

Effectiveness of Low-temperature plasma tonsillectomy for chronic tonsillitis.

A protocol of systematic review and meta-analysis



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AIM: Recurrent episodes of chronic tonsillitis (CT) can affect a patient's quality of life, physical and mental health. Clinicians often perform surgeries to remove them. Traditional surgical methods are varied, despite their advantages. However, this remains controversial. This study aimed to examine both the safety and efficacy of low-temperature plasma tonsillectomy (LTPT) in treatment of chronic tonsillitis, which may provide a substitute for clinicians and compensate for the short supply of therapeutic procedures.

METHODS AND ANALYSIS: This protocol is guided by the Preferred Reporting Items for Systematic.

REVIEW AND META-ANALYSIS: Protocols (PRISMA-P) and by the Cochrane Collaboration Handbook. We will formulate strict inclusion and exclusion criteria in English databases (PubMed, EMBASE, and Web of Science) and search literature in different clinical registration platforms (Cochrane Library). The including articles were evaluated by the Cochrane RCT evaluation criteria. The primary main endpoints will include the duration of operation, blood loss during surgery, time of formation and exfoliation of the pseudomembrane, average pain and duration post-operation, and time for normal diet. The Secondary endpoints will include complications of postoperative bleeding and infection. Stata 15.0 will be used for data analysis. Subgroup analysis, sensitivity analysis, and meta-regression were used to detect the sources of heterogeneity. Begg's Test will quantitatively detect publication bias quantitatively.

ETHICS AND DISSEMINATION: The results of this meta-analysis and meta-regression will be disseminated through publication in a peer-reviewed journal. The data used in this meta-analysis will not contain individual patient data; therefore, ethical approval is not required.

KEY WORDS: Chronic tonsillitis, Low-temperature plasma tonsillectomy, Meta-analysis, Protocol, Systematic review

Introduction

Chronic tonsillitis (CT) is caused by recurrent acute tonsillitis, poor drainage of the palatine tonsillitis recess, bacterial and viral residual infection in the crypt, and repeated stimulation to form chronic inflammation, which is common in children and is one of the most common

diseases in clinics¹. A prolonged inflammatory reaction can lead to pharynx discomfort, limb weakness, low fever, fatigue and other systemic manifestations². If the tonsils become obviously enlarged, it can affect breathing, swallowing, sleep disorders, growth development, etc.³⁻⁶ If the disease is serious, it can also lead to systemic diseases, such as rheumatic fever, acute arthritis, myocarditis and nephritis⁷⁻⁹. It seriously affects the quality of life, physical and mental health of patients, and places a heavy burden on family and society^{4,10-13}.

Tonsillectomy is the main method to treat recurrent CT and is one of the routine operations in otolaryngology.^{1,6} In the United States, at least 530,000 children under the age of 15 have tonsillectomies every year³.

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ABBREVIATIONS

CT: Chronic Tonsillitis

LTPT: Low-Temperature Plasma Tonsillectomy

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

The methods include tonsil exfoliation, coblation therapy, electrocautery, carbon dioxide laser resection, bipolar, high-frequency electric knife, ultrasonic knife, etc.^{4,14-16}. Despite their advantages, they remain controversial for a number of reasons, such as big surgical trauma, excessive bleeding, obvious postoperative pain, secondary infection and bleeding, etc.^{15,17,19}. Serious cases even cause irreversible damage to surrounding tissues which is not conducive to functional recovery^{20,21}. Therefore, clinical application has certain limitations.

With the development of medical technology, LTPT, as a minimally invasive surgery has been gradually applied in clinical practice. Compared with traditional operations, LTPT has definite curative effects, such as simple operation, clear anatomical structure, less trauma and bleeding, mild postoperative pain, less damage to peripheral tissues and rapid recovery^{1,4,22}. The principle of LTPT is to use radio frequency plasma electromagnetic radiation to decompose the diseased tissue at low temperature, promote vaporization of the cut part, make the tissue protein solidify rapidly, tissue cell collapse, blood vessel constriction and closure, but only 1-2 mm deep, only plays the role of destruction and separation of the tissue mucous membrane, while the vessels and surrounding tissue will not be affected²³. While ensuring safe operation, it has the advantages of reducing postoperative pain, reducing time of pain and normal diet, speeding up postoperative recovery and lowering the risk of complications^{4,17,22,24-26} which has a strong advantage and is an effective substitute for traditional surgical instruments²⁷. However, there are limitations due to the limited scope of the study and the small sample size. Evidence-based medicine is therefore needed to provide strong evidence of its efficacy.

This meta-analysis aims to provide some possible evidence for the efficacy of LTPT in the treatment of chronic tonsillitis, thus providing an alternative treatment regimen for patients with chronic tonsillitis and making up for deficiencies in conventional tonsillectomy for chronic tonsillitis.

Materials and Method

This meta-analysis will be conducted under the PRISMA-P and the Cochrane Collaboration Handbook and has been registered on the OSF (registration number:

DOI 10. 17605/ OSF.IO/ RWBAE). The search strategies, inclusion criteria, exclusion criteria, article quality assessment methods, data extraction and analysis strategies were jointly developed by all the authors.

SEARCH STRATEGY

The English databases (PubMed, Embase, and Web of Science), clinical registration platforms that comprise (Cochrane Library) will be searched independently by the two authors. Moreover, English terms included “chronic tonsillitis”, “Tonsillitis”, “recurrent tonsillitis”, “amygdalitis”, “antiaditis”, “tonsillectomy” or “Low-temperature plasma tonsillectomy”, “Low temperature plasma”, “cold plasmas”, “Coblation”, etc, while search time spans from the creation of database until December 30, 2020. Additionally, the Boolean algorithm is applied as a search formula to search for full-text articles along with subject terms and free words. Therefore, the search formula is given next: (“chronic tonsillitis” or “Tonsillitis” or “recurrent tonsillitis” or “amygdalitis” or “antiaditis” or “tonsillectomy”) AND (“Low-temperature plasma tonsillectomy” or “low temperature plasma radiofrequency ablation” or “Low-temperature plasma” or “cold plasmas” or “Coblation”) AND (“randomized clinical trial” OR “randomized controlled trial” OR “trial” OR “clinical trial”).

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria: (1) The patients who are diagnosed with “chronic tonsillitis” are included in this study irrespective of their race, age, and gender; (2) The intervention in the experimental group is low temperature plasma tonsillectomy; (3) The intervention of the control group was a traditional operation; (4) Reported at least one of the following outcomes: duration of operation, blood loss during surgery, time of formation and exfoliation of the pseudomembrane, average pain and duration post-operation, and time for normal diet, the complications of postoperative bleeding and infection; (5) The study type was a randomized controlled study. Exclusion criteria: (1) Patients who carry chronic tonsillitis along with other diseases will be omitted; (2) When selecting articles, they will be excluded if abstracts, letters, case reports, reviews, or non-clinical studies were selected; (3) Articles possessing reproduced data will also be ruled out.

ARTICLE RETRIEVAL PROCESS

First, the stringent screening of literature will be conducted by two of the authors independently by following the flowchart depicted below (Fig. 1). After that,

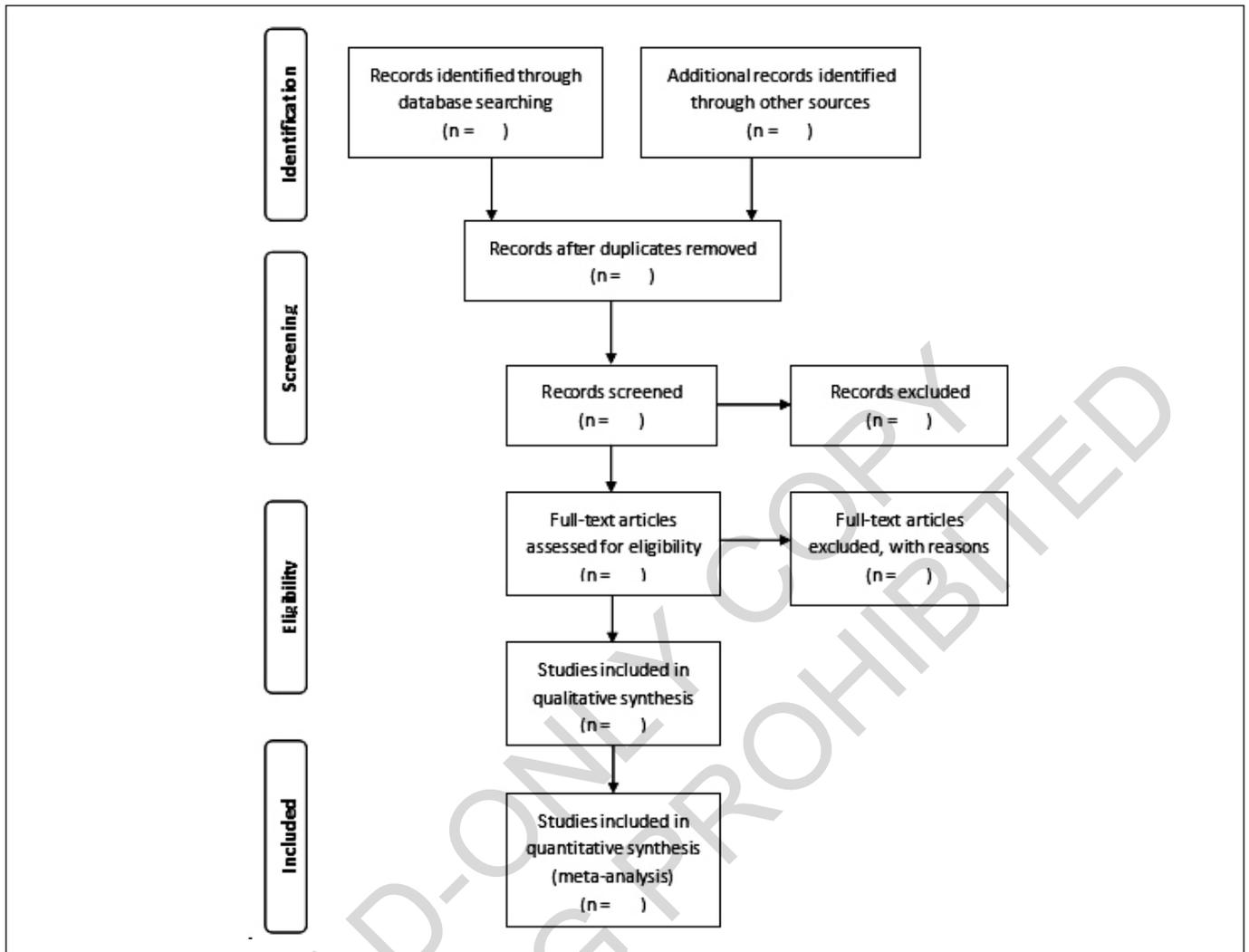


Fig. 1: Flow diagram of the identification and selection studies.

data analysis was performed on all the selected articles. Furthermore, in case of disagreement in the course of the screening process, the final decision regarding inclusion or exclusion will be made by the intervention of a third author after discussion.

DATA EXTRACTION

Two of the authors independently evaluated and extracted all candidate articles. In case of disagreement, a third author after discussion with the first two authors reached a consensus.

Furthermore, an Excel document will be used to record information from each of the articles, which encompasses the first author along with the year of publication, the country of publication, the total number of cases and gender, follow-ups, treatment and control strategies, etc. (Table I).

THE MAIN ENDPOINTS

The primary main endpoints will include the duration of operation, blood loss during surgery, time of formation and exfoliation of the pseudomembrane, average pain and duration post-operation, and time for normal diet. The Secondary endpoints will include complications of postoperative bleeding and infection.

QUALITY ASSESSMENT OF THE STUDIES

We will evaluate the quality of the articles included in this study according to the Cochrane Collaboration Handbook. It has six parts which are named: Sequence Generation, Allocation Concealment, Blinding, Incomplete outcome data, No selective outcome reporting, Other sources of bias; with “yes,” “no,” and

TABLE I - Main characteristics of the studies included in the meta-analysis.

Index	Note
Included full-text article	Authors, publication year
Country of publication	Country
Design	Study type
Gender	Male/ female (number in each group)
Age	Age in each group (SD or max/min)
Interventions	Type of therapy for each group
Duration of operation	duration of operation in each group
Blood loss during surgery	The average of blood loss during surgery in each group
Time of formation of pseudomembrane	The average time of formation of pseudomembrane in each group
Time of exfoliation of pseudomembrane	The average time of exfoliation of pseudomembrane in each group
Average pain and duration postoperation and time for normal diet	average pain and duration postoperation and time for normal diet in each group
Adverse events	adverse events in each group
Follow-up	Follow-up time period of postoperation

“unclear” as evaluation results. The quality of the selected articles was evaluated by two independent authors using RevMan software. If there is a difference of opinion, a third author will participate in the discussion and the quality of the article will be determined. The final quality assessment results are presented in graphic form.

DATA ANALYSIS

The chief information regarding selected articles along with any pertinent question (s) will be summarized by the authors in line with the aim of this systematic review through (Table I), which encompasses the type of study along with procedures and population description in addition to pertinent issues that have a connection with the outcomes. Furthermore, a meta-analysis could be performed after data extraction only if the number of full-text articles opted for was not fewer than seven.

Therefore, the meta-analysis will probably be executed by employing Stata15.0, to compute pooled effect size (ES) bearing an estimate of 95% CI. Additionally, heterogeneity test along with subgroup analysis in addition to sensitivity analysis, apart from publication bias, as well as meta-regression will also be carried out in case of availability of sufficient articles.

HETEROGENEITY TEST

We undertook Cochrane’s Q test in addition to Higgins I-squared statistic to gauge the heterogeneity of the tri-

als. Moreover, A $P < 10$ or $I^2 > 50\%$ was considered to indicate significant heterogeneity. Random-effects model or fixed-effects model was used to pool the data according to the statistical heterogeneity by the chi-squared test (I^2 values of $<25\%$, $50\%-75\%$ and $> 75\%$ were considered to represent low, moderate and severe statistical inconsistency).

In addition, the origin of heterogeneity was analyzed by applying subgroup analysis along with sensitivity analysis in addition meta-regression. Similarly, RR and WMD/SMD were used as the effect sizes of the binary variables and continuous variables respectively.

SUBGROUP ANALYSIS

In order to analyze the subgroup, we will compare clinical characteristics, including article quality score, age, duration of LTPT, and follow-up time period. Moreover, after completing subgroup analysis by following some clinical features, it is indicated that the feature may be responsible for heterogeneity because each group has complete homogeneity but collectively they are heterogeneous.

SENSITIVITY ANALYSIS

Among the two methods employed for sensitivity analysis, one is applied to alter the analysis model, while the other is applied to exclude articles in succession. Furthermore, an analysis model is selected based on I^2 value. Similarly, the random-effect model was applied if the I^2 was greater than 50%, however, a fixed-effect model was applied when I^2 value was less than 50%. Moreover, the article can be deemed as the source of heterogeneity if its removal leads to variation in heterogeneity in the course of the sequential elimination of articles.

META-REGRESSION

When performing meta-regression analysis, age, duration of LTPT, follow-up time period, etc. can be used as covariates to determine the sources of heterogeneity. If $P < 0.05$, it indicates that the covariates are sources of heterogeneity.

PUBLICATION BIAS

In the case of ≥ 10 articles, quantitative publication bias can be detected by employing Begg’s Test. $P > 0.05$, indicating the absence of publication bias. However, $P < 0.05$, indicates publication bias.

Discussion

Surgery is chronic tonsillitis preferred way after invalid conservative treatment, although conventional tonsillectomy can remove tonsils, but as a result of the tonsils blood supply is rich, easy bleeding during operation, leads to unclear the anatomical structure and all kinds of complications are easy to appear during and after the operation. Therefore, there is an urgent need to seek a safe and less damaged treatment.

LTPT can effectively remove the tonsils, and its thermogenic effect can denature collagen and coat the tonsils, avoiding inflammatory mediators to stimulate nerve endings^{23,27} to protect the wound better. LTPT has small thermal damage to the surrounding tissues of the tonsils, postoperative tissue edema, less bleeding and infection risk²⁸. The traditional operation is time-consuming, blood loss is more, trauma is bigger, postoperative recovery is slow^{29,30}. Compared with the traditional method, LTPT has less postoperative pain and better prognosis, can increase the time of formation and exfoliation of the pseudomembrane and reduce postoperative bleeding^{22,31-32}. This study showed that in patients who used LTPT, the time of duration of operation, average pain and duration post-operation, and time for normal diet was shortened. The time of formation and exfoliation of the pseudomembrane increased. The blood loss during surgery reduced. The incidence of complications of postoperative bleeding and infection was reduced. Therefore, this appears to provide a new approach for treating chronic tonsillitis, but it lacks strong evidence for further study. At present, the disadvantage of low temperature plasma tonsillectomy is that it may cause delayed hemorrhage due to prolonged time of formation and exfoliation of the pseudomembrane, so diet nursing was necessary³². This study is expected to provide the following results: First, the effectiveness of LTPT, operating time, blood loss during surgery, time of complete formation of the false membrane, time of fall off the false membrane, time of average pain and return to normal diet will be used to evaluate the effectiveness of treatment. Second, safety of the method was evaluated according to quality of life of the patients and the number of adverse events. In addition, in the process of analysis, some deficiencies may be found in the experimental design of low-temperature plasma tonsillectomy treatment, so as to provide some ideas for follow-up study.

Riassunto

Episodi acuti ricorrenti su tonsillite cronica (TC) possono influenzare la qualità della vita, la salute fisica e mentale del paziente. I medici spesso eseguono interventi chirurgici per eliminarli. I metodi chirurgici tradizionali sono vari, nonostante i loro vantaggi, e sono controversi. Questo studio mirava a esaminare sia la sicurezza che

l'efficacia della tonsillectomia al plasma a bassa temperatura (LTPT) nel trattamento della tonsillite cronica, che può fornire una alternativa per i medici e compensare la scarsità di scelta delle procedure terapeutiche.

Il protocollo di studio è fondato su Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) e dal Cochrane Collaboration Handbook. Formuleremo rigorosi criteri di inclusione ed esclusione nei database inglesi (PubMed, EMBASE e Web of Science) e ricercheremo la letteratura in diverse piattaforme di registrazione clinica (Cochrane Library). Gli articoli inclusi sono stati valutati secondo i criteri di valutazione Cochrane RCT.

Gli endpoint principali includeranno la durata dell'operazione, la perdita di sangue durante l'intervento chirurgico, il tempo di formazione ed esfoliazione della pseudomembrana, il dolore medio e la durata della convalescenza post-operatoria e il tempo di ritorno ad una dieta normale. Gli endpoint secondari includeranno le complicanze del sanguinamento postoperatorio e dell'infezione. Stata 15.0 verrà utilizzato per l'analisi dei dati. L'analisi dei sottogruppi, l'analisi di sensibilità e la meta-regressione sono state utilizzate per rilevare le fonti di eterogeneità. Il test di Begg rileverà quantitativamente il bias di pubblicazione.

Etica e diffusione: i risultati di questa meta-analisi e meta-regressione saranno diffusi attraverso la pubblicazione in una rivista peer-reviewed. I dati utilizzati in questa meta-analisi non conterranno i dati dei singoli pazienti; pertanto, non è richiesta l'approvazione etica.

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