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Tonsillectomy and risk of post-tonsillectomy haemorrhage – a protocol for a randomised clinical trial

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ABSTRACT

INTRODUCTION. Tonsillectomy is one of the most common procedures in the ear, nose and throat field, and 7.7% of the Danish population had undergone a tonsillectomy by the age 20 years in 2012. One feared complication is post-tonsillectomy haemorrhage (PTH), which in a Danish register-based study was found to increase from 3% in 1991 to 13% in 2012. PTH represents a significant risk and deaths are reported in the literature. The aim of the trial is to compare hot and cold haemostasis during tonsillectomy and assess, firstly, the risk of PTH and, secondly, the reported pain perception.

METHODS. This is a single-centre, two-arm, interventional randomised controlled trial. The study targets patients > 12 years of age referred for tonsillectomy. Participants will have both tonsils removed; on one side cold haemostasis will be performed and on the other hot diathermia will secure haemostasis. The participants will subsequently receive three questionnaires in the course of a month concerning bleeding episodes and pain perception. Owing to the study design, patients and surgeons act as their own controls.

CONCLUSIONS. The results of the study may guide future research and practice of tonsillectomy to reduce the risk of PTH.

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Tonsillectomy is one of the most common procedures in the ear, nose and throat field; and in 2012, the annual incidence was 129 per 100,000 inhabitants in Denmark [1]. Tonsillectomy is primarily performed among persons under 40 years of age, and 7.7% of the Danish population had undergone a tonsillectomy by the age of 20 years in 2012 [1].

One feared complication is post-tonsillectomy haemorrhage (PTH) and as it occurs in the upper

airways and may set in abruptly and extensively, it represents a significant risk especially in children and young adults and deaths are reported in the literature [1].

PTH incidence ranges from 0.5% to 33% and the variability is mainly due to the lack of an exact definition of a bleeding episode [1-4]. PTH is divided into *primary* PTH occurring within 24 hours of tonsillectomy and *secondary* PTH occurring more than 24 hours after tonsillectomy. However, as tonsillectomy is often conducted on a day-surgery basis, some studies define *early* PTH as bleeding occurring during hospital stay and *late* PTH as bleeding occurring after discharge and within 30 days [5]. As shown in a Danish study, the incidence of secondary PTH follows a bell-shaped curve from day one after tonsillectomy to normally no risk 14 days after tonsillectomy when the tonsil eschar is discharged and the tonsillar bed is healed [6]. PTH incidence peaks on day 0 and day 6 [6].

It is known that the risk of PTH increases with patient age, male gender, overweight, concomitant medication with anticoagulants, indication for tonsillectomy, less experienced surgeon, surgical techniques and tonsillectomy performed during winter months in Denmark [4]. A Danish register-based study showed an increased PTH incidence from 3% in 1991 to 13% in 2012 [6]. The authors stated that part of the increase may likely be explained by a more comprehensive registration of PTH incidents during the study period. However, the analyses lacked control for several of the confounders mentioned above [6].

Tonsillectomies may be categorized according to the technique used for dissection and haemostasis. In as Swedish register-based study, cold dissection with cold haemostasis was associated with the overall lowest risk of late PTH [6]. The authors showed that the risk of late PTH increases with the use of bipolar diathermy for dissection and further increases if used for haemostasis in the tonsillar bed [5]. The highest post-operative risk of PTH was found with monopolar electrocautery, coblation, various lasers and the harmonic scalpel [4]. The bipolar technique seems associated with the lowest risk of early PTH, whereas the cold technique is associated with the lowest risk of late PTH [4].

A multicentre observational study from England and Northern Ireland including 13,554 patients found an over-all 3.3% risk of PTH. The highest risk of PTH was found when hot technique was applied for both dissection and haemostasis where the relative risk of PTH was 3.1 compared with cold steel tonsillectomy. The relative risk of PTA was 2.2 when dissection was conducted with cold steel and diathermy compared with cold steel tonsillectomy exclusively [7].

A Danish retrospective register-based study including 1,365 patients found a 3.4% re-operation rate due to PTH and, when grouped, patients older than 35 years had a 2.3 times higher risk of PTH than patients aged less than 35 years. The authors found no association between gender or type of surgery for the risk of PTH [8].

A review article from 2019 including ten published articles (n = 3,987) concluded that suturing tonsil pillars after tonsillectomy may lower the risk of PTH. Five studies explored post-operative

pain reduction after tonsil pillar suturing, concluding that further investigation is needed [9].

An observational prospective cohort study conducted in Denmark, Sweden and Norway demonstrated differences in approaches regarding tonsillectomies in comparable populations. One finding was that combined cold surgical and cold haemostatic techniques were more commonly used in Sweden (22.7%) than in Norway (10.4%) and Denmark (6.2%) [10].

In Denmark, no standard exists on how to perform haemostasis during tonsillectomy. In our opinion, the preferred techniques in Denmark in the past decades have been cold dissection of the tonsil, some use knotting of the tonsil pillar, whereas others use diathermy on the tonsil pillar and most perform a secondary hot diathermy of the tonsil bed to achieve per-operative haemostasis [10]. Additionally, to our knowledge, radiofrequency, ultrascision, laser, diathermy scissor, harmonic scalpel and "other" electrically driven surgical instruments are seldomly used for tonsillectomy. Despite, the above-mentioned studies, it has been difficult to change the surgical habit among Danish ear-nose-throat (ENT) surgeons, likely also due to the observation that surgical time may increase and the primary PTH rate is higher when performing cold haemostasis during tonsillectomy.

The aim of this trial is to compare hot and cold haemostasis during tonsillectomy, regarding, firstly, risk of PTH and, secondly, patient-reported pain severity. Our null hypothesis is that no difference exists in PTH and pain perception between cold and hot haemostasis in tonsillectomy.

METHODS

This is an interventional, randomised, two-armed controlled trial. The protocol is registered with clinicaltrials.gov (Trial identifier NCT05161754) and adheres to the SPIRIT guidelines. Results will be reported according to the CONSORT guidelines. The protocol is approved by the regional scientific ethics committee (H-20036864). Positive and negative findings will be published in a peer-reviewed journal. Patients are included from the Department of Otorhinolaryngology, Nordsjællands Hospital, Hillerød, Denmark.

Inclusion criteria

Patients aged ≥ 12 years of age referred for bilateral tonsillectomy are eligible.

Exclusion criteria

Tons *a chaud* (presents peritonsillar abscess or parapharyngeal abscess)

Patients suspicious of tonsil cancer

Patients using prescriptive anticoagulation medication

Patients with a known coagulopathy

Randomisation and blinding.

Eligible patients accepting to participate are randomiaed at a 1:1 ratio to one of two parallel groups, and all patients are included in the analyses on an intention-to-treat basis. Participants are enrolled via REDCap Software (Tennessee, USA). On the day of tonsillectomy, randomisation is performed by the surgeon using a random permuted blocks technique available in the REDCap system. The surgical procedure is obviously not blinded for the surgeon and, since the surgical procedure is documented in the patient files, it is not blinded for the patient either.

Interventions

Participants are randomised to undergo *cold dissection and cold haemostasis* on one side and *cold dissection and hot haemostasis* on the other side. *Cold dissection and cold haemostasis* are defined by dissection with cold steel followed by setting a knot around the tonsillar pillar after dissection and performing compression of any bleeding in the tonsillar bed for five minutes (repeated three times if required); furthermore, sutures in the tonsillar bed may be performed. *Cold dissection and hot haemostasis* are defined as dissection with cold steel followed by hot haemostasis using bipolar diathermia 15 W.

By this design, every patient is treated with both interventions and thus act as their own control.

Practical assessment

All participating surgeons will have performed at least ten tonsillectomies before they can enroll in this study protocol.

If bleeding exceeds 200 ml during the procedure, the surgeon is allowed to continue with hot haemostasis. The option of calling a senior colleague (ENT specialist) is always available.

If the surgeon cannot obtain haemostasis without diathermy, the surgeon will provide this during the operation and mention what was done in the patient file and in the case report in REDCap post-operatively. The patient will not be excluded from the study and further data collection but will be excluded from the specific analysis regarding the interventional randomized controlled trial comparing cold and hot haemostasis.

In our set-up, we use the category *cold dissection* when cold steel and/or blunt dissection are used and *hot dissection* when diathermy electrocautery is used. Haemostasis is also divided into the *cold hemostasis* techniques when using packs, ties, sutures, adrenaline infiltration and no device; and *hot haemostasis* when using an electrical device, normally diathermy electrocautery.

Patients will be observed for four to six hours post-operatively on the ward and then discharged, which is the same observational time and procedure used today. If a patient, parents or physician are insecure about post-operative bleeding/pain or other complications, the patient will stay at the hospital overnight l, which is also the procedure used today. Post-operative information is given and pain relievers with paracetamol, ibuprofen and, for some patients, additional morphine are prescribed.

Before being discharged, the patient/parents will be informed orally and in writing about

precautions and what to do if a bleeding is observed and how to be admitted to hospital by calling 112. Furthermore, a direct 24-hour/seven-days-a-week phone number to the ENT Department is provided.

When at home, the patients will receive an automatically generated REDCap e-mail on days 6, 12 and 30 after tonsillectomy, giving them unique access to a REDCap questionnaire asking a few questions: Has a bleeding been observed? Is the bleeding from the left or right side? What analgesic medications have been consumed? Furthermore, the questionnaire includes a question about pain perception using a visual analogue scale 1-10.

Statistics

An *a priori* power analysis was conducted before initiating the trial. To define the probability of confirming or rejecting the null hypothesis, we used the results from Juul et al. [6]. Based on 7,308 PTH in the 1991-2012 period and the increasing incidence of PTH ending at 13% in 2012, we set the risk of bleeding within three weeks from tonsillectomy among > 12-year-olds to 12% when removing both tonsils, equaling 6% when removing one tonsil.

To estimate the risk of bleeding when using hot haemostasis, we used results from Söderman et al. who calculated an odds ratio of 2.8 and Lowe et al. who calculated a relative risk of 2.2 [5, 7]. To make the sample size calculation conservative, we set the risk of excess bleeding to 2, equalling double the risk of PTH when using hot haemostasis.

The incidence of tonsillectomies in the Department of Otorhinolaryngology at Nordsjællands Hospital is estimated to be equal to the pre-Corona number in 2019 when 429 tonsillectomies were performed among patients > 14 years of age.

The power of the study = 1-beta, (probability of rejecting the null hypothesis when, in fact, it is false or the probability of avoiding a type II error) is set at 80%. The level of significance = type I error (probability of rejecting the null hypothesis in favour of a false alternative hypothesis) is set at 95%.

To calculate the study sample size, we used power and sample size [11] and estimated that 175 cases would need to be enrolled. We estimate that 25% of patients will not complete the questionnaire in the study period, and therefore set the sample size to 175 + 25% = 218 cases.

As the design of the study is strong, being a randomised clinical trial on the same patient performed by the same surgeon, a correlation will be expected, which will diminish the sample size needed. However, we are unaware of a comparable study estimating the correlation coefficient and, consequently, we have chosen to perform the sample size calculation conservatively.

The paired sample T-test will be used to compare the two groups. The threshold for statistical significance will be a p-value < 0.05. Data will be analysed with commercially available software (R version 4.1.3).

Participant selection and inclusion period

The participating department is located at a university hospital and patients are primarily selected and referred from the secondary sector, i.e. ENT specialists. Participants and, if aged 12-17 years old, parents or guardians are required to provide oral and written informed consent to participate before entering the trial. The surgeons are medical doctors at the ENT Department at Nordsjællands Hospital, primarily registrars undergoing specialist training.

Inclusion started on 28 March 2022, and we expect to include five patients weekly and thereby include all patients before 1 October 2023. Once anonymised, published participant data may be shared upon request from researchers for verification of the results of this trial or for meta-analyses. The trial protocol and participant information may be made available upon request. Data will be available until five years after publication. Data sharing requests should be addressed to the corresponding author.

Ethics and data management

All data will be stored in REDCap (Tennessee, USA), a clinical research database, in accordance with the GDPR rules and the Danish Data Protection Act. The study will be conducted according to the principles of the World Medical Association Declaration of Helsinki. All patients and parents/guardians of patients aged 12-17 years old will receive oral and written information about the trial before signing a declaration of consent. The trial has been approved by the regional scientific ethics committee (record number: H-20036864) and complies with the requirements of the Danish Data Protection Agency (record number: REG-076-2021).

Trial registration: ClinicalTrials.gov Identifier: NCT05161754. Registration date: 20042021; version 2: 20042021.

DISCUSSION

This trial aims to explore whether a cold haemostasis decreases episodes of secondary PTH and whether patients report a difference in pain perception between the side with cold and hot haemostasis, without leading to more bleeding episodes, prolonged pain perception or more adverse events. If so, we will recommend that ENT colleagues nationally and internationally primarily perform cold haemostasis during tonsillectomy and reserve diathermy for cases in which haemostasis will not be obtained by the “cold” technique.

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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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