PLOS ONE

STUDY PROTOCOL

Surgical laser therapy for cryptoglandular anal fistula: Protocol of a systematic review and meta-analysis

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Citation: Mei Z, Zhang Z, Han Y, Du P, Yang W, Wang Q, et al. (2023) Surgical laser therapy for cryptoglandular anal fistula: Protocol of a systematic review and meta-analysis. PLoS ONE 18(1): e0279388. https://doi.org/10.1371/journal.pone.0279388

Editor: Endi Lanza Galvão, Universidade Federal dos Vales do Jequitinhonha e Mucuri, BRAZIL

Received: June 15, 2022

Accepted: December 6, 2022

Published: January 4, 2023

Data Availability Statement: No datasets were generated or analysed during the current study. All relevant data from this study will be made available upon study completion.

Funding: This work was supported by the National Natural Science Foundation of China (grant no. 81774112), a grant from Siming Scholars from Shuguang Hospital (grant no. SGXZ-201913) and Clinical Research Plan of SHDC (No. SHDC2020CR2007A). The funders had no role in

Abstract

Introduction

Anal fistula is the natural evolution of perianal abscess and one of the most common perianal diseases for adults. For complex fistula, it is still very challenging for anorectal surgeons to manage. With the introduction of laser technique in surgery, it is becoming more and more widely used for the treatment of cryptoglandular anal fistula. During the past decade, numerous studies have reported the clinical effectiveness and postoperative outcomes of different forms of laser treatment for anal fistula. However, as these studies were varied in terms of baseline characteristics, the evidence for the true clinical effectiveness of laser treatment for anal fistula need further critical appraisal. Therefore, the purpose of this study is to evaluate the outcomes of surgical laser therapy for cryptoglandular anal fistula stratified by laser type and Parks' classification through a synthesis of quantitative and qualitative evidence.

Methods and analysis

This study will be carried out with adherence to the Cochrane Handbook. We will search PubMed, Cochrane Library, and Embase until June, 2022 to identify all relevant interventional and observational studies examining the effects of laser therapy on the clinical outcomes for cryptoglandular anal fistula. Data extraction from eligible studies will be performed independently by two unblinded authors using standardized extraction forms. Risk of bias assessment for each study will be conducted using Cochrane tool for randomized controlled trials (RCTs) and the Newcastle–Ottawa scale (NOS) tool for observational studies. The DerSimonian-Laird random-effects model will be used to calculate the pooled estimates. Heterogeneity will be examined by subgroup analysis stratified by laser type and Parks' classification and other study characteristics. Potential publication bias will be assessed by funnel plot symmetrical and Egger's regression tests.

study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: APFCP, Asia Pacific Federation of Coloproctology; ASCRS, American Society of Colon and Rectal Surgeons; CI, confidence interval; Emtree; EMBASE, Subject Headings; ESCP, European Society of Coloproctology; GRADE, the Grading of Recommendations, Assessment, Development and Evaluation; LIFT, ligation of the intersphincteric fistula tract; MeSH, Medical Subject Heading; MRI, magnetic resonance imaging; NOS, Newcastle Ottawa Scale; PDT, photodynamic therapy; PRISMA-P, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; RR, relative risk; SMD, standardized mean difference; WMD, weighted mean difference.

Conclusions

The synthesis of quantitative and qualitative evidence of this systemic review will yield updated and comprehensive evidence of laser treatment on specific outcomes, which can provide anorectal surgeons with high level evidence-based recommendations to improve patient care and clinical outcomes. **OSF registration number:** DOI 10.17605/OSF.IO/36ADW.

Introduction

Anal fistula, also known as fistula-in-ano, is the natural progression of perianal abscess. In fact, the disease begins with suppurative inflammation of the anal crypts, and if left untreated, the inflammation can spread to the adjacent anorectal spaces, including pelvirectal space, retrorectal space, ischiorectal space, perianal space and transsphincter space [1]. At present, the theoretical basis for the pathogenesis of cryptoglandular perianal fistula is still controversial. According to the cryptoglandular theory of perianal fistulas, they develop from the rectal glands, originate from the intersphincteric plane and perforate the internal sphincter. Rectal glands involved in the inflammatory process (including secondary pro-inflammatory factors) may play a significant role in the development of cryptoglandular anal fistula [2]. The two main goals of anal fistula treatment are successful healing and preservation of the anal sphincter. Complex anal fistulas remain extremely difficult to treat in the field of anal surgery [3–6]. Although there are a number of surgical treatment options available, such as ligation of the intersphincteric fistula tract (LIFT), video-assisted anal fistula treatment, adipose-derived stem cells, endorectal advancement flap, anal fistula plug and fibrin glue [7–11], their use is severely limited due to the high recurrence rate and the influence of sphincter function. The long-term effect and success rate of these surgical approaches are not as satisfactory as the traditional surgical method fistulotomy for simple anal fistula [12,13].

Laser, as a newly surgical technique, has grown in popularity in recent years, particularly for the treatment of benign perianal diseases such as anal fistula [14]. The laser fiber was first introduced to fistula surgery due to its good tissue penetration, and the laser beams were used to destroy and wipe out the fistula. One of its advantages is that it can be used to diagnose and treat disease in confined spaces [1,15]. Another significant advantage is that low laser power can coagulate diseased tissue without vaporizing it [16]. Photodynamic therapy (PDT) [17,18] is another application of laser that is based on the principle that laser causes tissue necrosis by activating photosensitizer without increasing tissue temperature [16]. During fistula laser closure, the laser fiber is introduced from the outside of the fistula and precisely reaches the lesion site. The laser energy can shrink the surrounding tissue, causing protein denaturation. Its advantages include ease of operation, less invasion, faster recovery, and fewer postoperative complications.

Numerous studies, as well as a few quantitative or qualitative analyses have reported on the clinical efficacy and postoperative outcomes of various types of laser treatment for anal fistula [19–22]. However, because these studies differed in terms of study design, sample size, Parks' Classification for anal fistula patients, laser treatment patterns, and reported outcomes, the evidence for the true clinical effectiveness of laser treatment for anal fistula requires further critical appraisal. As a result, we will critically evaluate the postoperative outcomes for laser treatment of anal fistula using a synthesis of quantitative and qualitative evidence stratified by both laser treatment patterns and Parks' Classification.

Methods and analysis

Protocol registration

We will perform and report this qualitative evidence synthesis protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [23] (S1 Table) and the Cochrane Handbook (http://handbook.cochrane.org). The registered protocol of this study can be found at the Open Science Framework (OSF) website (https://osf.io/36adw) with the registration number of DOI 10.17605/OSF.IO/36ADW.

Data sources and search strategies

The following three major databases (PubMed, Embase, and Cochrane Library,) will be systematically searched from inception through June, 2022 by adapting specific search strategies which are presented in details in Table 1. These studies will be identified if they have interventional or observational study design examining the outcomes or effect of laser ablation for cryptoglandular anal fistula. We will apply Medical Subject Heading (MeSH) terms or EMBASE Subject Headings (Emtree) terms along with the corresponding free text words that are pertaining to perianal fistula, laser ablation, and outcomes. The following keywords will be used to identify relevant studies: including terms on anal fistula ((anus OR anal OR anorectal OR perianal) AND (fistula OR fistulotomy OR fistulectomy)) AND laser therapy (laser OR fistula laser closure OR FiLaC) AND treatment outcomes (outcomes OR complication OR reoperation OR continence OR manometry OR healing OR recurrence OR dehiscence). These search terms will be combined with the Boolean operators OR and AND. Reference lists of included studies will be hand searched to identify additional relevant work. Furthermore, we

Table 1. Search strategy for Pubmed database.

***Anal fistula terms*:**
1 "Rectal Fistula"[Mesh]
2 ((anus OR anal OR anorectal OR perianal) AND (fistula OR fistulotomy OR fistulectomy)) [Title/Abstract]
3 (fistula-in-ano OR FIA) [Title/Abstract]
4 2 OR 3
5 1 OR 4
***Laser therapy terms*:**
6 "Laser Therapy"[Mesh]
7 "Photochemotherapy"[Mesh]
8 (laser OR fistula laser closure OR FiLaC OR photochemotherapy) [Title/Abstract]
9 6-8/OR
Treatment outcome terms
10 "Treatment Outcome"[Mesh]
11 "Postoperative Complications"[Mesh]
12 "Reoperation"[Mesh]
13 "Fecal Incontinence"[Mesh]
14 "Wound Healing"[Mesh]
15 "Recurrence"[Mesh]
16 "Surgical Wound Dehiscence"[Mesh]
17 (outcomes OR complication OR reoperation OR continence OR manometry OR healing OR recurrence OR dehiscence) [Title/Abstract]
18 10-17/OR
***Final search results*: *Combining Anal fistula and Laser therapy and Treatment outcome*:**
18 5 and 9 and 18

https://doi.org/10.1371/journal.pone.0279388.t001

will also conduct manual search of abstracts from annual scientific meeting of the American Society of Colon and Rectal Surgeons (ASCRS), European Society of Coloproctology (ESCP) and Asia Pacific Federation of Coloproctology (APFCP). For duplicate data in more than one publication, we will select the study with the largest sample. Search results will be imported into Endnote X9 software (Thomson Reuters for Windows version) to check for duplicate entries which will be removed accordingly. For duplicate records that cannot be recognized by the Endnote software, we will manually remove them by comparing publication authors, titles and publication dates. Two authors will independently conduct the literature search, screen of titles and abstracts, selection of included studies and data extraction. A third author will resolve discrepancies by discussion and adjudication who will examine the studies independently.

Eligibility criteria

According to PRISMA guideline, the PICOS framework will be constructed in terms of population, interventions, comparisons, outcomes and study question or design to determine eligibility criteria. Studies satisfying the following inclusion criteria will be involved for the qualitative and quantitative analyses.

Study Question—Are the effectiveness, safety and outcomes of surgical laser treatment favorable and varied for cryptoglandular anal fistula stratified by Parks' classification and different forms of laser?

Study Design—Interventional studies (randomized or nonrandomized clinical trials) or observational studies published in any languages will be eligible for inclusion;

Populations—Participants diagnosed with cryptoglandular anal fistula through clinical manifestations and/or endoanal ultrasound or magnetic resonance imaging (MRI) according to Parks' classification (mainly involving intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric fistulas).

Intervention/exposure—Laser ablation, fistula laser closure, photodynamic therapy or FiLaCTM treatment method as the primary intervention or exposure of interest. Based on the reported literatures and gain medium of lasers, we will classify them into gas lasers (including carbon dioxide [CO2] lasers), solid-state lasers (including the Nd:YAG laser) and semiconductor lasers or diode lasers. Moreover, if possible, we will also classify lasers by mode of operation including continuous-wave lasers and pulsed lasers.

Comparators—Studies will be included if they are single-arm or compared with patients not receiving laser ablation or $FiLaC_{TM}$ treatment.

Outcomes—Studies will be included if any one of the reported primary outcomes are involved [24], which are classified as short-term outcomes including postoperative complications (including postoperative urinary retention, infection, incontinence, and bleeding that need interventions) and reinterventions which are assessed during hospitalization or one month after laser treatment; medium and long-term outcomes including success rate or recurrence rate, clinical fistula healing and radiological healing, development of additional fistulas, fistula symptoms, incontinence, psychological impact of treatment, patient satisfaction and quality of life which are assessed 3 to 6 months or one year after laser treatment.

In addition, in the presence of more than one paper of the available publications in laser fistula treatment from the same authors, all the publications will be reviewed and relevant information will be abstracted, but only the most recent or complete one will be selected.

Data extraction

We will conduct data extraction on the characteristics of eligible studies from reports using a piloted, structured data extraction form by two independently authors. The results of the data

abstraction will be further crosschecked by a senior author. All discrepancies will be resolved by mutual discussion. The structured data extraction form is composed by the following variables: name of the first author of the publication, study publication year, study design and set, original region the study conducted, time range of the participant enrolment, participant characteristics [(mean or median age at enrolment, gender, BMI of intervention measures, Parks classification of the disease, previous anal surgery history and comorbid disease (diabetes, autoimmune disease, or colitis)], intervention or exposure measures (laser parameters and type for FiLaC), comparison measures, criteria for ascertainment of anal fistula diagnosis and outcome ascertainment.

Methodological quality assessment

For interventional studies such as RCTs, risk of bias will be assessed using the Cochrane risk of bias tool with the assessment of indicators of selection bias, performance bias, detection bias, attrition bias, and reporting bias [25]. For observational studies, we will use the Newcastle–Ottawa scale (NOS) tool to assess the study quality (risk of bias) [26]. A total of nine points will be awarded to each study in terms of the selection of the study groups, the comparability of the study groups and the ascertainment of the exposure and the outcomes. The NOS score ranges from zero to nine, and high-quality study is defined as a study with quality scores being more than 7 and moderate to low-quality study as no more than 7 [27].

Grading of evidence

For RCTs, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach will also be conducted to rate the quality of evidence for each outcomehttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC6949116/ - R18 [28]. Two authors will independently assess risk of bias, inconsistency of results, indirectness of evidence, imprecision, and publication bias. Overall quality is allocated very low, low, moderate, or high.

Statistical analysis

All statistical analyses will be carried out with the software Stata 15.0 (Stata Corp LP, College Station, TX). Data from observational studies, RCTs and non-randomized studies will be analyzed separately. If the quantitative data are provided, a meta-analysis will be carried out for specific outcomes. If we are unable to pool data statistically using meta-analysis, a narrative synthesis of results adhering to the Synthesis Without Meta-analysis (SWiM) guideline will be conducted [29]. To assess the pooled treatment effects, we will measure relative risk (RR) and 95% CI for dichotomous outcomes [30]; while for continuous outcomes, we will combine weighted mean difference (WMD) (for the same outcome measurement) or standardized mean difference (SMD) (for different outcome measurement) and its corresponding 95% confidence intervals (CIs) [31]. We will use the Mantel Haenszel approach to pool dichotomous outcomes and the inverse variance method to pool continuous outcomes, respectively. We will examine between-study heterogeneity using the Cochrans Q-statistic and quantify the proportion of the total variation due to between-study heterogeneity using the I^2 statistic. We consider an $I^2 > 50\%$ representing substantial heterogeneity [32,33].

We will apply a random effects model, a more conservative approach to calculate the pooled estimates. Subgroup analysis (or meta-regression) based on the available variables will be performed to examine the potential factors contributing to between-study heterogeneity if there are sufficient data available for the study outcomes. Also, if possible, we will stratify the outcomes based on the fistula tract length to more than 3 cm and less than 3 cm from the anal verge. Publication bias will be assessed by inspection of funnel plot asymmetry and Egger's

regression test provided that 10 or more studies are included in the meta-analysis for the studied outcome [34]. Leave-one-out sensitivity analysis will be conducted to assess the robustness of pooled estimates. For all statistical analyses, a value of $P < 0.05$ will be deemed statistically significant.

Ethics and dissemination

Ethical approval is not required as all the data we will be analyzed are obtained from published literatures. The results of our study will be disseminated in a peer-reviewed journal.

Discussion

The benefit of laser treatment for cryptoglandular anal fistula is controversial. The recommendation of the application of this procedure for those patients is challenging due to the highly heterogeneous results of both interventional and observational studies conducted in these few decades.

Our study raises several concerns worth addressing: is laser therapy suitable for all types of anal fistula stratified by Parks' classification? Is there any difference in the effectiveness of different forms of laser in the treatment of anal fistula? Whether there is any difference between short-term and long-term effects of laser therapy. Although there is more and more relevant evidence in recent years, it is obvious that no literature can fully address these concerns. Through critical systematic evaluation and quantitative synthesis of available data, we hope to give the most comprehensive answer to these questions so far.

The current study has a number of strengths in terms of the following aspects. Firstly, we will include the largest literatures in the relevant area, providing up-to-date evidence to evaluate the effectiveness, short-term and long term outcomes of laser treatment. Secondly, we will strict adherence to the Cochrane Library and PRISMA guidelines for systematic review and meta-analysis to conduct and report this study process. We have also developed systematic and comprehensive database search strategies for all the searched databases including PubMed, Embase, and Cochrane library without search date restriction in order to obtain relevant literatures as much as possible from all around the world, which may avoid the potential of publication bias on the pooled findings to a great extent, thus the repeatability of results could be much improved. Thirdly, we will conduct a transparent methodologic quality assessment of the included studies using either Cochrane tool for RCTs or the NOS checklist recommended for cohort studies. Fourth, we will also plan to use multiple approaches to test the potential heterogeneity, publication bias and the robustness of the results for each outcome, including subgroup analyses, sensitivity analyses, trim-and-fill analysis or meta-regression if possible.

Conclusions

The real effectiveness, especially postoperative short-term and long-term outcomes of laser treatment on cryptoglandular anal fistula has not yet been determined. How to evaluate the exact effectiveness of laser treatment and the best indication for anal fistula surgery is the main purpose of this study. The synthesis of quantitative and qualitative evidence will yield updated and comprehensive evidence of laser treatment on specific outcomes, which can provide anorectal surgeons with high level evidence-based recommendations to improve patient care and clinical outcomes.

Supporting information

S1 Table. PRISMA-P checklist.
(DOC)

Author Contributions

Conceptualization: Zubing Mei, De Zheng.

Data curation: Zubing Mei, Zhijun Zhang.

Formal analysis: Zubing Mei, Ye Han.

Funding acquisition: Zubing Mei, De Zheng.

Investigation: Zubing Mei, De Zheng.

Methodology: Zubing Mei.

Project administration: Zubing Mei, De Zheng.

Resources: Zhijun Zhang, Ye Han, Peixin Du, Wei Yang.

Software: Zubing Mei.

Supervision: Zubing Mei.

Validation: Zubing Mei, Zhijun Zhang, Ye Han, Peixin Du, Qingming Wang, De Zheng.

Visualization: Peixin Du.

Writing – original draft: Zubing Mei.

Writing – review & editing: Zubing Mei.

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