3) Bulbar and membranous Urethra: 2 (2 vs. 0) Membranous urethra: 26 (18 vs. 8) Spongy, bulbar, membranous urethra: 3 (3 vs. 0)
Atak [9]	RCT	51 (21 vs. 30)	Ho:YAG vs. cold knife	12	63.85 ± 7.98 vs. 59.70 ± 15.29	1.109 ± 0.328 vs. 1.23 ± 0.298	Iatrogenic: 33; bladder neck contracture: 18	Bulbar: ($N=33$); bladder NECK ($N=8$)
Dutkiewicz [10]	RCT	50 (25 vs. 25)	Ho:YAG vs. cold knife	12	61.2 ± 16.1 vs. 65.7 ± 11.9	1.86 ± 1.26 vs. 1.66 ± 1.02	Iatrogenic: 32; Urethritis: 18	Penile: 19 (10 vs. 9); Bulbar: 8 (3 vs. 5) Posterior urethra: 27 (12 vs. 17)
Jain [11]	RCT	90 (45 vs. 45)	Ho:YAG vs. cold knife	6	18–60	< 2cm	Iatrogenic: 29 (16 vs. 13); Traumatic: 10 (2 vs. 8) Urethritis: 42 (23 vs. 19); Idiopathic: 9 (4 vs. 5)	Penile: 21 (10 vs. 11); Bulbar: 22 (13 vs. 9) BM junction: 36 (16 vs. 20) Posterior urethra: 11 (6 vs. 5)
Jhanwar [12]	Prospective	107 (52 vs. 55)	Ho:YAG vs. cold knife	3, 6	38.13 ± 12.3 vs. 39.38 ± 13.4	1.34 ± 0.251 vs. 1.31 ± 0.252	NA	NA
Aboulela [13]	Retrospective	42 (21 vs. 21)	Ho:YAG vs. cold knife	1, 6, 12	6.25 ± 3.04 vs. 6.28 ± 3.49	1.02 ± 0.4 vs. 1.0 ± 0.41	Idiopathic: 23 (12 vs. 11)	Penile or bulbous: 20 (10 vs. 10) Membranous: 22 (11 vs. 11)
Yenice [14]	Prospective	63 (29 vs. 34)	Ho:YAG vs. cold knife	3, 6, 12	55.3 ± 8.9 vs. 54.8 ± 9.5	< 2cm	Iatrogenic: 42 (21 vs. 21); Traumatic: 12 (5 vs. 7) Urethritis: 6 (2 vs. 4); Idiopathic: 3 (1 vs. 2)	Bulbar: 107

RCT randomized controlled trial, *NA* not available; *Nd:YAG* neodymium-doped yttrium aluminum garnet; *Ho:YAG* holmium yttrium aluminum garnet

Table 2 Quality assessment of included studies

Study	Design	Randomization[1]	Double blinding[2]	Follow-up[3]	Total points/rank
Jadad					
Jablonowski [8]	RCT	1	1	1	3/High
Atak [9]	RCT	2	1	1	4/High
Dutkiewicz [10]	RCT	1	1	1	3/High
Jain [11]	RCT	2	1	1	4/High

NOS		Selection				Comparability		Exposure			
		REC	SNEC	AE	DO	SC	AF	AO	FU	AFU	
Jhanwar [12]	Prospective	1	1	1	1	1	1	1	1	1	9/High
Aboulela [13]	Retrospective	1	1 1		1	1	1	1	1	1	9/High
Yenice [14]	Prospective	1	1 1		1	1	0	1	1	1	8/High

Jadad Jadad score was used to assess the quality of included RCTs, *NOS* Newcastle-Ottawa Scale was used to assess the quality of non-RCTs, *REC* representativeness of the cohort, *SNEC* selection of the none posed cohort, *AE* ascertainment of exposure, *DO* demonstration that outcome of interest was not present at start of study, *SC* study controls most important factors, *AF* study controls for other important factors, *AO* assessment of outcome, *FU* follow-up long enough for outcomes to occur ('long enough' is defined as 1 year), *AFU* adequacy of follow-up of cohort(≥ 80%)

[1]Randomization of the studies (2 points, computer-generated random number or similar; 1 point, not described; 0 point, non-randomization or inadequate method); [2]Double blinding (2 points, identical placebo tablets or similar; 1 point, not described; 0 point, no blinding or inadequate method); [3]Follow-up (1 point, number and reasons for dropouts and withdrawals described; 0 point, number or reasons for dropouts and withdrawals not described); The quality score ≥ 3 points wasranked as high

"*" Means that the study is satisfied the item, and "/" means not. The quality score ≥ 7 points was ranked as high

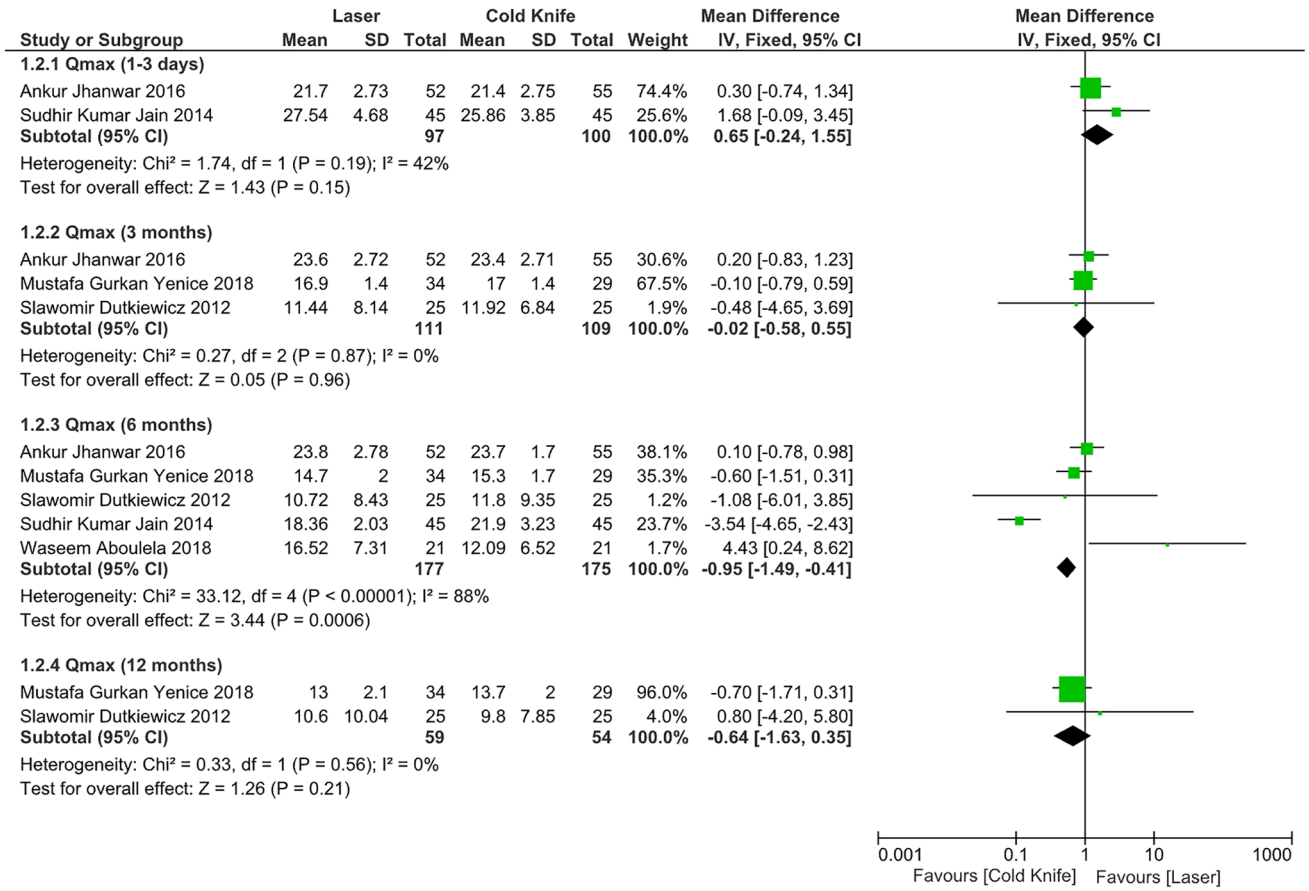

Fig. 2 Forest plot of maximum urinary flow (Q_{max}) after laser urethrotomy and after cold knife urethrotomy

Stricture recurrence was reported in four studies involving 271 patients (Fig. 3). Patients treated with laser tended to have a lower rate of stricture recurrence at 3 and 6 months after treatment (3-month: OR 0.49, 95% CI 0.17–1.41; 6-month: OR 0.59, 95% CI 0.30–1.18), although no significant difference was reached, the pooled outcome showed that patients undergoing laser therapy were close to having a significant higher risk of recurrence (OR 0.53, 95% CI 0.28–1.02).

Complications

In regard to complications (Fig. 4), patients with laser therapy had significantly lower risk of bleeding (OR 0.08, 95% CI 0.01–0.43) and re-operation (OR 0.39, 95% CI 0.19–0.81), which was consistent with the outcomes of recurrence. Nevertheless, laser and cold knife had similar rate of fluid extravasation (OR 3.25, 95% CI 0.76–13.98) and overall complication occurrence (OR 0.78, 95% CI 0.35–1.74).

Other perioperative parameters

Four studies compared the operation time between laser and cold knife for urethral stricture (Fig. 5). The combined outcome supported that cold knife required less operation time (MD 4.09, 95% CI 3.35–4.82), although Jhanwar's study weighed 91.6% and substantial heterogeneity existed ($I^2 = 92\%$).

In terms of VAS pain score, data from two studies indicated no significant difference was observed after laser or cold knife treatment (MD 0.13, 95% CI – 0.14 to 0.39).

Discussion

Summary of main findings

As the standard treatment for urethral stricture with up to 90% of success rate, open urethral reconstruction requires prolonged training and sophisticated equipment [15]. Subsequently, alternative options such as urethral dilation and

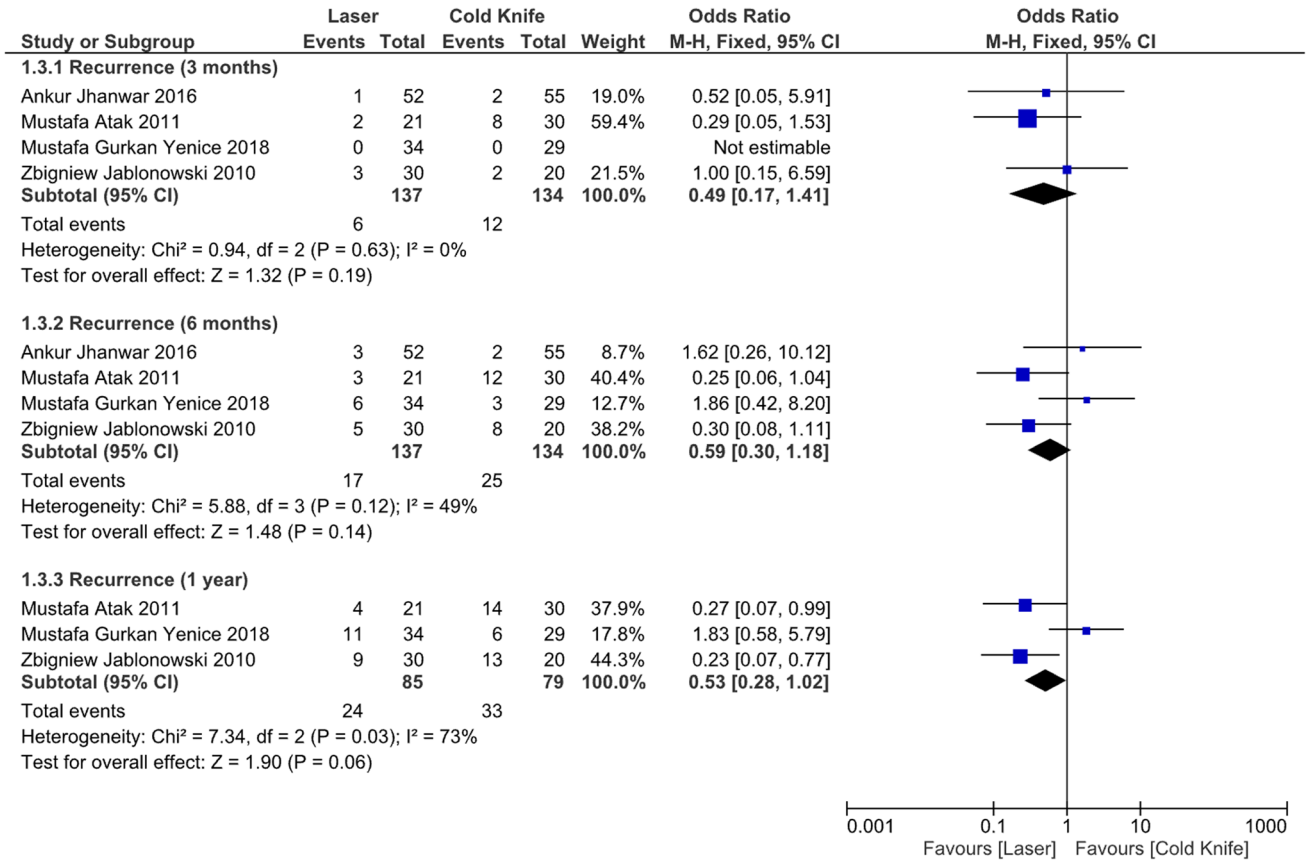

Fig. 3 Forest plot of stricture recurrence after laser urethrotomy and after cold knife urethrotomy

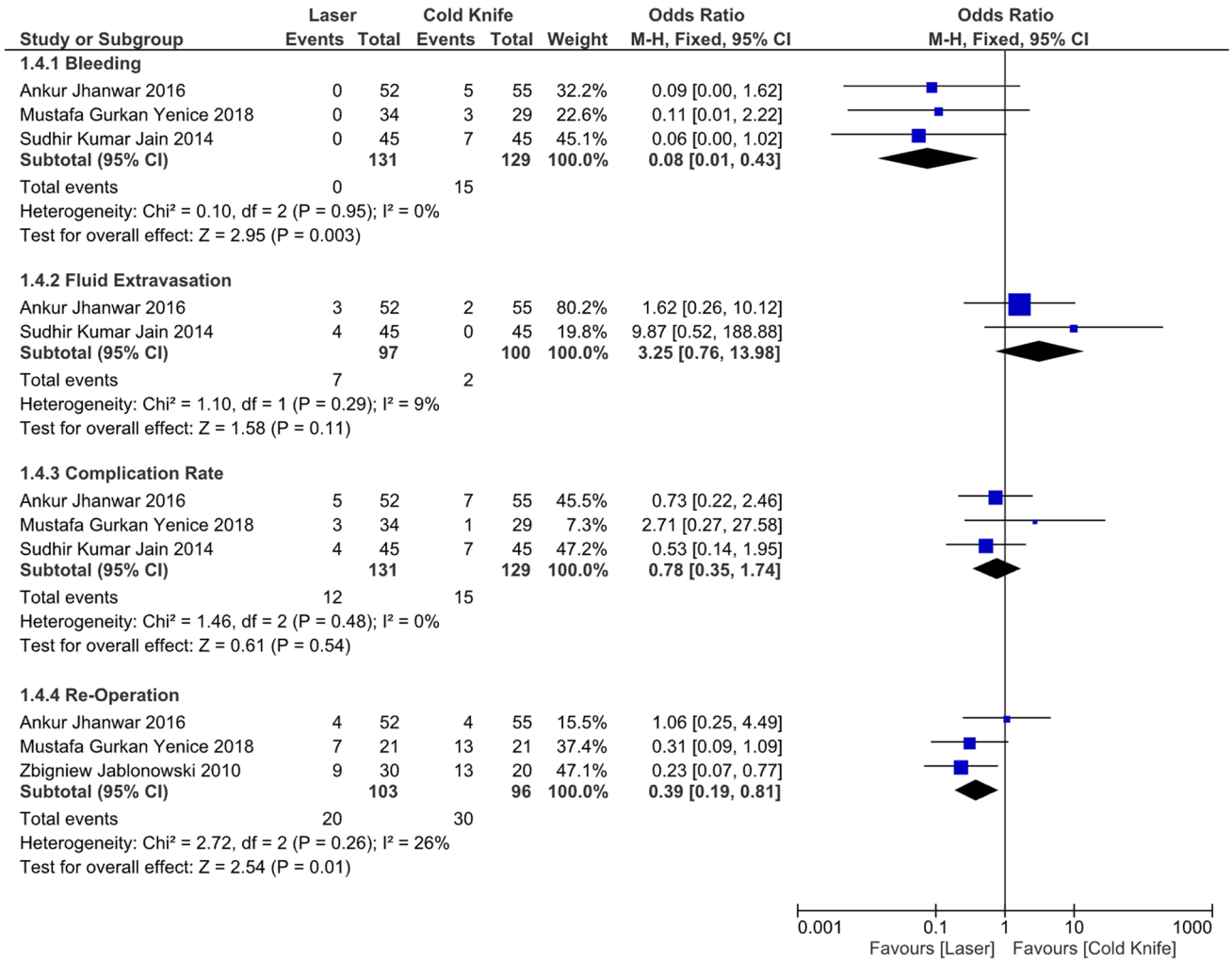

Fig. 4 Forest plot of complications and reoperation after laser urethrotomy and after cold knife urethrotomy

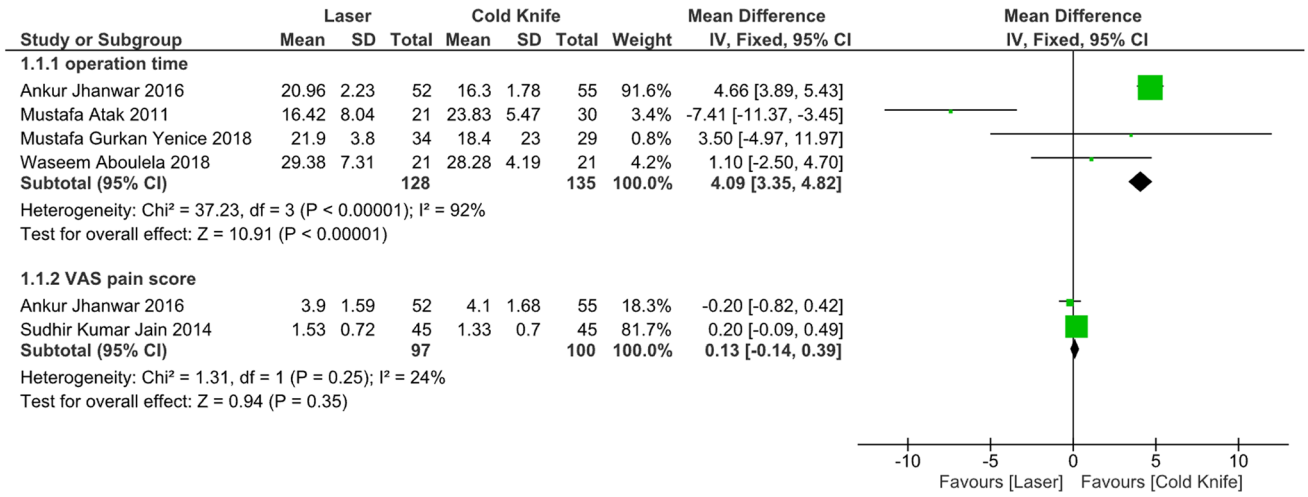

Fig. 5 Forest plot of operation time and Visual Analog Scale (VAS) pain score after laser urethrotomy and after cold knife urethrotomy

internal urethrotomy have been commonly used [16]. A survey in US found that 63% of 431 urologists, who annually treated more than six patients with urethral stricture, preferred internal urethrotomy for urethral stricture [3]. Similarly, Ogbonna stated that internal urethrotomy was the primary choice for urethral stricture in Nigeria, which might owe to the lower economic burden and briefness in time compared to urethroplasty [17]. Two available procedures of internal urethrotomy are cold knife and laser. A meta-analysis by Jin [18] included non-comparative trials and claimed laser urethrotomy owned a higher success rate than cold knife (laser versus cold knife: 79.4% versus 68.5%, $P = 0.004$). A later meta-analysis of comparative trials by Castellanos [5] included four articles but only compared the 3-month (OR 0.55, 95% CI 0.18–1.66), 6-month (OR 0.39, 95% CI 0.19–0.81) and 12-month recurrence rate (OR 0.44, 95% CI 0.26–0.75) plus 6-month Q_{max} (MD – 3.33, 95% CI – 4.76 to 5.25) after cold knife or laser, and they claimed laser had lower 6-month and 12-month recurrence rate (two trials involved) but better 6-month Q_{max} (two trials involved). A problem of Castellano's study is their interpretation of 6-month Q_{max}. As the data provided by the original studies included in their analysis both indicated that cold knife had better performance, they concluded that laser urethrotomy was superior to cold knife regarding 6-month Q_{max}, which was contrast to the actual outcome.

Compared to Castellanos's study, the advantage of the current meta-analysis is we included three more recent comparative trials and subsequently analyzed more parameters regarding both efficacy and safety of those two surgical procedures. In line with Castellanos's data, we found cold knife had better 6-month Q_{max}, although which was contrast to their wrong interpretation of data. Moreover, contrast to their conclusion, no significant difference of short-term or long-term recurrence rate was reached. Notably, in regard to 12-month recurrence, Atak [9] (published in 2010) and Jablonowski [8] (published in 2011) reported that laser had significantly lower recurrence rate, but Yenice's [14] data (published in 2018) were opposite, which might be attributed to the different practical experience of surgeons and also the advancement of equipment for urethrotomy. The combined OR indicated that laser was extremely approaching to have lower 12-month reoccurrence rate, which was consistent with our finding that less patients required reoperation after laser urethrotomy. In terms of the safety of those two surgical procedures, we observed that laser had less risk of bleeding, which was actually unsurprising because an advantage of laser urethrotomy is the scar tissue remaining on the incision to prevent hemorrhage [5]. Other complications such as fluid extravasation and fever were also reported but there was no significant difference between two groups. Another interesting founding of the current study was that laser group required more operation time, which was discordant with the finding that laser group had less bleeding. Possible explanations of this are the technical difficulty of laser urethrotomy and the lack of experience [14]. Last but not the least, similar VAS pain score was reported in two groups.

Urethral stricture length was reported to be correlated with the outcomes of urethrotomy. Shoukry stated that outcomes for children with stricture < 1 cm were better than those > 1 cm after laser urethrotomy [19] and Launonen found children with stricture length < 2 cm had higher success rate of treatment than children with stricture > 2 cm (24/29 vs. 0/5) after cold knife [20]. Moreover, Kamp also claimed that stricture length was a risk factor for stricture recurrence among adult patients [21]. However, none of our selected studies assessed if stricture length could independently predict the success rate or classified the outcomes based on stricture length. Similarly, different reporting standard of stricture location was used by the selected trials, causing it difficulty to analyze the correlation between stricture location and postoperative parameters. In terms of the etiology of stricture, iatrogenic injury was the primary cause of stricture in most of the included studies, while urethritis and trauma were also common. The impact of the location and etiology on treatment effect was not determined yet, despite Launonen proclaimed that no impact was observed on treatment success rate [20]. In Atak's study [9], the laser group had a lower rate of posterior urethral stricture but a higher recurrence-free rate, although no significant correlation was found. Yenice conducted his study including patients all diagnosed with primary bulbar urethral stricture, and no difference of postoperative outcomes was revealed between the two groups except that the laser group had significantly shorter operation time [14].

Clinical and research implications and limitations

So far, there is no consensus on the superiority between cold knife and laser urethrotomy. As mentioned above, one of the advantages of laser urethrotomy over cold knife is its coagulation ability leading to less bleeding, which has been confirmed by our analysis. Another advantage of laser urethrotomy is the better visualization during operation, but it also required more medical training and economic expenditure, restricting its wide availability [22, 23]. The current work also confirmed laser and cold knife had similar short-term and long-term Q_{max} except that the 6-month Q_{max} of patients treated with laser urethrotomy was only 0.95 mL/s less than the cold-knife group. Also, the recurrence rate was similar between cold knife and laser urethrotomy, let alone the 12-month recurrence rate was extremely close to favor the laser group. Hence, the efficacy of those two techniques

was close. However, since laser group also had lower reoperation rate besides less bleeding and similar risk of other complications, laser urethrotomy seemed to be a better recommendation for urethral stricture. Considering that the laser group needed more operation time, more systematic medical training should be widely given to physicians to increase their experience and skills, expecting to potentially decrease operation time.

Compared to previous meta-analysis, this study not only assessed the efficacy, but also compared the safety of cold knife and laser urethrotomy. Another advantage of our study is that heterogeneity was generally low across all analyses. However, our study should not be interpreted without limitations. First, given that we have systematically searched the mainstream database and included all the comparative trials of cold knife versus laser for urethral stricture, we could eventually select only seven articles and the patient size ended up with 453. High-quality trials with larger population should be conducted in the future to verify our findings. Second, as different energy could be used in laser urethrotomy, outcomes would be more reliable if we could perform subgroup analysis stratified by energy, which was stopped because of data insufficiency. This could also be an aim for future trials. The third limitation of our study is, similar to Castellanos's study [5], that data were not analyzed on the basis of the location of stricture and stricture length since those trials did not stratify those outcomes based on location and stricture length. Fourth, all the trials included in our analysis were conducted in developing countries and data from developed countries were lacking, requiring more trials to be conducted in developed countries, in particular, in western countries.

Conclusion

In the current meta-analysis, we found patients treated with cold knife and laser urethrotomy had similar efficacy in terms of short-term and long-term recurrence rate and Q_{max}, except the cold-knife group had slightly better 6-month Q_{max}. However, the laser group had less risk of bleeding and lower rate of reoperation but also longer operation time. No significance was reached in the comparison regarding other parameters.

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Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals Not applicable as there are no human participants and/or animals.

Informed consent Not applicable as there are no study participants.

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