Tonsillectomy compared with conservative management in patients over 16 years with recurrent sore throat: the NATTINA RCT and economic evaluation

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Scientific summary

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Scientific summary

Background

Sore throats cost the NHS over £120M per annum, including ≈ £60M for general practitioner (GP) consultations and medical therapy. The place of tonsillectomy in the management of sore throat remains uncertain.

Objectives

Clinical

- To establish the clinical effectiveness of tonsillectomy, compared with conservative management, for tonsillitis in adults.
- To report the number of adverse events (AEs), visits to the GP/walk-in clinic/accident and emergency, prescriptions issued and additional interventions required to manage sore throats and related events through weekly Sore Throat Alert Return (STAR) response data and primary care patient records.
- To adjust the estimate of effectiveness in the light of other baseline covariates, including severity of tonsillitis.
- To evaluate the impact of alternative sore throat patient pathways by observation and statistical modelling of outcomes.
- To assess to what extent trial participants were representative of the total population of sore throat patients referred to ear, nose and throat (ENT) clinics.
- To inform future research.

Qualitative process evaluation

- To examine the acceptability of the trial, treatments and unforeseen consequences from the perspective of participants and stakeholders, including ENT staff and GPs.

Economic evaluation

- To compare costs incurred by the NHS, Personal and Social Services (PSS) and participants to manage recurrent sore throats in adults.
- To compare quality-adjusted life-years (QALYs) using the area-under-the-curve method based on Short Form questionnaire-6 Dimension (SF-6D) scores derived from longitudinal Short Form questionnaire-12 items (SF-12) responses throughout the study and during self-reported sore throat episodes.
- To compare the cost-effectiveness measured in terms of the incremental:
    - cost per sore throat day avoided
    - cost per QALY gained
    - net benefit – estimated based on self-reported number of sore throat days and responses to a contingent valuation questionnaire administered at baseline asking participants' willingness to pay (WTP) to avoid a sore throat day.

Methods

Design

A multicentre, randomised controlled trial comparing the effectiveness of tonsillectomy for recurrent sore throat with that of non-surgical conservative management in a 1:1 ratio over a 24-month period.

Surgeons, participants and site staff could not be blinded to the allocated procedure. The main trial began following the completion of a feasibility study and included a qualitative process evaluation, as well as an economic evaluation. The design, conduct and reporting of the trial were informed by patients. Crossover of participants between arms was permitted.

Interventions

- Tonsil dissection: dissection of the palatine tonsils preferably within 6 weeks, and no more than 8 weeks, following randomisation (dissection method at the discretion of the participating centres).
- Conservative (non-surgical) management (i.e. deferred surgery): participants entering the conservative management arm were asked to defer surgery for up to 24 months on the understanding that they would be reviewed at 12 months.

Setting and participants

A total of 453 patients were recruited to the main trial from 27 NHS secondary care hospitals in Great Britain. Eligible patients were identified via general ENT referrals and established sore throat-specific referral pathways, some of which were run by ENT nurse practitioners.

Inclusion criteria

- Aged ≥16 years.
- Recurrent sore throats that fulfil current Scottish Intercollegiate Guidelines Network (SIGN) guidance for elective tonsillectomy.

Exclusion criteria

- Previous tonsillectomy.
- Listed directly (i.e. added to waiting list without prior elective ENT outpatient appointment) during emergency admission (e.g. owing to peritonsillar abscess/quinsy).
- Primary sleep breathing disorder.
- Suspected malignancy.
- Tonsilloliths (as primary referral).
- Pregnant or breastfeeding.
- Bleeding diathesis (including haemophilia, sickle cell disease and platelet dysfunction).
- Therapeutic anticoagulation.
- Inability to complete self-reported questionnaires and sore throat returns.

Main outcome measures

Primary outcome

The primary outcome measure was the total number of sore throat days over the 24 months following randomisation.

The number of sore throat days was collected by a database that was designed for use in the trial (the STAR database). This database allowed participants to respond weekly to alerts by providing the number of sore throats that they had experienced in the previous 7 days (between 0 and 7 sore throat days). From the beginning of the trial, participants were able to choose their preferred method for receiving these alerts: e-mail, text message or interactive voice response (IVR) via telephone.

Secondary outcomes

A participant who had suffered from a sore throat in the past week (i.e. sore throat days >0) was asked to provide information on the severity of the sore throat(s) and additional data for health economics and other secondary outcomes in a STAR questionnaire.

Quality-of-life data, reported as the SF-12 physical component score (PCS) and mental component score (MCS) and additional symptoms of tonsillitis, were collected every 6 months.

The impact of alternative NHS sore throat pathways was measured by observation and statistical modelling of outcomes. The extent to which trial participants represented the total population of sore throat patients referred to ENT clinics was assessed through analysis of site screening logs.

Adverse events

Information regarding the AEs related to the trial intervention was collected during telephone calls at 1 and 2 weeks post tonsillectomy; all tonsillectomy arm serious adverse events (SAEs) were recorded throughout the duration of the trial for all participants.

Economic evaluation

The cost-effectiveness of tonsillectomy compared with conservative management was evaluated by estimating the total costs incurred by the NHS and PSS, and averaging these costs across participants in each trial arm. Three different analyses were undertaken: (1) a cost-effectiveness analysis (CEA), (2) a cost–utility analysis (CUA) and (3) a cost–benefit analysis (CBA). All three analyses measured costs using the same methodology but differed in their measure of effectiveness. An incremental cost-effectiveness ratio was estimated for the CEA and the CUA by dividing the difference in average total costs by the difference in average total effects. The CEA estimated the incremental cost per sore throat day avoided. The number of sore throat days was derived from the primary outcome data. The CUA estimated the incremental cost per QALY gained. QALYs were derived using the SF-6D algorithm, which estimates utility values based on responses to the SF-12, which was administered at baseline and 6, 12, 18 and 24 months post randomisation and at the time of a sore throat episode. The CBA estimated the incremental net benefit, comparing costs and benefits in monetary terms. Participants' WTP values, estimated from the contingent valuation study, were multiplied by participants' self-reported number of sore throat days to estimate the reduction in patient benefits in monetary terms; from this costs were subtracted to give the net benefit.

Qualitative process evaluation

Qualitative and cognitive interviews were carried out by researchers from Newcastle University for the feasibility study, pilot and main trial. Interviews were held with adult patients with acute tonsillitis who had been referred to ENT outpatient clinics for recurrent sore throats, ENT staff who were working at a National Trial of Tonsillectomy IN Adults (NATTINA) trial site and GPs. These interviews addressed the acceptability of the trial/treatments, unforeseen consequences from the perspective of participants and how patient experience may shape future research.

Statistical analysis

The primary statistical analysis was carried out on an intention-to-treat (ITT) basis, retaining patients in their randomised arms and including protocol violator and ineligible patients. Patients randomised to conservative management were asked to commit to 'deferred surgery'. We anticipated that a number of patients would take the opportunity to switch to surgery. We also undertook sensitivity analyses, including a per-treatment (as treated) and a per-protocol analysis. The cumulative total number of sore throat days reported on a patient level was provided separately for each randomised arm. Negative binomial regression was used to compare these, adjusting for stratification variables (baseline severity as a fixed effect and site as a random effect). The summary comparative statistic reported is the incident rate ratio (IRR). The analysis took account of incomplete weekly returns by use of an exposure variable included in the model. The analysis of secondary outcomes followed a broadly similar strategy to the primary outcome. Analyses were adjusted for baseline severity and site, and repeated measures were analysed using random-effects models with appropriate error structure.

Results

Primary outcome

The participants in this trial reported a median of 27 [interquartile range (IQR) 12–52] sore throats over the full 24 months of follow-up. Fewer sore throats were reported in the tonsillectomy arm (median 23, IQR 11–46) than in the conservative management arm (median 30, IQR 14–65). When the primary outcome (total sore throats) was compared between the two randomised arms on an ITT basis, a reduction in sore throats was seen in the tonsillectomy arm. The tonsillectomy arm had 0.53 [IRR, 95% confidence interval (CI) 0.43 to 0.65] times the total sore throat days over the 24-month period than those in the conservative management arm. Sensitivity analyses on the ITT population confirmed this result. The analysis of the per-protocol population of 224 participants had, on average, a greater reduction in the number of sore throats, with patients in the tonsillectomy arm having 0.42 (IRR 95% CI 0.31 to 0.55) times the total score throats compared with the conservative management arm. Around 25% of participants did not receive the treatment that they were randomised to, which meant that some opted not to receive a tonsillectomy and some opted to cross to tonsillectomy. There is evidence to suggest that those with larger numbers of sore throats following randomisation were more likely to either opt for or remain in the tonsillectomy arm. Conversely, those with slightly smaller numbers of sore throats following randomisation were more likely to remain in conservative management or opt out of the tonsillectomy arm. Despite these crossovers, the ITT, per-protocol and per-treated analyses all confirmed that there was a significant reduction in total sore throats for those randomised to tonsillectomy.

Secondary outcome measures

The benefits of tonsillectomy were also seen in the secondary outcome measures. Tonsillectomy Outcome Inventory-14 (TOI-14) scores improved in both arms, but show a greater improvement in the tonsillectomy arm than the conservative management arm, where at 12 months the difference between the mean scores was −13.17 units (95% CI −17.41 to −8.92 units), indicating a reduction in symptoms. The SF-12 MCS and SF-12 PCS also show significant and beneficial differences in favour of the tonsillectomy arm over time [SF-12 MCS scores 3.71 units higher (95% CI 2.10 to 5.47) and SF-12 PCS 2.77 units higher (95% CI 0.30 to 5.23) in the tonsillectomy arm than the conservative management arm].

Adverse events

There were 52 episodes of post-operative haemorrhage reported in 231 participants undergoing tonsillectomy (22.5%). Of these episodes, 35 were reported as SAEs: 8 as mild events, 22 as moderate events and 5 as severe events. No deaths were reported. Seventeen episodes were recorded as AEs, for which patients did not attend hospital. All episodes of bleeding were managed conservatively with no returns to theatre.

Economic evaluation

On average, tonsillectomy was more costly and more effective than conservative management. In the CEA, the incremental cost to avoid a sore throat episode was £24 per sore throat day. From the contingent valuation, the mean WTP to avoid a sore throat day was £43 (95% CI £2 to £100). In the CUA, tonsillectomy had an 87% probability of being considered cost-effective at a £5000 threshold for an additional QALY; this increased to 100% as the threshold values for an additional QALY increased. In the CBA, tonsillectomy had a 69% probability of having a higher net benefit than conservative management.

Qualitative study

Trial processes were deemed as acceptable, with only a few sites experiencing barriers to treatment. The use of technology to collect data was particularly well received. However, there were some challenges with recruitment, particularly for staff who lacked equipoise. ENT staff alluded to having to negotiate surgery dates with patients, which, at times, meant that they had to deviate from trial protocols. Some patients did not fully understand the process of randomisation. Patients who had received surgery were unanimous in reporting to be happy to have undertaken this, despite the challenging recovery period.

Limitations

There was some evidence that those with the most severe extent of disease were reluctant to enter the study (around 5 points higher scores overall on the TOI-14). Some symptoms may not be a result of tonsillitis. Not all patients were offered, or chose, to watch the trial recruitment video. The ITT analysis is likely to offer a conservative underestimate of the true impact of tonsillectomy in reducing sore throat days, as a result of patients crossing over to receive tonsillectomy. A challenge of the economic evaluation was the progressive loss of data over the 24-month follow-up.

Conclusions

Tonsillectomy in adults is a clinically effective intervention. It was more costly but had a high probability of being considered cost-effective over the range of analyses conducted. Participants with recurrent tonsillitis, who met current UK NHS guidelines to undergo tonsillectomy, suffered significantly fewer sore throat days over 24 months than similar participants treated conservatively.

How should health services react?

Pre-NATTINA, UK guidelines were a translation of level 1 evidence in children, applied to adults. Access to tonsillectomy in the UK was governed by application of national guidance, which is predicated on a qualifying number of episodes of tonsillitis. NATTINA participants in the tonsillectomy arm reported, on average, fewer healthcare contacts, fewer sore throat days and higher QALYs than those in the conservative management arm. Within the UK, tonsillectomy is listed as a 'procedure of limited clinical value' (The Royal College of Surgeons of England. *Procedures of Limited Clinical Value: Royal College of Surgeons Briefing*. London: The Royal College of Surgeons of England; 2011). To the best of our knowledge, NATTINA is the first definitive trial to demonstrate that tonsillectomy performed according to the current UK national guidelines is effective for patients, and the probability of it being considered cost-effective is high. Guideline reassessment, in particular how guidelines translate into healthcare commissioning, is called for.

How should practitioners and patients respond to these findings?

We have identified communication issues at the primary–secondary care interface in our qualitative work. There is, therefore, a need to convert the findings of NATTINA into a practical decision support tool for patients and surgeons.

Implications for research (in priority order)

The top research priority to emerge from NATTINA is to determine the optimum timing of tonsillectomy in adults with recurrent acute tonsillitis. Work is required also to optimise metrics for disease burden severity, and to exploit the novel real-time data collection methods elaborated in NATTINA. There is also a need to better understand optimum treatment strategies, including oral steroids, for tonsillitis in primary care.

Trial registration

This trial is registered as ISRCTN55284102.

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