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Cold steel versus impedance-dependent tissue sealer tonsillectomy – a study protocol for a randomised controlled trial

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ABSTRACT

INTRODUCTION. Approximately 7,000 tonsillectomies are performed annually in Denmark on a benign basis. The cold steel surgical technique is the gold standard. The risk of post tonsillectomy bleeding (PTH) in a centre in Jutland is 7.9%. A new impedance-dependent tissue sealer (IDTS) device has been developed, with preliminary results showing a reduction in operation time, perioperative bleeding and post-operative risk of bleeding of 4.5%.

METHODS. A randomised, controlled, double-blinded multicentre trial of cold steel tonsillectomy versus IDTS will be performed on 1,250 patients. The main endpoint is PTH, perioperative bleeding, operation time and post-operative pain. The secondary outcomes are days until return to work, food intake, activity and quality of life. Included in the study are patients with indication for surgery weighing ≥ 16 kg, and excluded are patients with malignancy, bleeding disorders and unwillingness to participate in the study.

CONCLUSIONS. To our knowledge, the present study is the largest randomised controlled trial in ENT surgery in the Nordic countries. The study will potentially provide evidence on PTH regarding two tonsillectomy methods.

FUNDING. The authors have no potential conflicts of interest to declare. The study is supplied with instruments from Medtronic needed for the surgical procedures. Furthermore, a minor part of the funding of the entire project is provided by the aforementioned company. The funding providers have no role in design or conduct of the study.

TRIAL REGISTRATION. Clinicaltrials.gov with the identification number NCT05270109.

Tonsillectomy, with or without adenoidectomy, performed on children and adults alike, is one of the most frequent surgical procedures in the ear, nose and throat (ENT) specialty worldwide, and the number of operations has increased in recent decades [1-5]. In Denmark, approximately 7,000 operations are performed annually [6], based on benign indications such as recurrent episodes of acute tonsillitis and upper airway obstruction due to adeno-tonsillar hypertrophy [7].

Tonsillectomy is associated with significant morbidity [3], such as post-operative pain and, more severely, post-tonsillectomy haemorrhage (PTH) [7-12]. Post-operative pain pertains for approximately two weeks and may, in

severe cases, result in delayed discharge or readmission for pain control, hydration and possibly treatment of underlying infection [3]. The incidence of PTH varies between 0.3 and more than 10% [1, 11, 13, 14] and is a major and potentially life-threatening complication of tonsil surgery [3, 8].

Because the evidence base for tonsil surgeries in Denmark is low, the Danish National Clinical Guideline from 2019 [15] recommends securing the monitoring of tonsil surgeries via uniform registration of procedures and diagnoses in Denmark. Further recommendations [15] include monitoring tonsil surgeries in a database by registering surgical method, extent of surgery (tonsillectomy versus tonsillotomy) and length of post-operative hospital stay, which is not properly described in Danish patients [15]. The criteria for offering patients tonsil surgery vary in Denmark, and the diagnostic criteria are not well-defined, especially for recurrent acute tonsillitis and chronic tonsillitis [15]. Furthermore, variation exists in the applied surgical techniques especially with respect to which instruments are used for the removal. The data needed to clarify the optimal choices in these cases may be obtained from properly designed clinical databases [16].

The Danish Tonsil Database is a population-based clinical database established in 2017 in the Central Denmark Region. It is a copy of the concept underlying The National Tonsil Surgery Register in Sweden, which was founded in 1997 and covers more than 80% of all tonsil surgeries performed in Sweden. Several retrospective studies based on data from the Swedish register have been published [8, 17].

As from 2021, ENT departments of the Region of Southern Denmark and the North Denmark Region have entered collaborative efforts to establish a Danish tonsil database. The database contains pre-, per- and post-operative information about tonsil surgery, including surgical method and instruments.

Although cold steel tonsillectomy is considered the gold standard surgical technique, several hot techniques have been developed for tonsillectomy, including bipolar techniques, diathermy and coblation [2]. Hitherto, these hot instruments have not proven superior to the gold standard in terms of reducing PTH, and recommendations suggest that these hot techniques should be used with caution [2, 3, 5, 8, 18, 19]. In cold steel tonsillectomy, the peritonsillar space is dissected with metal instruments, and bleeding is typically controlled by compression or ligation.

Recently, a new impedance-dependent tissue sealer (IDTS) device (BiZact) was approved for all benign indications for tonsillectomy [20]. Preliminary results are promising in terms of a PTH rate of 4.5%, shortened operative time by a median 5.1 minutes (range: 1.5-26.5 minutes) and reduced intraoperative blood loss to 1-10 ml [20]. With the IDTS, the peritonsillar space is dissected and sealed in one step using adjustable energy from a ValleyLab FT10 Energy Platform (Medtronic), measuring the impedance of the tissue grasped with the instrument, thereby securing haemostasis before the surgeon cuts the tissue.

Ideally, if a gold standard technique is to be replaced by a new technique, the decision should be based on scientific studies conducted using randomised designs.

The aim of the study was to evaluate whether tonsillectomy performed with an IDTS is non-inferior to tonsillectomy performed with cold steel instruments in terms of PTH and post-operative pain.

METHODS

Design

The project is designed as a Danish randomised, controlled multi-centre trial of tonsillectomy by conventional cold steel surgical technique versus IDTS. The study is blinded for patients until six months after surgery and it is assessor blinded.

Randomisation is computerised via the tonsil database and utilises block randomisation for each department in a random table of 2000 with equal numbers of group assignments. The randomisation is apparent only to the surgeon on the day of the surgery and the day before.

Course

All elective and acute patients referred for tonsillectomy, with or without adenoidectomy, on benign indications will be assessed for eligibility at the participating ENT departments (**Figure 1**). Patients who sign a declaration of consent will be enrolled and randomised in the study to either standard cold steel tonsillectomy or IDTS tonsillectomy (**Figure 2**).

FIGURE 1 Participating ear, nose and throat departments in Jutland include: Aalborg University Hospital and Thisted Hospital. Gødstrup Hospital. Esbjerg Hospital. Lillebælt Hospital, Vejle. Sønderjyllands Hospital, Sønderborg.

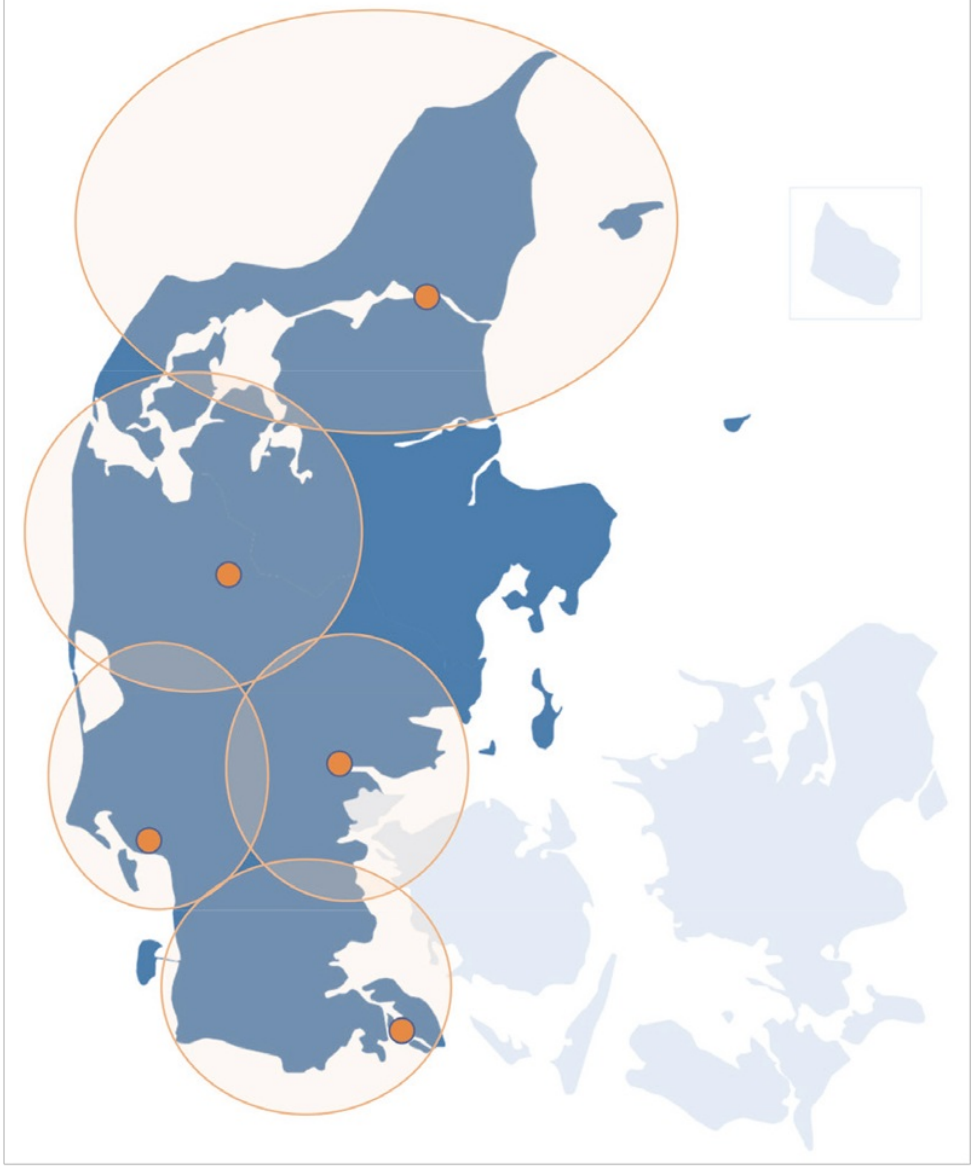
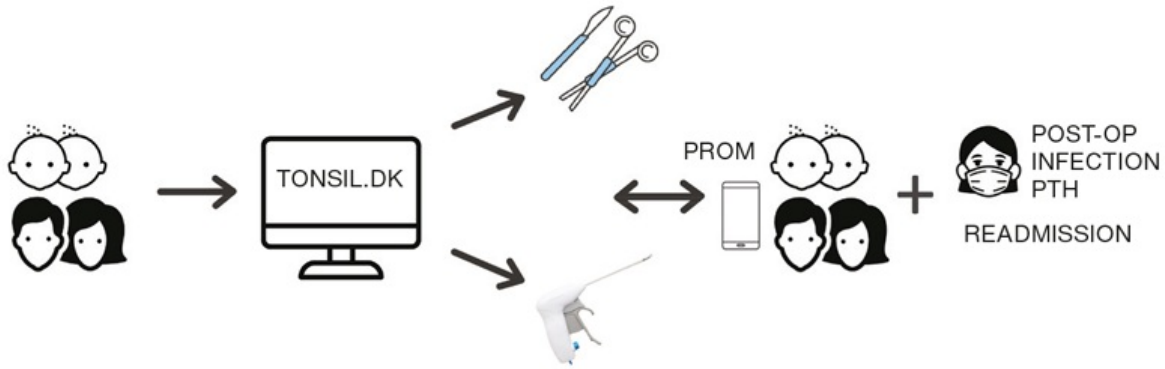


FIGURE 2 Eligible patients who have signed a written consent form are included in the study. Patient information is entered into the tonsil database by the surgeon. The computer randomly assigns patients to one of the two study arms via block randomisation. The control group undergoes standard cold steel tonsillectomy. The investigational group receives tonsillectomy with an impedance-dependent tissue sealer device. The per-operative procedure is equal for both groups as are the post-operative recommendations. The patients or their caregivers answer daily questionnaires on their mobile device regarding adherence to post-operative recommendations; pain scores on a Likert scale for adults/Wong-Baker scale for children; activity level; food consumption; unscheduled contacts to the healthcare system; return to school, work or childcare; satisfaction with the procedure; health-related quality of life on the EuroQol-5 domain-5 level (EQ-5D-5L) questionnaire; and quality of taste and smell. In case of post-tonsillectomy haemorrhage, infection or rehospitalisation for rehydration, the doctor will present a detailed account hereof in the database.



PROM = patient-reported outcome measures; PTH =post-tonsillectomy haemorrhage.

After surgery, all patients will be brought to the recovery room for 1-4 hours or hospitalised for a day depending on the recommendations of the hospital. Before hospital discharge, a surgeon will check for post-operative haemorrhaging, and the patient and any caregivers will receive oral and written recommendations for the post-operative period. Patients or caregivers are requested to follow the recommendations and instructed to contact the ENT department or to call an ambulance if post-operative haemorrhage occurs.

No planned post-operative visits at the hospital will be conducted. During the first six post-operative months, included patients/caregivers are asked to complete online questionnaires using their mobile device: daily, for the first two post-operative weeks; and at one and six months post-operatively (**Table 1**).

TABLE 1 Overview of data entered in the online register by both physician and patients.

	Preoperative information	Day of surgery	Post-operatively		
			day 1-14	day 30	6 months
Reported by physician					
Surgical experience	x				
Demographic data	x				
Indication for surgery	x				
Surgical procedure		x			
Intraoperative blood loss		x			
Operative time		x			
Post-operative observation period			x		
Post-operative bleeding			x	x	
Treatment of bleeding			x	x	
Infection			x	x	
Reported by the patient/caregivers					
Pain: For adults scored on a 0-10 Likert scale; for children, on the Wong-Baker scale			x		
Compliance with the post-operative pain recommendations			x		
Unscheduled contacts to the healthcare system			x	x	
Food consumption			x		
Physical activity			x		
Return to work, school or childcare				x	
Patient satisfaction with surgical outcome					x
Health-related quality of life	x				x
Smell and taste questionnaire	x				x

Outcome assessment

Primary endpoints

- Incidence of PTH defined as haemorrhage requiring haemostasis with bipolar electric coagulation, ligature, compression and/or medical treatment with anti-fibrinolytics within the first 24 hours after surgery (early PTH) and until 30 days after surgery (late PTH).

- Intraoperative blood loss assessed by a standardised protocol utilising the gravimetric method. After surgery, 100 ml of NaCl, weighed on a scale for precision (Kern & Sohn, PCB 6000-1), is aspirated. The suction canister is also weighed on the scale, as is the dry gauze. After surgery, the canister of blood including NaCl is weighed and the dry weights of the canister and gauze, including the NaCl are subtracted. This leaves the total blood loss of the operation. It is assumed that 1 g blood = 1 ml blood.

- Operative time in minutes from the Boyle-Davis gag is placed until it is removed. The operating room nurse is responsible for obtaining the time measurements.

- Post-operative pain is assessed on an 11-point numeric rating scale ranging from 0 “no pain” to 10 “worst possible pain”. For children, the Wong-Baker Faces rating scale will be used.

Secondary endpoints

- Patient reported: Unscheduled contacts to the healthcare system, patient satisfaction, health-related quality of life, patient-reported quality of smell and taste via taste screening questions, followed by further investigation should the patient report altered taste at six months.

Variables

- Patient-reported outcome measures of post-operative recovery (return to normal diet, physical activity; and return to work, school or childcare), compliance with post-operative recommendations (**Table 2**).

TABLE 2 Overview of measurements, timing, and definitions.

Outcome measure	Instrument	Definition of outcome measure
Preoperatively		
Preoperative outcome measures:		
Demographics	Tonsil database	Age, gender, height, weight, smoking habits
Indication for surgery	Tonsil database	Primary and secondary diagnosis resulting in indication for surgery
Day of operation		
Surgical outcome measures:		
Surgical procedure	Tonsil database	Tonsillectomy or adenotonsillectomy performed with either cold steel or IDTS according to randomisation
Surgical experience	Tonsil database	Lifetime number of tonsillectomies
Intraoperative blood loss	Tonsil database	Blood from suction and gauze weighed in g converted to ml
Operative time	Tonsil database	Time in min. from placement of Boyle-Davis gag to removal of gag
Post-operative observation period	Patient record	Time in post-operative hours in hospital stay defined as time in recovery room or ward before hospital discharge
Day of treatment		
Post-operative complications:		
Bleeding	Tonsil database	Yes/no
Treatment of bleeding	Tonsil database	Method of haemostasis: compression, tranexam acid/ desmopressin, bipolar coagulation, transfusion and/or other
Treatment of infection	Tonsil database	Yes/no
Daily on post-operative day 1-14		
Pre- and post-operative patient-reported outcome measures:		
Pain	Online registration form on the patient's mobile device	Pain measured between 2 dosages of prescribed analgesic 3 hrs after intake of the latest dosage on a standardised 11-point numeric rating scale[a] For children, the Wong-Baker Faces rating scale will be used with the same pain graduation
Food consumption	Online registration form on the patient's mobile device	Time in days until normal consumption of food
Physical activity	Online registration form on the patient's mobile device	Time in days until return to normal activity level
Unscheduled contacts to the healthcare system	Online registration form on the patient's mobile device	Contacts to general practitioner, on-call doctors and emergency rooms regarding tonsillectomy
Number, type and reason for contact		
Compliance to recommendations	Online registration form on the patient's mobile device	Compliance to recommended pain medication, dose and timing
On post-operative day 30		
Return to work, school or childcare	Online registration form on the patient's mobile device	Time in days from first to last day of sick leave
6 mos. after surgery		
Satisfaction with surgical treatment	Online registration form on the patient's mobile device	Patient satisfaction with achieved symptom relief after surgery measured on a 5-point Likert scale[b]
Preoperatively and 6 mos. after surgery		
Smell and taste	Screening questions	Change in smell and taste
Health-related quality of life	EQ-5D-5L	Variables according to questionnaire

EQ-5D-5L = EuroQol-5 domain-5 level; IDTS = impedance-dependent tissue sealer.
a) 0: no pain, 1-3: mild pain, 4-6: moderate pain, 7-9: severe pain, 10: worst possible pain.
b) Range: 1: not at all satisfied, 2: somewhat satisfied, 3: satisfied, 4: very satisfied, 5: extremely satisfied.

Inclusion criteria

First-time tonsillectomy due to; tonsillar hypertrophy, recurrent tonsillitis (including previous peritonsillar abscess), chronic tonsillitis, systemic complications to tonsillitis, other (mononucleosis), periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA), tonsillar plugs, peritonsillar abscess and signed written consent.

Exclusion criteria

Diseases in the haematopoietic system, antithrombotic or anticoagulant drugs in the recovery period, suspicion of or known malignancy, patients or parents who are unable to read or speak Danish, patients or parents who are unable to use the online application for self-evaluation, patients or parents who are unable to give informed consent and body weight below 16 kg.

Power considerations

The sample size calculation is based on data from the Danish Tonsil Database. In a 12-month period, the frequency of PTH causing reoperation with haemostasis was 7.9%. With an expected non-inferiority treatment difference between the IDTS and the cold steel instrument, a significance level of 0.05, a power of 80% and a non-inferiority limit of 4%, the required sample is 1,126 patients. Taking a drop-out rate of 10% into account, a total of 1,250 patients are required.

Statistical analysis

Endpoints will be evaluated as differences between treatment groups. Categorical data are analysed by χ^2- or Fisher's exact test. Depending on normal distribution, continuous data are analysed by either un-paired Student's t-test or the Mann-Whitney rank sum test. An intention-to-treat principle will be used, including all randomised participants in the analysis. Stratification will be performed and confounding factors (sex, age, surgical indication, BMI, smoking, comorbidity) will be analysed in a multiple logistic regression model. Repeated measurement data will be analysed in a mixed effects model for repeated measurements (ANOVA) with group and time as systematic factors and patients as random effect. The model takes into account random variations over time. Post-hoc tests will be based on the Kenward-Roger approximation to test all included patients despite missing data. The significance level is set at 0.05.

Ethical considerations and project feasibility

The study is reported and approved by the Danish Data Protection Agency, case number 1-16-02-152-22, and the Medical Research Ethics Committee, case number 2202151.

The study will be conducted according to the Helsinki Declaration. Participation in the study is voluntary and requires written consent. The participants will receive oral and written information and be guaranteed confidentiality.

The collaborating departments have the necessary professional competence, capacity and equipment, and each site has a co-investigator. All ENT departments have signed cooperation agreements, reference number 1-10-81-95-21 and data processor agreements, case number of the main agreement 1-52-81-216-21.

Safety

It is not expected that the intervention under investigation will cause risks or side effects other than the well-known effects related to tonsil surgery. All unexpected peri- and post-operative complications and adverse events will be registered. Furthermore, an interim analysis will be conducted after inclusion of 650 patients. Should the results of the interim analysis reveal that one of the interventions is associated with significant adverse events, the study will be terminated.

Data sharing

The data upon which this study is based will be available from the corresponding author upon reasonable request.

Funding

A sponsor agreement has been signed with Medtronic, the producer of BiZac. Support received under this agreement is only for legitimate purposes within Danish legal guidelines. No conflicting obligations exist. The research is not for commercial market approval.

Trial registration: The study is registered with clinicaltrials.gov (identification number NCT05270109).

DISCUSSION

This protocol describes a Danish randomised controlled multicentre trial the primary aim of which is to evaluate whether IDTS tonsillectomy is non-inferior to cold steel tonsillectomy with regards to PTH and pain.

The study has four key strengths: It is a randomised controlled trial with block randomisation, securing that patients are enrolled consecutively in the surgical treatment groups; a vital step to avoid selection bias. A further key strength is the multicentre setup considered the ideal way to generate data that allow for generalisation. Furthermore, the multicentre setup facilitates enrolment of the large number of participants required for the protocol. In this study, the multicentre setup consists of cooperation between five treatment centres from three regions, including secondary and tertiary treatment centres. This ensures a wide population-based inclusion in the project. Furthermore, the project will be both assessor and patient blinded to prevent any observer and confirmation bias.

A number of limitations to this study should also be acknowledged. The most significant limitation is the lack of a definition of PTH worldwide. The literature thoroughly describes primary and secondary bleeding, occurring before and after 24 hours, respectively. However, it fails to provide a clear definition of severity. In this study, we will define severity by interventions needed for PTH.

A potential limitation of the study coincides with one of the strengths - the multicentre setup brings a risk that each centre may not enrol equally, thereby producing a risk of selection bias. To remedy any such selection bias, the outlying dataset will potentially need to be excluded, which will weaken the results. Furthermore, the comprehensive logistics of multicentre studies occasionally result in unexpected heterogeneity in clinical practices between centres. Such heterogeneity may induce confounders affecting the interpretation of the results.

In our study we collect daily patient-reported outcomes on pain management, which may potentially alter patients' compliance due to the Hawthorne effect.

To our knowledge, the present study is the largest randomised controlled trial in ENT surgery in the Nordic countries to test if IDTS tonsillectomy is non-inferior to cold steel tonsillectomy with regards to PTH, surgery time and post-operative pain.

The study will contribute knowledge to the current literature regarding the clinical course after standard cold steel tonsillectomy and provide evidence regarding the potential benefits of the IDTS technique compared to cold steel.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with

the article at ugeskriftet.dk/dmj

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