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Comparison of BioLIFT versus LIFT for the treatment of trans-sphincteric anal fistula: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Identifying the optimal treatment for anal fistula has been challenging. Since first reported in 2007, the ligation of the intersphincteric fistula tract (LIFT) procedure has reported healing rates between 40% and 95% and is being increasingly adopted. The BioLIFT is an augmentation of the LIFT with an intersphincteric bioprosthetic mesh and has reported healing rates between 69% and 94%. Despite increased costs and potential complications associated with mesh, the evidence comparing healing rates between BioLIFT and LIFT is unknown. This study details the protocol for a systematic review and meta-analysis of BioLIFT and LIFT to compare outcomes associated with each procedure.

Methods and analysis MEDLINE, EMBASE and the Cochrane Database will be searched from inception using a search strategy designed by an information specialist. Randomised controlled trials, prospective and retrospective cohort studies, consecutive series, cross-sectional studies and case series with more than five patients will be included. Both comparative and single group studies will be included. The eligible population will be adult patients undergoing BioLIFT or LIFT for trans-sphincteric anal fistula. The primary outcome will be primary healing rate. Secondary outcomes will capture secondary healing rate and complications. Abstract, full text and data extraction will be completed independently and in duplicate by two reviewers. Study risk of bias will be assessed using Risk of Bias In Non-randomized Studies - of Interventions and the Risk of Bias (RoB 2.0) tool. Quality of evidence for outcomes will be evaluated using Grading of Recommendations, Assessment, Development and Evaluations criteria. A meta-analysis will be performed using a random-effects inverse variance model. Subgroup and sensitivity analyses will be explored in relation to complex fistula characteristics and patients who have undergone previous LIFT. Heterogeneity will be assessed using the I^2 statistic.

Ethics and dissemination This review does not require research ethics board approval. This study will be completed in September 2022. The findings of this study will be disseminated through peer-reviewed international conferences and journals.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Search strategy will be designed by health information specialist and reviewed by second specialist as per Peer Review of Electronic Search Strategies framework.
⇒ Risk of bias will be rigorously assessed using Risk of Bias In Non-randomized Studies - of Interventions and Cochrane Risk of Bias (RoB 2.0) tool for individual studies and Grading of Recommendations, Assessment, Development and Evaluations criteria for outcomes
⇒ Given the known heterogeneity in reported outcomes of anal fistula, The Core Outcome Measurement in Effectiveness Trials systematic review for anal fistula will be reviewed to ensure comprehensive capture of clinically significant outcomes and complications.

INTRODUCTION

Approximately 30%–50% of patients with a perianal abscess will subsequently develop an anal fistula.[1] An anal fistula is defined as a persistent tract that creates an abnormal connection between the anal canal and the perianal skin.[2] These fistulas are classified based on their anatomic course relative to the sphincter complex as initially described by Parks *et al*.[2]

The optimal treatment of anal fistulas has proven to be challenging. Many sphincter-preserving techniques such as the fistula plug or fibrin glue have shown positive early results however longer follow-up studies reveal only limited success rates.[3 4] The ligation of the intersphincteric fistula tract (LIFT) procedure was first reported by Rojanasakul *et al* as a sphincter-preserving technique for the treatment of primarily transphincteric fistulas.[5] This technique is usually performed in two stages and involves initial placement of a seton to allow fibrosis and maturation of the fistula tract. Once the tract has matured, an

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intersphincteric approach is undertaken to identify, ligate and excise the intersphincteric portion of the fistula tract without dividing the sphincter musculature.[6 7] Since first reported, there have been numerous series published as well as at least six systematic reviews describing the success of the LIFT procedure.[3 8–12] The reported healing rates in all studies range from 40% to 95% with a pooled success rate of between 70.6% and 76.5% in meta-analysis. Additionally, the adoption rate of the LIFT procedure has increased since first being reported in 2007.[3]

The BioLIFT procedure, first described by Ellis in 2010, is a modification of the LIFT procedure and includes a standard LIFT procedure with the additional placement of a biological mesh in the intersphincteric plane.[13] The proposed benefits of the interposed biological mesh are related to its position as a physical barrier between the ligated ends of the fistula tract and its incorporation into the tissue with time. The potential disadvantages include complications associated with the mesh such as foreign body reaction, increased operating time, the environmental impact and the increased costs estimated to be more than US$1000.[14]

There have been several published studies describing a series of patients who have undergone the BioLIFT procedure as well as several retrospective studies comparing BioLIFT to the LIFT procedure.[15–17] A retrospective cohort study from our institution spanning 10 years and 119 cases revealed a superior healing rate with BioLIFT compared with LIFT after multivariate logistic regression (OR=2.38 (95% CI 1.01 to 5.62); p=0.048) and a primary healing rate of 75% for BioLIFT.[14] Other studies reported a healing rate between 69% and 94% but had smaller number of patients.[13 16] Our aim is to perform a systematic review and meta-analysis of BioLIFT versus LIFT to compare the healing rates and complications associated with each procedure.

METHODS AND ANALYSIS

This systematic review will be conducted based on a review protocol registered with the International Prospective Register of Systematic Reviews. The protocol for this review has been prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.[18] The completed checklist is shown in online supplemental appendix 1. The research question to be addressed is as follows: 'To compare healing rates and complication rates of LIFT and BioLIFT procedures for the treatment of transphincteric fistulas through a systematic review of literature and data synthesis of prospective comparative studies, retrospective comparative studies and case series'.

Eligibility criteria

Population

Adult patients 18 years and older receiving treatment for trans-sphincteric anal fistula.

Intervention

Patients undergoing the BioLIFT procedure. This procedure follows the same steps as the LIFT procedure with the placement of an interpositioned, bioprosthetic mesh within the intersphincteric plane after the tract has been ligated.

Comparison

Patients undergoing the LIFT procedure, defined broadly as dissection along the intersphincteric plane starting from the skin and continuing superiorly until the fistula tract is encountered, followed by ligation of the intersphincteric component of a transphincteric fistula tract. Studies that involve a variation of the LIFT such as video-assistance or curettage of the tract will also be included.

Outcomes

The primary outcome will be the primary healing rate of the fistula tract. This will be defined clinically as complete healing of both the external opening and the intersphincteric incision. Secondary outcomes of interest will capture overall complications including secondary healing rate defined as successful healing after a second procedure or spontaneous healing after recurrence. Other complications will also be collected including incontinence, pain, bleeding, infection and paresthesia. Additionally, we will collect re-operation rates and time to recurrence, defined as the reappearance of the fistula after initial healing. Studies will not be excluded by minimum follow-up duration but this data point will be collected.

Study designs

We will include randomised control trials, prospective and retrospective cohort studies, consecutive series and cross-sectional studies. Case reports, case series with less than 20 patients, editorial letters and review articles will be excluded. Both comparative (ie, BioLIFT vs LIFT) and single group studies will be included but separately analysed.

Information sources

We will search MEDLINE, EMBASE and the Cochrane Database of Controlled Trials from inception using a predetermined search strategy developed by a health information specialist with expertise in systematic reviews and a clinical expert in the field of colorectal surgery (RPM).

Search strategy

The search strategy will be comprised Medline subject headings and key words. A copy of the Medline search strategy is provided in online supplemental appendix 2. There will be no language or date restrictions. The search strategy will be peer-reviewed by a second health information specialist using the Peer Review of Electronic Search Strategies framework to ensure robust data capture.[19] We will also search grey literature to include abstracts presented at relevant society meetings (American Society of Colon and Rectal Surgeons; Canadian Society of Colon

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and Rectal Surgeons) from the past 3 years and ongoing key websites (eg, clinicaltrials.gov) to explore ongoing and upcoming studies relevant to our review.

Selection process

Two authors (SHA and RH) will complete abstract screening, independently and in duplicate using Covidence systematic review manager software (Veritas Health Innovation, Melbourne, Australia, available at https://www.covidence.org/home). Full text screening will be completed in duplicate by two authors (SHA and RH). To ensure consistent application of selection criteria, the two reviewers (SHA and RH) will carry out a pilot exercise comparing their study selection. This will be done during each stage of selection, after review of the first 50 abstracts and the review of the first 25 full texts. All disagreements will be settled by a third-party reviewer (RPM). The study selection process will be summarised in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart (online supplemental appendix 3).

Data collection

Two authors (SHA and RH) will complete data extraction independently and in duplicate using a standardised data extraction form implemented in Microsoft Excel (Microsoft Corporation). A pilot extraction exercise of three studies will be performed to ensure consistency in approach between reviewers. Data elements to be collected will include those related to basic publication characteristics (including year, journal, authorship list and country), study methods (including design and elements necessary for risk of bias appraisal), patient characteristics (including enrollment criteria and key demographic measures such as age, gender, body mass index (BMI), inflammatory bowel disease (IBD) status, comorbidities, immunosuppressive medications, smoking status), fistula characteristics (location, height, recurrence, number of fistulas) interventions compared (surgeon expertise, testing of the fistula repair, length of follow-up, type of mesh used, mesh overlap, type of suture used, perioperative antibiotics, redo operation, duration of seton kept in situ preoperatively) and outcome data (primary healing rates, secondary healing rates, complications). Binary outcomes will be collected as n (%) and continuous outcomes will be collected as mean (SD).

Covariates thought to be associated with treatment success or failure will also be collected. These include complexity of the fistula such as location, high (>30% of external sphincter) versus low fistula, recurrent fistula and multiple fistulas. Covariates also include patient factors such as BMI, IBD, immunosuppressive medications, medical comorbidities, smoking status, previous radiation, previous perianal procedures and baseline incontinence. We will also collect data on non-cryptoglandular fistulas such as those related to IBD, tuberculosis and malignancy but will not be included in covariate analysis. Authors of included studies will be contacted for any necessary clarifications.

Risk of bias assessment

The Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) criteria will be used to assess the risk of bias of included studies.[20] The ROBINS-I tool is a validated bias assessment for non-randomised studies. Comparative studies are evaluated on seven distinct domains with signalling questions for each domain to assist with identification of bias. Judgements within each domain are then carried forward to an overall risk of bias judgement for the outcome being assessed. The risk of bias for any randomised trials will be evaluated using the revised Cochrane Risk of Bias tool for randomised trials (RoB 2.0).[21] The RoB 2.0 tool consists of five domains with signalling questions and addresses potential bias from the randomisation process, intended interventions, missing outcomes, measurements of the outcome and selection bias. Two authors (SHA and RH) will complete risk of bias assessments using the aforementioned tools. Disagreements will be settled by a third-party reviewer (RPM). Sensitivity analysis based on high methodological quality studies will be performed. Quality of evidence for each outcome will be evaluated using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria which includes risk of bias, inconsistency, indirectness, imprecision and publication bias.[22] A summary of findings will be created using GRADEPro version 3.6 (GRADE Working Group).[23]

Data synthesis and statistical analysis

The literature search for this review may identify both comparative studies and single group studies, the latter of which will be focused on reporting experience with the application of the LIFT or BioLIFT procedure; in the planned review, the former will be assessed and analysed separately from the latter. Clinical and methodological heterogeneity will be assessed by the research team for the set of included studies to establish their degree of similarity in terms of patient populations and study methods. If multiple comparative studies are identified that directly compared (ie, simultaneously collected and compared endpoints) LIFT and BioLIFT procedures, whether prospective or retrospective, a meta-analysis will be performed using a random-effects, inverse variance approach. For groups of studies presenting single arm study data related to outcomes of interest for either the LIFT or BioLIFT procedure, separate sets of single group, random effects meta-analyses will be performed to assess the evidence of benefits and harms for each intervention; narrative summaries of these findings will be prepared with the realisation that comparisons based on these data are weaker based on likely increased heterogeneity. Statistical heterogeneity will be assessed for meta-analyses using the I^2 statistic, with a value of 50% or higher suggesting the presence of important heterogeneity. Forest plots will be presented for all syntheses, and pooled estimates will

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be removed from these plots in cases where the presence of high statistical heterogeneity cannot be addressed. In addition to primary analyses, subgroup and sensitivity analyses will also be explored in relation to complex fistula characteristics, patients who have undergone a previous LIFT, and fistulas associated with IBD.

Patient and public involvement

None.

Ethics and dissemination

This systematic review and meta-analysis does not require research ethics board approval. This study will be completed in September 2022. The findings and discussions of this study will be disseminated through peer-reviewed national and international conferences and journals. This study will identify the evidence base available for comparisons between outcomes for BioLIFT and LIFT or the lack thereof which may warrant further research in this field.

DISCUSSION

Identifying the optimal surgical option to treat anal fistula continues to be difficult. The ideal treatment provides healing, has a low recurrence rate, and carries only minimal risk of incontinence. Since the LIFT procedure was first described in 2007, reported healing rates have ranged between 40% and 94%. A recent 2019 systematic review and meta-analysis of LIFT outcomes identified 26 studies totalling 1378 patients and a weighted mean success rate of 76.5%.[8] Only two studies were randomised controlled trials. Likewise, healing rates for the BioLIFT procedure have ranged between 63% and 94% in individual studies, most of which are case series.[13 15 16] To our knowledge, this study would be the first systematic review comparing healing rates of BioLIFT versus LIFT.

Anticipated challenges include pooling data between studies with considerable heterogeneity. According to a recent Core Outcome Measurement in Effectiveness Trials systematic review for the treatment of anal fistula, substantial heterogeneity was found in defining outcomes.[24] Thus our review will attempt to minimise any variation in outcomes by defining them in the methods. In addition, the possibility of overlooking a clinically significant outcome is low given we have reviewed the most frequently reported outcomes in the aforementioned study to ensure that our review captures all clinically significant outcomes. If a clinically significant difference exists between the two procedures, the results of this review and meta-analysis could lead to practice changes in the management of anal fistula. If there is a paucity of evidence, it will push for the need for future investigations.

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Contributors SHA, RH, RG and RPM are responsible for aiding in the conception of this work, drafting and revising the manuscript and are accountable for all aspects of this work. TZ, HM, IR, LW, RPB, MF are responsible for aiding in the conception of this work, revising the manuscript, and approving the final and submitted version, and provide accountability in all aspects of this work. TZ, HM, IR, LW, RPM, RPB and MF are all colorectal surgeons who also provided their content expertise. RPM is the guarantor of the protocol.

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