Multicentre clinical study of haemorrhage after coblation tonsillectomy in children: a prospective study protocol

Hongming Xu,1 Shuyao Qiu,2 Shilei Pu,1 Bin Hu,1 Dabo Liu,2 Xiaoyan Li1

ABSTRACT

Introduction Post-tonsillectomy haemorrhage (PTH) is the most common and significant life-threatening complication following tonsillectomy, especially in children. Coblation tonsillectomy (CTE) at low temperature is extensively used in China and has gradually replaced conventional tonsil dissection. However, risk of late PTH has been shown to increase with the use of hot instruments. The aim of this study is to detect post-CTE haemorrhage (PCTH) rates and analyse risk factors of PCTH in China, through a nationwide multicentre prospective study.

Methods and analysis This investigator-initiated, prospective, multicentre clinical trial will involve children with tonsil disease who will undergo CTE from 22 research centres in different cities in China. All operations will be performed using the same technique of extracapsular tonsillectomy. Data will be collected for all patients enrolled in this study through a preoperative visit, intraoperative data and a postoperative visit. The measurement data conforming to a normal distribution will be expressed by means±SDs, and a Student’s t-test will be used for comparison. Non-conditioned logistic regression analysis will be used to analyse the preoperative, intraoperative and postoperative risk factors for haemorrhage rate after CTE. P<0.05 will be considered statistically significant.

Ethics and dissemination This study protocol was approved by the Ethics Committee of Shanghai Children’s Hospital/Shanghai Jiao Tong University (reference number 2021R096-E01). All patients will provide written informed consent. Results of this study are to be published in respected, peer-reviewed journals and findings presented at scientific conferences in the field of paediatric otolaryngology.

Trial registration number NCT05206799.

INTRODUCTION

Tonsillectomies are one of the most frequently performed surgical procedures in otolaryngology to resolve upper airway obstruction and recurrent or chronic throat infections, and to manage recurrent childhood ear disease. Despite numerous efforts, haemorrhage is the most common and significant complication following tonsillectomy.1,2 Post-tonsillectomy haemorrhage (PTH) is not rare, ranging from 1.5% to 20%, and is a potentially life-threatening complication, especially in children.3

There are many proven methods of tonsillectomy, including cold knife dissection, laser, guillotine, bipolar and unipolar electrosurgery, and most recently described, coblation. Coblation tonsillectomy (CTE) at low temperature has gradually replaced conventional tonsil dissection, and is extensively used in China.4 The main advantages of the coblation technique are shorter operation times and low perioperative blood loss.5 However, the risk of late PTH has been shown to increase with the use of hot instruments.6

The aim of this study is to detect post-CTE haemorrhage (PCTH) rates and analyse risk factors of PCTH in China, through a nationwide multicentre prospective study.

METHODS AND ANALYSIS

Patient and public involvement Patients and the public will be involved in the design, conduct, reporting and dissemination of this research.
Trial design
This study is an investigator-initiated, multicentre prospective observational cohort study of the haemorrhage rate and risk factors after CTE in children (figure 1—study flow chart). The study started on 15 January 2022 and is scheduled to end on 14 January 2024. The study will be conducted in accordance with ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Shanghai Children’s Hospital, Shanghai Jiao Tong University, which is the study initiator. Each clinical centre will obtain their own ethics approval by their respective committees. Before the study starts, written informed consent forms will be obtained from patients willing to participate in the study and will be approved by the institutional review board/independent ethics committee of Shanghai Children’s Hospital, Shanghai Jiao Tong University (2021R096-E01). The protocol of the trial has been registered at http://clinicaltrials.gov (NCT05206799).

Study objectives
The primary objective of this study is to obtain haemorrhage rates after CTE in children of the Chinese population. The major secondary objective is to research haemorrhage risk factors after CTE in Chinese children.

Study population
Children with tonsil disease who will undergo CTE from 22 research centres in different cities will be screened, during the study period. The participants will have to agree on the following requirements: (1) the indication of tonsillectomy, according to clinical practice guidelines for standardised low-temperature plasma radiofrequency ablation tonsillectomy and adenoidectomy in children; (2) complete history collection and preoperative examination; (3) age over 0 years but less than or equal to 18 years. Exclusion criteria are: (a) children with a history of adenoid or tonsillectomy; (b) association with refractory bleeding diseases; (c) cleft palate; (d) Down syndrome, Prader-Willi syndrome or other chromosomal abnormalities; (e) neuromuscular diseases (including cerebral palsy); (f) other medical conditions making the patient medically unstable for surgery; (g) contraindications of surgery and anaesthesia; (h) inability to obtain informed consent.

Data collection
Data will be collected at individual centres with online case record forms based on an Electronic Data Capture (EDC) system for every patient recruited. All subcentres have access to the EDC system for data entry through the internet. Access to the data entry system will be protected by a username and password delivered during the registration process. All participants’ names will be displayed in the EDC system using initials. Data managers of each centre can find basic information of participants to follow up; however, this information will not be disclosed to all centres.

The main risk factors that may affect haemorrhage rates after CTE will be collected in this study. Risk factors due to the patient’s own condition include, gender, age, body mass index, education status of the primary guardian, date of symptoms onset, parameters of polysomnography, concomitant symptoms other than sleep disorders, history of other systemic diseases, tonsil size, adenoid size, etc. Risk factors due to surgical intervention include surgery date, surgery time, intraoperative blood loss, use of suture haemostasis technique, use of medicine during anaesthesia, brand and model of plasma radiofrequency used in the operation, etc. Risk factors due to postoperative intervention measures include diet conditions after surgery, Use of medicine after surgery (painkillers, antibiotics, non-steroidal anti-inflammatory drugs, etc), symptoms of cough after surgery, fever after surgery, complete blood count parameters (if postoperative bleeding occurs), etc. Hence, risk factor variables for statistical analysis are estimated to be 25–30.

Each centre will maintain a secure trial file including a protocol, local investigator delegation log, ethics approval documentation, participant list, etc. A final summary printout of included patients with major variables will be produced for each centre together with the final data submission to double check for completeness and accuracy.

Preoperative patient visit and screening questionnaire
Patients who meet the inclusion criteria will be visited 1 day before surgery. Screening questionnaire (online supplemental file 1) information, including basic patient information, medical history, physical examination and laboratory results, will be collected and filled out by residents. A paper or electronic medical record of all the subjects will be checked by the visiting physician for complications history questions in the screening questionnaire. If medical history records are not available,
data will be recorded faithfully and be considered during statistical analysis.

**Operative details and outcome measures**

Bilateral CTE will be performed on an inpatient basis with general anaesthesia and endotracheal intubation. Surgeons will perform CTE using their preferred or available brand of coagulation equipment. All operations will be performed using the same technique of extracapsular tonsillectomy.

Non-steroidal non-aspirin anti-inflammatory analgesics will be used postoperatively if needed, during the hospital stay. In the case of constant postoperative fever (temperature of 38.0°C or higher, lasting for more than 4 hours) with bacterial infection, antibiotics will be given, always a β-lactam, either oral or intravenous administration, if not contraindicated. When started, the treatment will continue for 7 postoperative days.

Data will be collected for all patients enrolled in this study through a preoperative visit, intraoperative data and a postoperative visit. Preoperative visits will be made 24–48 hours before surgery. The inclusion and exclusion criteria will be reviewed, and informed consent will be signed on the day of the preoperative visit. Medical history, physical examination data, laboratory examination data and polysomnography data will be obtained on the day of preoperative visit. Medical history includes the presence and severity of snoring, open mouth breathing, nasal congestion, runny nose, sleepwalking, enuresis, somniloquy, rhinocesmus, occlusive nasal sound, attention disorder, and the presence and severity of recurrent tonsillitis. Physical examination information includes grading of adenoid hypertrophy (4-grade method) and tonsil hypertrophy (Brodsy’s method), and an assessment of adenoid facial appearance. Laboratory examination includes allergen serology and coagulation test results. Polysomnography data include OAIHI (Obstructive apnea hypopnea index), LSao2 (%) (Lowest oxygen saturation) and Sato2 (Oxygen saturation) <90% duration (min).

Intraoperative data will be collected on the day of surgery and recorded in the EDC system of this clinical study within 24 hours after the surgery. These data include surgery date, start and end time of operation, the doctor’s name and practising period (number of tonsillectomy cases that have been performed), intraoperative blood loss, adenoidectomy status, suture haemostatic status, glucocorticoids status during anaesthesia, haemostatic status during anaesthesia, and the brand and model of coagulation equipment used.

If the subject did not experience postoperative bleeding, a postoperative visit was performed on day 21 (±1 day). Observations included whether or not the patient was eating semifliud (includes porridge, flour, noodles), whether or not the patient was participating in strenuous exercise (competitive sports, such as running, playing ball, swimming, etc, excluding normal walking and daily activities), symptoms of cough, haemostasis, intravenous hormone use, intravenous antibiotic use, painkiller use and number of postoperative fevers. The type, frequency and dose of postoperative medication will also be recorded. Postoperative visits (occurrence of postoperative bleeding) also include emergency observation, readmission, frequency of admission, use of compression for haemostasis, blood routine and coagulation function test results, and bleeding grading (Windfuhr five-level method).

- Grade 1 was any postoperative haemorrhage with a spontaneous cessation, where ice packing was administered and sufficient.
- Grade 2 bleeding needed further treatment under local anaesthesia. This was either by infiltration of 1:250,000 epinephrine containing 1% lidocaine, or additional bipolar coagulation.
- Grade 3 bleeding needed suture ligation under general anaesthesia was necessary. In cases with diffuse bleeding, the tonsillar pillars were sutured.
- Grade 4 bleeding patients who had been returned to the operating room for persistent or excessive bleeding, in whom local measures to control bleeding had failed, or shock was imminent from continued blood loss, or ligation of the external carotid artery was mandatory.
- Grade 5 bleeding was any postoperative haemorrhage with lethal outcome regardless of what treatments had been carried out.

Postoperative haemorrhages were classified either as primary (within 24 hours of the operation) or secondary (24 hours postoperatively).

**Sample size**

The sample size will depend on the number of centres recruited and their respective caseloads. Each centre will also complete a screening of all eligible patients during the study.

With 25–30 variables potentially associated with bleeding rates after tonsillectomy in children, mentioned in the Data collection section, the minimum sample size required is approximately 250–300 bleeding patients to avoid violating the principle of approximately 10 outcome events (ie, bleeding) per variable in the regression. According to reports in the literature on the incidence of PTH, a lower incidence of 1.5% was chosen as the estimated incidence of PTH to ensure adequate enrolment of patients with postoperative bleeding. Therefore, the total number of participants required is 20,000. Given the rate of loss to follow-up, 25,000 participants will be recruited. The sample size has been determined with the guidance of professional statisticians from the Clinic Research Unit of Shanghai Children’s Hospital. The case collection system was established in January 2022, and the database will be locked once the sample size is reached.

**Statistical analysis**

All institutional-level data will be anonymised prior to publication. Categorical variables will be described as counts and proportions, which will be compared using X²
tests. Continuous variables will be described as means and SDs if normally distributed, or medians and IQRs if not normally distributed. Comparisons of continuous variables between groups will be performed using t-tests, one-way analysis of variance or an equivalent non-parametric test as appropriate. Univariate analysis will be performed to test factors associated with PCTH. Single-level and hierarchical multilevel logistic regression models will be constructed to identify factors independently associated with these outcomes and to adjust for differences in confounding factors. Factors will be entered into models.

**Current status**

The study has been approved by the Ethics Committee of Shanghai Children’s Hospital, Shanghai Jiao Tong University. A project kick-off meeting has been held for 22 clinical research centres. Subjects have been recruited since 15 January 2022. Three research centres are now recruiting subjects.

**DISCUSSION**

Tonsillar surgery was recorded in the first century AD, with complications and bleeding that have been greatly reduced in the 20th century. The earliest adenoid surgery was performed in the 1860s by Hans Wilhelm Meyer, a Danish doctor. The 1990s ushered in a new era of adenoid surgery under direct vision. In the 21st century, tonsillar and adenoid resection methods such as laser, microbotomy, bipolar cautery and ultrasonic coblation based on the stripping principle have been popularised. Coblation has been widely used for tonsillectomy for more than 10 years in China because it provides a bloodless surgical field for operators and reduces intraoperative bleeding without frequent replacement of surgical instruments. However, there is still a certain probability of postoperative bleeding, infection and other complications reported in the literature.

There are several reports which provide evidence for an increased secondary haemorrhage with CTE. Windfuhr et al.\(^\text{26}\) reported a high rate of return (9.5%) to surgery for controlling haemorrhage following CTE. Divi and Benninger\(^\text{27}\) reported a secondary haemorrhage rate of 5.4% in their retrospective study for CTE. Javed et al.\(^\text{28}\) reported a high incidence of secondary haemorrhage following CTE; they compared coblation with the cold steel method and reported that 9.1% of patients needed surgical intervention to control secondary haemorrhage. However, Belloso et al.\(^\text{29}\) showed that coblation for tonsil dissection offers significant advantages in the postoperative period compared with dissection tonsillectomy with bipolar diathermy haemostasis. CTE is associated with a lesser incidence of delayed haemorrhage that is more significant in children. A study in which surgery was performed by a single surgeon showed the PTH rate was 5.0% for cold steel and 5.8% for CTE—like previous results.\(^\text{30}\) Several other studies, including a meta-analysis, did not show the superiority of cold steel surgery over coblation surgery in terms of PTH, either.\(^\text{31}\)\(^\text{32}\) A comparison between diathermy tonsillectomies and CTEs also revealed inconsistent results. The National Prospective Tonsillectomy Audit showed that coblation was better than monopolar diathermy and comparable with bipolar diathermy in PTH.\(^\text{33}\) In a study of over 17,000 procedures, coblation alone was not associated with a higher PTH rate as compared with other techniques. The patient’s personal condition may also be related to postoperative bleeding.\(^\text{34}\) It is necessary to obtain postoperative haemorrhage data of CTE via a nationwide clinical study, with wide application of CTE in China. Little literature that reports about how the use of different coblation equipment affects postoperative tonsillectomy haemorrhage rates exists. Therefore, surgeons will be allowed to use their preferred or available brand of coblation equipment. Differences between different equipment groups will also be compared.

Inuzuka et al.\(^\text{35}\) analysed 325 adult patients and found smoking status and sex to be significant risk factors of PTH in adults. Kshirsagar et al.\(^\text{36}\) reviewed 138,998 procedures performed on adolescents from 2005 to 2011. Haemorrhage occurred in 156 cases (0.1%) and was associated with age and obesity. Multivariate analysis revealed that haemorrhage was about 2.3 times more likely to occur in obese children. There was no association between haemorrhage and gender. However, Ordemann et al.\(^\text{37}\) analysed 1418 patients under the age of 15 years who underwent tonsillectomy with or without adenoidectomy and found no correlation between weight-for-age percentile and occurrence of PTH. Mudd et al.\(^\text{38}\) reviewed 6710 children who underwent tonsillectomy.\(^\text{10}\) A total of 222 children required surgical control of PTH.

Some studies believe that postoperative bleeding is related to the experience of the operator. Carney et al.\(^\text{39}\) found that there was a significant learning curve with respect to both primary and secondary haemorrhage rates. Previous studies have reached similar conclusions.\(^\text{40}\) However, Manimaran et al.\(^\text{41}\) analysed 1284 patients who underwent tonsillectomy with or without adenoidectomy and found reactionary haemorrhage after tonsillectomy was similar in procedures performed by trainees and consultants. Praveen et al.\(^\text{42}\) found a high incidence of secondary haemorrhage in CTE performed by experienced consultant surgeons compared with middle-grade surgeons.

Perioperative medication may also be associated with postoperative bleeding. Diercks et al.\(^\text{43}\) analysed 741 children; the rate of bleeding requiring operative intervention was 1.2% in the acetaminophen group and 2.9% in the ibuprofen group. A review from the Cochrane Collaboration that included 1100 children in 15 studies found that non-steroidal anti-inflammatory drugs did not significantly increase the risk of bleeding as compared with placebo or other analgesics, did not significantly alter the number of perioperative bleeding events requiring non-surgical intervention and resulted in less vomiting.\(^\text{16}\)
Frielich et al reported that dexamethasone (0.15 mg/kg) significantly reduced the incidence of postoperative nausea and vomiting without increasing the risk of postoperative haemorrhage. Junaid et al reported that regular use of antibiotics in post-tonsillectomy patients does not prevent or reduce postoperative complications.

Environmental factors may also be associated with postoperative bleeding. Račić et al found a significant correlation between increased primary PTH rates and operative haemorrhage. Junaid reported that regular postoperative bleeding. Račić et al found a significant correlation between increased primary PTH rates and operative haemorrhage. Junaid reported that regular

Though many studies have been carried out on post-tonsillectomy, surgical results are inconsistent. Coblation is a new, minimally invasive technology that has been widely used in China only in recent years. So far, there are no large-scale studies in China about haemorrhage after CTE in children. The primary objective of the study is to obtain haemorrhage rates after CTE in Chinese population. The major secondary objective is to research haemorrhage risk factors after CTE in Chinese children.

Ethics and dissemination

This research will not increase the risk or economic burden of patients and the patients’ rights will be fully protected. The study will be conducted in accordance with the ethical principles of the Shanghai Children’s Hospital. The study protocol was approved by the Ethics Committee of Shanghai Children’s Hospital/Shanghai Jiao Tong University (reference number 2021R096-E01). All patients will provide written informed consent. Results of this study are to be published in respected, peer-reviewed journals and findings presented at scientific conferences in the field of paediatric otolaryngology.

Acknowledgements

We thank our colleagues in all the clinical centres participating in this study.

Contributors

XL and DL participated in study design, statistical hypotheses and sample size calculation. HX and SP participated in manuscript preparation, sample size calculation, writing the protocol of preoperative patient visit and screening period questionnaire. SQ and BH were involved in manuscript preparation, writing the protocol of operative details and outcome measures.

Funding

This work was supported by the National Natural Science Foundation of China (grant number 82171121).

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Supplemental material

This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Xiaoyan Li http://orcid.org/0000-0003-3080-9321

REFERENCES