Evaluation of the Efficacy and Safety of Laser versus Cold Knife Urethrotomy in the Management of Patients with Urethral Strictures: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Keywords

Urethra · Urethral stricture · Urethral stenosis · Laser · Cold knife · Urethrotomy · Urethral reconstruction · Efficacy · Safety · Recurrence rate

Abstract

Introduction: Urethral strictures generate great morbidity. Two procedures have been described for their management – laser and cold knife techniques – which are still widely used. We aim to assess the safety and efficacy of laser versus cold knife urethrotomy. **Materials and Methods:** We conducted a systematic search of the literature using MEDLINE, EMBASE, LILACS and Cochrane databases and gray literature. Primary outcomes were urethral stricture recurrence, time-to-recurrence and complication rate. Secondary outcomes were quality of life and maximum urinary flow rate (Qmax). Data analysis was obtained using Review Manager 5.2. **Results:** Out of 137 publications, 4 articles were included in the meta-analysis. At 3 months, the recurrence rate was similar in both groups (0.55, 95% CI 0.18–1.66), but at 6 and 12 months, it was significantly lower in the laser urethrotomy group (0.39, 95% CI 0.19–0.81 and 0.44, 95% CI 0.26–0.75).

The analysis of Qmax at 6 months post-intervention suggested a greater improvement in the laser urethrotomy group. A qualitative analysis showed that complications in both procedures were minor and infrequent. **Conclusions:** Laser urethrotomy has a lower recurrence rate at 6 and 12 months compared to cold knife urethrotomy. Complications in both procedures are minor and infrequent. Results should be interpreted cautiously, since they were evaluated only for a short term.

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Background

Urethral stricture is one of the oldest urological entities reported in the literature, with treatments described since 600 BC [1]. Its prevalence in developed countries is estimated to be 0.6% and is thought to be higher in undeveloped countries [2].

A vast majority of urethral strictures are secondary to surgical instrumentation. For instance, the prevalence of a stricture following transurethral resection of the prostate ranges between 3 and 5% [3]. Other reported

etiologies are urethritis and failed hypospadias repair [4].

Urethral stricture is a prevalent condition associated with great morbidity. It can cause obstructive urinary symptoms, which depending on the severity and the degree of the stricture, can be severe, jeopardizing the patient's quality of life (QoL) and leading to obstructive uropathy, urinary tract infection and renal disease [5].

Internal urethrotomy is a commonly used procedure for treating urethral strictures, especially in undeveloped countries. Nonetheless, strong evidence capable of generating a recommendation based on the postoperative outcomes and complications of the laser urethrotomy versus the cold knife urethrotomy is lacking. Therefore, our aim was to compare the efficacy and safety of both techniques in patients with urethral stricture according to the best available evidence.

Methods

Protocol

A research protocol was developed by the authors and approved by the Ethics Committee of our institution in May 2016.

Search Strategy

In May 2016, using the terms “urethral stenosis,” “urethral stricture,” “urethrotomy,” “laser,” and “cold knife,” a systematic search of the literature with no time limit was performed in MEDLINE, EMBASE, LILACS, Cochrane, GreyNet, and OpenGrey databases.

The identified articles were independently reviewed by 2 authors according to the Consolidated Standards of Reporting Trials (CONSORT) [6]. We used the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement, checklist and flow diagram. Also, the methodology of non-formal consensus including the opinion of a third author was used when disagreements were encountered.

Inclusion Criteria

Randomized controlled trials (RCTs) comparing both laser and cold knife urethrotomy in human subjects were included.

Exclusion Criteria

Animal studies, studies in patients with lower urinary tract symptoms not explained by urethral stricture or studies where other procedures different from urethrotomy were performed (i.e., urethroplasty) were excluded.

Primary Outcomes

The primary outcome for efficacy was stricture recurrence. For safety, the primary outcome was the occurrence of complications. The secondary outcomes evaluated were maximum urinary flow rate (Qmax) and QoL.

Data Extraction

Using a standardized format, information about the study was extracted, including study design, risk of bias, epidemiologic char-

acteristics of the participants, type of intervention, etiology and location of the stricture, follow-up duration, recurrence rate, complications, QoL and Qmax.

Summary Measures and Statistical Analysis

Treatment effect was measured using risk ratio (RR) for dichotomous outcomes. For qualitative variables, weighted mean difference was used. A 95% CI was used in every case. When at least 2 studies were available for the same outcome, a heterogeneity analysis was made with a visual exploration of the forest plot and the heterogeneity (I^2) estimate. Statistical analysis was conducted with Review Manager 5.2 using fixed-effects models.

Risk of Bias in Individual Studies

For each study, the assessment of risk of bias was conducted using the Cochrane instrument for assessing the risk of bias; 7 domains were included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. For each domain, the risk of bias was determined to be high, low, or not clear.

Results

Study Selection

A total of 137 articles were found in the initial search, out of which 83 were found in MEDLINE, 35 in EMBASE, 18 in LILACS, and 1 in Cochrane databases. No results were found in the gray literature. Two authors reviewed the publications' titles and abstracts and selected those that fulfilled the inclusion criteria. They were analyzed with the CONSORT instrument to include those with an RCT design. After applying this instrument, 4 studies were finally selected, whose authors were Atak et al. [7], Jain et al. [8], Jabłonowski et al. [9] and Dutkiewicz and Wroblewski [10] (Fig. 1).

Studies Characteristics

The present review focused exclusively on RCTs. Included studies had 2 intervention groups: the laser urethrotomy and the cold knife urethrotomy. A summary of the studies characteristics is provided in Table 1.

Assessment of Risk of Bias

Table 2 shows the risk of bias in individual studies using the 7 domains previously mentioned.

Synthesis of Results

Recurrence rate

Recurrence rate at 3, 6, and 12 months was evaluated in Atak et al. [7] and Jabłonowski et al. [9] studies, which had similar outcomes.

Fig. 1. Systematic review flow diagram.

At 3 months, the RR for recurrence was 0.55 (95% CI 0.18–1.66, $p = 0.29$), which favored the laser urethrotomy. However, these results were not statistically significant (Fig. 2).

At 6 and 12 months, the analysis showed an RR of 0.39 (95% CI 0.19–0.81, $p = 0.01$) and an RR of 0.44 (95% CI 0.26–0.75, $p = 0.003$), respectively, which favored the laser urethrotomy group (Fig. 3, 4).

Complications

Neither Atak et al. [7] and Jabłonowski et al. [9] nor Dutkiewicz and Wroblewski [10] reported complications during or after the procedure.

Jain et al. [8] reported a 12.2% overall complication rate. In the laser group, an 8.9% rate was found due to contrast extravasation to the perineum and stricture recurrence. For the cold knife group, a 15.5% was found due to bleeding.

Quality of Life

Jabłonowski et al. [9] evaluated the International Prostate Severity Score and applied a QoL questionnaire before and after the procedure. No statistically

significant differences were found between both interventions.

Dutkiewicz and Wroblewski [10] evaluated QoL before and after the procedure and at 12-month follow-up. They found no statistically significant differences.

Maximum Urinary Flow Rate

For this outcome, the results of studies conducted by Dutkiewicz and Wroblewski [10] and Jain et al. [8] at 6 months were compared. The analysis showed a weighted mean difference of -3.33 (95% CI -4.76 to -1.90 , $p < 0.0001$), demonstrating a higher mean of maximum flow rate in the laser urethrotomy (Fig. 5).

Discussion and Limitations

In the United States, in 2001, the admission rate to the emergency department for symptoms secondary to urethral stricture was 6.9/100,000. According to data of the year 2000, 191 million US dollars were spent towards this condition [2]. In undeveloped countries, where the prevalence of the disease is greater, a higher rate of expendi-

Table 1. Description of included randomized clinical trials

	Study location	n	Age, years, mean (range)	Etiology of stricture	Localization of stricture	Intervention	Follow-up, months	Recurrence rate (12 months)	Main complications
Atak et al. [7], 2011	Zonguldak, Turkey	51	61 (24–85)	Iatrogenic (n = 33), bladder neck contracture (n = 18)	Bulbar (n = 33), bladder neck (n = 8)	HO:YAG laser (n = 21), cold knife (n = 30)	1, 3, 6, 9, 12	Laser 19.0%, cold knife 46.6%	None
Jabłonowski et al. [9], 2010	Lodz, Poland	50	62 (22–83)	Iatrogenic (n = 30), traumatic (n = 5), infectious (n = 1), undetermined (n = 14)	Membranous (n = 26), penile (n = 12), bulbar (n = 4), multiple (n = 8)	Nd-YAG laser (n = 30), cold knife (n = 20)	3, 6, 12	Laser 30%, cold knife 65%	None
Dutkiewicz and Wroblewski [10], 2012	Katowice, Poland	50	63 (17–78)	Iatrogenic (n = 32), idiopathic (n = 18)	Bulbar (n = 8), penile (n = 19), membranous (n = 13), prostatic (n = 19)	Holmium laser (n = 25), cold knife (n = 25)	3, 6, 12	–	None
Jain et al. [8], 2014	New Delhi, India	90	18–60	Inflammatory (n = 42), catheterization (n = 29), traumatic (n = 10), idiopathic (n = 9)	Penile (n = 21), bulbar (n = 22), bulbomembranous (n = 36), posterior (n = 11)	Holmium (n = 45), cold knife (n = 24)	1, 6	–	Extravasation of contrast agent, bleeding

Table 2. Risk of bias in individual studies

	Atak et al. [7], 2011	Jabłonowski et al. [9], 2010	Dutkiewicz and Wroblewski [10], 2012	Jain et al. [8], 2014
Random sequence generation	Low risk	Unclear	High risk	Low risk
Allocation concealment	Low risk	Unclear	High risk	Unclear
Blinding of participants and personnel	High risk	High risk	High risk	High risk
Blinding of outcome assessment	Unclear	Unclear	Unclear	Unclear
Incomplete outcome data	High risk	High risk	Low risk	Low risk
Selective reporting	Unclear	Unclear	Unclear	Unclear
Other biases	Unclear	Unclear	Unclear	Unclear

ture is estimated [1]. Regarding its management, urethroplasty is the standard of care, with up to 90% chance of success [11]. In this procedure, a preputial/penile skin flap is considered an excellent material for urethral reconstruction associated with lower incidence of stricture recurrence, especially when patients do not have suitable oral mucosa [12]. Other most commonly used treatment options are urethral dilation and internal urethrotomy [11].

Bullock and Brandes [13] conducted a survey among 431 members of the American Urological Association, and found that 63% of the urologists treated from 6 to 20 urethral strictures annually, internal urethrotomy being the most commonly used procedure (85.6%). The authors highlighted that most urologists were not trained in urethroplasty.

In 2016, a survey conducted among the members of the Sociedad Colombiana de Urología showed that 33% of participants preferred the use of internal urethrotomy as the initial management of urethral strictures. Almost 50% of them use internal urethrotomy for bulbar urethral strictures. When it comes to strictures localized in the penile urethra, 70% prefer a minimally invasive management [14].

As previously stated, open urethral reconstruction is the best choice for the management of urethral strictures; however, it requires an adequate medical training and optimal surgical facilities. These conditions are not available in many countries, resulting in the use of alternative methods such as the internal urethrotomy [15].

A study conducted in Nigeria (Ogbonna [16]) showed that both the urethrotomy and the urethral dilation may

Fig. 2. Forrest plot and meta-analysis of recurrence rate at 3 months.

Fig. 3. Forrest plot and meta-analysis of recurrence rate at 6 months.

Fig. 4. Forrest plot and meta-analysis of recurrence rate at 12 months.

Fig. 5. Forrest plot and meta-analysis of maximum urinary flow rate at 6 months.

manage up to 75% of patients with urethral strictures, which was associated with good short-term results. The authors stated that urethrotomy is a low-cost procedure and is 10 times less time consuming than urethroplasty, which is why they propose the former as the leading choice in the initial management of urethral strictures in the absence of trained personnel, adequate facilities or ease of referral to specialized care centres [16].

Greenwell et al. [17] in a study comparing internal urethrotomy versus urethroplasty with specific reference to cost effectiveness concluded that in urethral strictures with less than 60% chance of recurrence – less than 1 cm long with little spongiofibrosis – internal urethrotomy is a cost-effective initial treatment measure.

Jin et al. [18] published a meta-analysis in 2010 based on non-comparative observational studies. This study included 44 articles, out of which 19 evaluated laser urethrotomy and 25 evaluated cold knife urethrotomy. Consistent with our results, the authors found a success rate of 74.9% for the laser urethrotomy compared to 68.5% for the cold knife urethrotomy group, with a *p* value of 0.004. However, they mainly included descriptive studies. Moreover, the follow-up duration among studies was heterogeneous, which did not allow an adequate analysis of the recurrence rate.

Currently, the American Urological Association guidelines in male urethral stricture, with a strength-of-recommendation C, states that the laser urethrotomy and the cold knife urethrotomy may be used indistinctively [19]. This recommendation was solely based on 2 independent RCTs [7, 20].

In this article, we provide the first meta-analysis including only RCTs comparing both techniques. Although

at the 3rd-month follow-up the results did not show a statistically significant difference among the aforementioned techniques, at the 6th- and 12th-month follow-up, there was a statistically significant lower recurrence rate for the laser urethrotomy group when compared to the cold knife urethrotomy group.

Regarding complications, none were reported in 3 of the studies included in the meta-analysis and Jain et al. [8] only reported a few, which were all minor in nature.

The results of our study were limited by the short-term outcome evaluation among the publications included in the meta-analysis. Additionally, these 4 studies did not specify the results based on the location of the stricture.

Conclusions

Our results may demonstrate that at 6 and 12 months postoperatively, the laser urethrotomy technique offers a lower recurrence rate compared to the cold knife urethrotomy. Complications with any of these techniques were minor and infrequent. These results should be interpreted cautiously, since they were evaluated at short term. Further investigations using well-designed randomized clinical trials are needed in order to achieve the best management of urethral strictures based on where they are located.

Disclosure Statement

The authors have no commercial or financial incentive associated with the writing and publishing of this work.

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