**Role of celecoxib in postoperative analgesia in paediatric tonsillectomy: a double-blinded, randomised placebo-controlled trial.**

**2. Trial Registration**

**2a. Registry**

### ANZCTR [ACTRN12621001390875p]

### Hunter New England Human Research Ethics Committee [2021/ETH11236]

**2b. Data Set**

|  |  |
| --- | --- |
| **Data Category** | **Information** |
| Primary registry and trial identifying number | ANZCTR [ACTRN12621001390875p]  Hunter New England Human Research Ethics Committee [2021/ETH11236] |
| Date of registration in  primary registry | 29/08/2021 |
| Secondary identifying  numbers | N/A |
| Source(s) of monetary or material support | Gosford Hospital and Gosford Private Hospital |
| Primary sponsor  Contact for public queries | Central Coast Local Health District (CCLHD)  Celecoxib Research Team: CCLHD-ENTResearch@health.nsw.gov.au |
| Contact for scientific queries  Public title | Celecoxib Research Team: CCLHD-ENTResearch@health.nsw.gov.au  Role of celecoxib in postoperative analgesia in paediatric tonsillectomy: a double-blinded randomised placebo-controlled trial |
| Scientific title  Countries of recruitment | Role of celecoxib in postoperative analgesia in paediatric tonsillectomy: a double-blinded randomised placebo-controlled trial  Australia |
| Health condition(s) or  problem(s) studied | Post-operative pain following tonsillectomy with or without adenoidectomy |
| Intervention(s) | Liquid celecoxib at a dose of 2mg per kilo of body weight BD in addition to standard analgesic regimen. |
| Key inclusion and exclusion criteria | Inclusion criteria: participants aged 3-16 years undergoing tonsillectomy with or without adenoidectomy.  Exclusion criteria include participants with allergy to non-steroidal anti-inflammatory drugs (NSAIDs), opioids, paracetamol, or sulphonamides. Participants with significant comorbidities who are unfit for treatment with selected intervention, comorbidities include: syndromic children, children with eating or bleeding disorders, children with significant cardiorespiratory conditions, children with asthma and children with active infection or malignancy, any participants taking regular medication including NSAIDs, opioids or paracetamol on a regular basis, participants taking drugs that interact with opioids, paracetamol or NSAIDs, participants with a history of peptic ulcers or gastrointestinal bleeding, patients who do not speak English and females who are pregnant or nursing; this will be screened for during recruitment using routine questions. |
| Study type  Date of first enrolment  Target sample size | Interventional  Allocation: randomised  Intervention model: parallel assignment  Masking: double blind (researchers, surgeons, participants)  Primary purpose: improved pain outcomes  Phase: Phase 3  February 2022  140 participants |
| Recruitment status  Primary outcome(s) | Not yet recruiting  “Average pain on that postoperative day” as reported on a Wong-Baker FACES pain rating scale where 0 is “no pain at all” and 10 is “the worst pain I’ve ever felt”. |
| Key secondary outcomes | Amount of Oxynorm liquid taken (doses/day), records of complications including nausea, vomiting, bleeding, infection and representation to hospital. |

**3. Protocol Version**

**Issue date:** Version 1 [Created 29 Aug 2021]

**Protocol Amendment:**

Version 2 [Reviewed 28 Sept 2021]

**Version 3 [Reviewed 22 Feb 2022]**

**Authors(s):** *M.Z.; R.T.; N.K.; C.D.; V.P.*

**4. Funding**

This trial will be sponsored by the Central Coast Local Health District (CCLHD) through Gosford Hospital. Liquid Oxynorm (oxycodone), paracetamol and celecoxib will be obtained through Gosford Hospital or community pharmacy via prescription from operating doctors. Liquid placebo will also be obtained through Gosford compounding hospital. Funding will be provided by the research department from the University of Newcastle.

**5. Roles and Responsibilities**

**1. Contributorship**

*M.Z, R.T, N.K, C.D, V.P, S.S*

**Authors contributions:**

SS and MZ conceived of the study. MZ, RT, NK, CD and VP initiated design. ENT surgeons at Gosford hospital will deliver the intervention and RT, NK, CD and VP will recruit the participants, obtain consent, undertake data collection, conduct the primary statistical analysis and write the final manuscript.

**2. Sponsor Contact Information**

**Trial Sponsor**: Central Coast Local Health District (Gosford Hospital)

* **Sponsor’s Reference**: ENT Head of Department
* **Contact name**: Dr Shashinder Singh
* **Address**: Holden Street Gosford
* **Telephone**: 4320 2111
* **Email**: cclhd-hodsecretarysurgery@health.nsw.gov.au

**3. Sponsor and Funder**

Funding will be obtained through the Research Department of the University of Newcastle and University of New England. Funding will total to $1500 to cover the expense of the placebo medication.

**6. Introduction**

**1. Background and Rationale**

**Introduction**

Tonsillectomy is one of the most common surgical procedures worldwide and is most performed in the paediatric population, with or without adenoidectomy1,2. Tonsillectomy unfortunately carries with it a high degree of morbidity in the form of moderate to severe postoperative pain which typically peaks between days 3 and 7 and can continue up to 10 days3,4. Postoperative haemorrhage, functional limitation, nausea and vomiting5-7 are also common. Current analgesic regimens vary widely between the operating surgeons with no single standard of effective analgesic treatment8. Most surgeons utilise opiates such as oxycodone to alleviate pain9, which can present a clinical challenge due to concerns of adverse effects10-12. Almost all patients reported at least one adverse effect while using opioid analgesics; including nausea, vomiting and confusion which may only become apparent when the child returns home13-15. Opioids are responsible for 50% of postoperative respiratory failure events10, which is concerning as two-thirds of tonsillectomy mortality in children is attributed to airway complications16-19.

**Mechanism**

Large unpredictable variations in patient responses to opioid analgesia, narrow therapeutic windows and differences in opioid metabolism also contribute to the high incidence of opioid induced respiratory depression18,19. Despite the recovery for tonsillectomy being typically 2 weeks, 4.8% of adolescent patients continued to use opiates up to 90 days postoperatively, demonstrating the potential for opioid dependence exacerbated by persistent requirement for opioids after one week12,20.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been proposed as an alternative and as an adjunct to opioid analgesics post-tonsillectomy3,18,21-23. NSAIDs are the primary analgesia used for children less than 12 years old but efficacy in controlling post-tonsillectomy pain has yet to be fully verified24. As NSAIDS have an inhibitive effect on cyclooxygenase-1 (COX-1), there are concerns of postoperative haemorrhage which limit widespread utilisation25-28. There is clinical interest in celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, which has the analgesic, antipyretic and anti-inflammatory effects of classical COX-1 inhibitors without the adverse constitutional effects29. Early studies suggest celecoxib provides effective analgesia post-tonsillectomy for both adult and paediatric populations30-33, which decreases the use of opioids and in turn, the adverse effects of opiates such as nausea and vomiting3,7,30,34,35. Due to the potential benefits, a greater understanding of the safety and efficacy of celecoxib as an analgesic in the paediatric population must be obtained before its routine use in post-tonsillectomy patients.

**Existing knowledge**

34 peer reviewed studies were reviewed to gain insight into paediatric post-tonsillectomy pain management. Studies included were literature reviews, systematic reviews, randomised controlled trials (RCT) and cohort studies. Studies were excluded if they were published before 2011, not written in English, had less than 10 participants or included participants that were taking NSAIDS or opiates on a regular basis8,23,29-32,34,36-64.

Twelve identified studies examined the postoperative use of opioids23,36-47. Opioid medications, including codeine, oxycodone, and tramadol, were rarely associated with respiratory events when used within guidelines36. However, in high-risk populations, such as children with sleep disordered breathing undergoing tonsillectomy, children using morphine had an average increase of 11.17 desaturation events per hour on the first night postoperatively when compared to ibuprofen37. A 2021 literature review by Cramer, et al. found NSAIDs, including both classical NSAIDs and selective COX-2 inhibitors, were more likely to reduce acute post-operative pain than standard opioid regimens and were associated with less risk of adverse effects when used for a short duration at low dose23. Perioperatively, NSAIDs have been shown to reduce opioid consumption and postoperative nausea and vomiting36. Hobson et al, found that despite opioid rescue analgesia, paediatric populations still reported pain at the final assessment, indicating the need for further pain relief 38.

Thus, many studies have investigated the role of NSAIDs in post-tonsillectomy analgesia as an alternative to opiates. Of the studies identified, 11 studies have found the use of NSAIDs produced a good analgesic effect for post-tonsillectomy pain8,23,36,37,39,40,47-51. Cramer et al found that nonselective NSAIDs such as ibuprofen47 and selective COX-2 inhibitors by itself are more likely to reduce acute postoperative pain than standard opioid regimens23. However, 2 studies found that ibuprofen provided inadequate analgesia52,53, with >50% of patients reporting need for rescue opioid analgesic52. Tolska et al also found that although NSAIDs reduced pain intensity on the day of operation, most patients needed rescue analgesics. The authors concluded that while data for post-tonsillectomy analgesia was limited, current evidence points towards a multimodal analgesic regimen48. This supports findings from other studies36,49 such as that of Stamer et al, reporting that use of at least 2 different classes of non-opioid analgesics would decrease the “desire” for additional pain medication by 3.5 times as compared to an opioid-only analgesic regimen49.

Due to concerns of post-tonsillectomy haemorrhage, 15 studies investigated its rate associated with NSAID use34,39,42,47,51,53-62. Of these, 10 studies found nil increase in postoperative bleeding events34,39,42,47,51,53-57, whilst one review63found a non-significant increase in risk of bleeding requiring surgical intervention with NSAID intervention. Higher rates of bleeds at 4.2% of the population was found in one study60though the authors reported that even though the NSAID intervention continued, after the conclusion of the study period the haemorrhage rates dropped and was maintained at 2.52%, comparable to the pre-intervention population. A 2021 systematic review and meta-analysis of 151,031 patients concluded that in all measurements of bleeds, there was no difference in risk between NSAID and non-NSAID groups55.

Of NSAIDs, there is clinical interest in the COX-2 specific inhibitor celecoxib, with varied results in literature23,29-32,36,64. Ng et al found no significant reduction of pain or opioid use post-tonsillectomy within an adult population. This was attributed to implementation of a twice daily dose of 200mg celecoxib instead of a single 400mg dose29. By contrast, a significant reduction in pain was shown in two randomised control trials that were evaluated30,31. 400mg of celecoxib was shown to be an effective dose for acute, reactive inflammatory pain31. A 200mg dose of celecoxib was shown to reduce breakthrough narcotic consumption when compared to a placebo group30 and reduced co-analgesic, acetaminophen, consumption when compared to a placebo group32. This study also highlighted that the celecoxib intervention group displayed a clinically significant pain reduction within 24hours post-tonsillectomy with32. Regarding side effects, although COX-2 inhibitors increased the risk of cardiovascular events compared to NSAIDS64, recent evidence highlights that celecoxib shares a similar cardiovascular safety profile36. Only one RCT found that celecoxib consumption was associated with vomiting as compared to the placebo intervention29, but celecoxib appears superior to NSAIDS due to the reduction in gastrointestinal dysfunction and postoperative bleeding and anaemia36.

**Need for a trial:**

There remains a gap within the literature regarding the best approach for pain management following tonsillectomy in the paediatric population. The existing literature supports the use of a multimodal approach to analgesia post-tonsillectomy as there is no single analgesia that currently provides adequate pain relief5,23,36. Non-steroidal medications such as celecoxib have been proposed as an option to reduce rates of opiate consumption, thereby reducing the likelihood of developing adverse effects and dependence. However, there is also a gap in the literature with respect to the role of celecoxib in post-tonsillectomy analgesia in the paediatric population.

Given the frequency of tonsillectomies conducted worldwide1,2 and the significance of pain experience following the procedure3,4, it is imperative that an improvement is made to post-tonsillectomy pain management regimes. Celecoxib is an emerging drug with limited data to show its effectiveness in managing pain post-tonsillectomy in the paediatric population so research into this field has the potential to improve analgesic protocols following paediatric tonsillectomies.

This research can be looked at through the paradigm of positivism, as it looks to identify a single analgesic regime that is widely applicable. The research epidemiology will be synthesising empirical data into a composite report using quantitative data.

**Dose selection**

The Australian Medication Handbook guidelines have informed the paediatric celecoxib dose of 2mg per kilo of body weight BD65. This will be in addition to the current analgesia guidelines which involve the use of regular paracetamol (15mg/kg QID, four times daily for two weeks) and Oxynorm (oxycodone) liquid (0.1mg/kg) for rescue analgesia QID as required66,67. A liquid placebo, with the same smell and appearance as celecoxib will be used for the control group.

**2. Choice of Comparators**

The safety profile of oxycodone and paracetamol is well established and known. The safety profile of celecoxib has been established in the paediatric population, but efficacy in controlling post-tonsillectomy pain has yet to be verified with high quality evidence. There will be no active ingredients in the placebo medication. It will be made by the compounding pharmacy at Gosford Hospital in accordance with safety protocols.

**7. Objectives**

**1. Research Hypothesis**

It is hypothesised that participants taking celecoxib in addition to the current standard analgesic treatment will have a reduction in pain during the postoperative period as measured through a Wong-Baker FACES pain scale.

**2. Study Objectives**

**2.1 Primary Objective**

To evaluate the efficacy and safety of celecoxib for post-operative pain management in paediatric tonsillectomy patients.

**2.2 Secondary Objectives**

To determine whether participants taking celecoxib in addition to the current standard analgesic treatment will have decreased use of Oxynorm (oxycodone) liquid, less postoperative complications and a reduction in need for healthcare services within the 14 day post surgery period than the control group.

**8. Trial Design**

The study will be a double blinded, randomised, placebo-controlled trial. Participants will be recruited from the ENT surgical waitlist at Gosford Hospital and screened pre- and postoperatively to ensure they meet inclusion criteria. Participants will be recruited by the researchers personally or by using an information package distributed by the surgical team to the carers and participants. Informed written consent will be obtained pre-operatively. The participants will then be randomised via block randomisation using the REDCap software into control and treatment groups in a 1:1 ratio. Its allocation sequence will be concealed from the researchers who will be collecting the data.

**9. Study Setting**

The study will be conducted through Gosford Public Hospital and Gosford Private Hospital. The participants population will be from Central Coast Local Health District.

**10. Eligibility Criteria**

Participants (or their guardians) must provide written, informed consent for participation in this trial before any study procedures occur (see Appendix 1 for sample of the written information and Appendix B for the Informed Consent Form). Participants will be recruited by members of the research team at least 1 week prior to tonsillectomy via phone call and they will be sent the written information sheets and consent form via email; the informed consent will also be completed at this time. Participants eligible for the trial must comply with all of the following at randomisation:

**Inclusion Criteria:**

1. Aged 3-16 years

2. Undergoing tonsillectomy with or without adenoidectomy

Concurrent procedures such as adenoidectomy, insertion of grommets, and turbinate diathermy will not preclude inclusion in this trial.

**Exclusion Criteria:**

1. Allergy to non-steroidal anti-inflammatory drugs (NSAIDs), opioids, paracetamol, or sulphonamides

2. Significant comorbidities unfit for treatment with selected intervention. Comorbidities include syndromic children, children with eating or bleeding disorders, children with significant cardiorespiratory conditions, children with asthma and children with active infection or malignancy.

3. Any participants taking regular medication including NSAIDs, opioids or paracetamol on a regular basis

4. Participants taking drugs that interact with opioids, paracetamol or NSAIDs

5. History of peptic ulcers or gastrointestinal bleeding

6. Patients who do not speak English

7. Females who are pregnant or nursing; this will be screened for during recruitment using routine questions. Participants who say they may be pregnant or are trying for pregnancy will be excluded. Participants will also be reviewed by the anesthetic team prior to tonsillectomy.

**11. Interventions**

**1. Interventions**

Eligible participants will be randomised in a 1:1 ratio into control and intervention groups. Following tonsillectomy, all participants will be discharged with standard analgesic medication. At discharge, participants will be advised to not take other NSAIDs for the duration of the study. Analgesics provided will be regular paracetamol (15mg/kg QID for two weeks) and Oxynorm (oxycodone) liquid (0.1mg/kg) for rescue analgesia QID as required66,67. Antibiotics will be prescribed at the surgeon’s discretion. Following tonsillectomy, all patients will be discharged with standard analgesic medication and the study medication (package A or B). Analgesics provided will be regular paracetamol (15mg/kg, four times daily for two weeks) and Oxynorm (oxycodone) liquid (0.1mg/kg) for rescue analgesia as needed 66. Antibiotics will be prescribed at the surgeon’s discretion. Once the surgeon has prescribed the standard analgesic regimen, the hospital pharmacy will check the allocation from REDCap and prescribe either Package A or B as allocated. Patients in the treatment arm will receive a de-identified bottle of liquid celecoxib (Package A) at a dose of 2mg per kilo of body weight BD, as per current guidelines68. Patients in the placebo arm will be given a de-identified bottle of similarly appearing, pharmacologically inactive placebo (Package B). This will be provided by the compounding pharmacy at Gosford Hospital. This allocation will be concealed from the researchers’ collecting data, the operating surgeons and the participants and their families. Both the control and treatment groups will take their respective medication regularly for 14 days.

**2. Modifications**

Celecoxib or the placebo will be ceased in the advent of any adverse effects and participants will be withdrawn from the trial. Adverse events and withdrawals will be documented. There will not be routine blood test monitoring, although participants will be provided education by the prescribing doctor about symptoms of potential adverse effects. As a CYP2D6 inhibitor, any potential drug interactions will be monitored by the prescribing surgeon65.

* **Post-tonsillectomy complications:** including postoperative haemorrhage but excluding nausea and vomiting2,5,7.
* **Allergic Reactions:** allergic reactions have been observed in rare cases65. If this is suspected, the trial medication will be withdrawn from the participants and this will be reported as an **adverse event**.
* **Renal Function Impairment and hyperkalaemia**65**.**

Any significant safety issues or adverse effects will be reviewed by an independent general practitioner, paediatrician or ENT surgeon not affiliated with the clinical trial. In the event of pain not lasting 14 days, participants can cease analgesic medication when they feel their pain is well managed.

**3. Adherence**

Reminder sessions will occur via phone, automated text message or email. This session will include:

* Reminder to complete the online form; including the importance of recording pain, opioid use and adverse effect data Importance of representing to the hospital in the event of adverse effects
* Adherence to placebo as well as celecoxib

Reminder messages will be sent to the participants' careers on days 3, 5, 7, 10 and 14 during the afternoon, or earlier in participants who have been non-compliant with completing the survey. Participants will be contacted a maximum of once per day by the researchers.

**Adherence Assessments:**

Adherence to celecoxib will be monitored via an electronic survey. Use of celecoxib, paracetamol, and rescue Oxynorm will be monitored through this system.

**4. Concomitant Care**

**Rescue Medication**

Oxynorm (oxycodone) liquid (0.1mg/kg) will be used for rescue analgesia as required67. Any dose taken will be documented during data collection.

**Prohibited Concomitant Medications**

The administration of selective cyclo-oxygenase-1 inhibitors is prohibited during this trial; administration will preclude exclusion from the data. Participants should continue to take medications for other conditions as normal. After day 14, all medications will be permitted for trial participants.

**12. Outcomes**

Participants or their guardians will record data using an online form. Data will be collected on days 1, 3, 5, 7, 10 and 14 post-operatively, which coincides with peak post-tonsillectomy pain (day 7)69 and after pain usually subsides (day 10)3,4. Change in outcomes between the control and intervention groups will provide the basis for data analysis.

**1. Primary Outcome Measures**

The primary outcome measured in this study is “average pain on that postoperative day” as reported on a Wong-Baker FACES pain rating scale where 0 is “no pain at all” and 10 is “the worst pain I’ve ever felt”70,71. This will be self-reported by all the participants aged > 5 years and with parent guidance in children aged 3 or 4 years.

The Wong-Baker face scale is chosen as it is an established face scale71, requiring no understanding of abstract numerical values or words. It is suitable for self-report of pain even in young children under 8 years, which is more desirable than the Visual Analogue Scale72 due to the ability for young participants to report pain directly rather than relying on carer report73.

**2. Secondary Outcome Measures**

Secondary outcomes will be the amount of Oxynorm liquid taken (doses/day), first postoperative pain free day, caregiver satisfaction; and the number and incidence of adverse events experienced, such as nausea, vomiting, diarrhoea, constipation, bleeding or drowsiness. Postoperative bleeding complications and subsequent surgical or conservative management will be recorded on day 14 with a yes/no question.

**13. Participant Timeline**

The main outcomes of interest are pain management following paediatric tonsillectomy and associated pain course, incidence of adverse events and reduction in use of Oxynorm liquid. Participants will be followed for 14 days following tonsillectomy; with no other follow up required.

**Figure 1. Timeline of Data Collection and Analysis**

**Chart, waterfall chart

Description automatically generated**

**14. Sample Size**

A formal sample size calculation was conducted for the primary outcome. Analysis was based on the definition of treatment success as a relative reduction in postoperative pain score of ½ a standard

deviation as measured on the Wong-Baker FACES pain rating. To detect a reduction of half a standard deviation in VAS pain score with 80% power at a significance threshold of 5%, 63 participants per group is required, for a total of 126 participants. Assuming a loss-to-follow up rate of 10%, the total recruitment target is 140 participants.

**15. Recruitment**

Gosford Hospital will recruit participants off the ENT waiting list and screen against the inclusion and exclusion criteria. Gosford Hospital facilitated 200 tonsillectomies in the 6 months between January 2021 and July 2021; it is expected that there will be similar numbers during the recruiting period. Participants will be recruited by the researchers, separate from the surgical team handling the participant’s medical care. All participants will be required to give their informed consent and be provided with an information packet [see Appendix B]. Participants will be recruited before undergoing tonsillectomy. There will be no financial incentive for participating in this study.

**16. Allocation**

**1. Sequence Generation**

Participants will be randomly assigned to either control or experimental group with a 1:1 allocation as per a computer-generated randomisation sequence stratified by age and gender (block randomisation). Block sizes will not be disclosed, to ensure concealment.

**2. Concealment Mechanism**

Randomised allocations will be delivered to pharmacy staff in sealed white envelopes with no distinguishing features containing a randomisation number. Researchers who will be undertaking data collection and the operating doctors will be blinded from the allocation groups. The surgical team will be provided with unmarked packages (either A or B) to provide to participants. These packages will contain either the liquid placebo or celecoxib depending on REDCap randomisation. Participants and their guardians will also be blinded to their allocation.

**3. Implementation**

Participants and their guardians who return informed consent and who fulfil the inclusion criteria will be randomised. Randomisation will be requested by a researcher who has no role in the medical care following tonsillectomy.

**17. Blinding**

**1. Blinding**

Collection of data will be via an online automated form filled out by the participants or their caregiver which will feed data into separate data sheets to ensure that the data is de-identified and the researchers are blinded to the allocation status of the participants. Researchers will be blinded throughout the data collection and data analysis process. Treating surgeons as well as participants and their guardians will be blinded to the allocation into control or intervention groups.

**2. Emergency Unblinding**

Emergency unblinding will be done in any situation that is medically necessary or if the patient withdraws from the study and requests it. As data analysis will be done with the intention to treat principle, all data collected from this study will be included in the final analysis.

**18. Data Collection Methods**

**1. Data Collection Methods**

Data will be collected via Google forms. Participants will be assigned to Group 1 or Group 2 depending on the nature of their intervention (Celecoxib or control). Whether Group 1 or Group 2 is the intervention group will be unknown to the researchers until after the completion of data collection. Data collected will be automatically input into Excel for data analysis.

Participants or their caregivers will receive an email with details of their assigned group and instructions for completing the surveys. They will also receive links to the surveys for day 1, 3, 5, 7, 10 and day 14.

The day 1, 3, 5, 7, and 10 surveys will include the following questions:

1. Which group are you / your child in? (Group 1 or Group 2).
2. What was the average pain you/ your child experienced today where 0 where 0 is “no pain at all” and 10 is “the worst pain I’ve ever felt”?
3. How many doses of Oxynorm have you / your child had today?
4. Did you / your child experience pain today? (Yes/No).
5. If you answered no to question 4, how many days ago did you / your child last experience pain?

6. Have you / your child experienced any; (Bleeding, nausea, vomiting, drowsiness, other?). 7. Is there anything else you would like us to know?

Day 14 survey will also include the extra questions:

1. Have you / your child had any post-operative bleeding?
2. If you answered yes, did you / your child require another surgery?
3. How many days after your surgery did you stop taking your medications?

Researchers will be checking on those days which surveys have not been completed and participants will be contacted via phone call.

**2. Retention**

To maximise participant retention and completion of follow-up, researchers will:

* Promote uptake through education packets given to participants before their initial consultation
* Maintain interest in the study through reminder phone call, text message or email
* Discuss pain levels with participants post-tonsillectomy and ensure any questions are referred to the appropriate sources

**19. Data Management**

**1. Data form and data entry**

The information/data will be stored on REDCap software at Gosford Hospital. If participants withdraw from the study, their data will be erased from the database and any hard copy documentation will be disposed of in confidential bins. The data will be kept for the duration of study data collection and analysis and for 3 years after the completion of the study.

**20. Statistical Methods**

**1. Outcomes, Additional Analysis, Analysis Population and Missing Data**

Demographic and clinical characteristics of randomised participants will be summarised by group. Numeric variables will be reported as mean with standard deviation or median with interquartile range (IQR) if skewed. Categorical variables will be reported as frequency count and percentage. Pain scores will be summarised by group at days 1, 3, 5, 7, 10, and 14.

The primary outcome will be reported as the mean difference with 95% confidence interval in post-operative pain score at Day 7 (intervention versus control) and will be analysed using a t-test and a linear regression adjusted for gender and age group. All participants with non-missing outcome data will be included in the analysis and participants will be analysed according to their randomised group allocation as per the intention-to-treat (ITT) principle. Secondary outcomes will be compared between groups using chi-squared tests/logistic regression for binary outcomes (such as Day 14 postoperative bleeding) or log-rank tests/Cox regression for time-to-event outcomes (such as first pain-free day).

A sensitivity analysis for compliance will be conducted for the primary outcome. Safety data will be reported per group as total number of adverse events, number of participants with adverse event(s), and number of events by severity category. All analyses will be conducted at a significance level of 0.05. Analysis will be performed in SAS or SPSS or JAMOVI. Statistical analysis will be performed using the REDCap software. Data analysis will be reviewed by statisticians affiliated with UON.

**21. Data Monitoring**

**1. Interim Analysis**

No interim analysis will be required as data collection will be performed over a 2 week duration for participants and a 6 month duration for researchers. Due to the short time required for data collection, all data analysis will be conducted after the complete data set has been obtained.

**22. Harms**

A secondary outcome to be collected will be the number and incidence of adverse events experienced, specifically nausea, vomiting, diarrhoea, constipation, bleeding or drowsiness. Adverse events are defined as any unwanted medical occurrence in a participant without regard to the origin of this event i.e. any events due to common post-tonsillectomy complications or adverse effects of medication. Adverse effects experienced that are not listed above will be documented separately. If participants experience an adverse effect but are not assigned to the intervention drug, this will be reported as not related to Celecoxib. All adverse effects occurring post-tonsillectomy will be recorded until day 14 post-operation.

Severe adverse events are any unwanted medical occurrences that the researchers believe is causally related to the study-drug and results in a life-threatening condition (immediate risk of death), severe or permanent disability or prolonged hospitalisation. Any adverse event that meets the criteria for a severe adverse event (SAE) between study enrolment and day 14 post-operatively will be reported to the Head of Department, logged in the incident management system and fully investigated, although this is not expected to occur. If celecoxib is discontinued as a result of an adverse event, researchers will document the circumstances of the discontinuation.

**23. Auditing**

**1. Data Monitoring and Quality Assurance**

Data will only be available to the researchers.

**24. Research Ethics Approval**

This protocol and the template informed consent forms contained in Appendix I will be reviewed and approved by the sponsor and the applicable REGIS [Research Ethics Governance Information System] committee with respect to the scientific content and compliance with human subject regulations.

**25. Protocol Amendments**

Informed consent form, participants information and recruitment packaged and other requested documents, and any subsequent modifications, will also be reviewed and approved by the ethical review bodies. There are currently no protocol amendments.

**26. Consent or Assent**

**1. Consent or Assent**

Consent for participation will be obtained via the form in appendix B. Researchers and trained administration staff will obtain consent from the participants and their guardians. This will be obtained before any data collection begins. Medical staff participating in the tonsillectomy will not be obtaining consent from participants. All participants who are <18 years of age will require the consent of a parent or guardian. Any participant who is unwilling to disclose their participation in the trial to their parent or guardian will not be eligible for this study.

**2. Ancillary Studies**

There are currently no planned ancillary studies. If an ancillary study is proposed, a signed consent form must be obtained from every participant in the ancillary study, if the data collection/request is not covered in the original informed consent process for the main clinical trial.

**27. Confidentiality**

All study related information will be stored securely at Gosford Hospital. All participant information will be deidentified, stored on REDCap under password protection at the ENT office at Gosford Hospital.

**28. Declaration of Interests**

There are no declarations of interest.

***R.T., N.K., V.P., C.D.:*** are students undertaking this research projects as part of the research portion of the Bachelor of Medical Science/Doctor of Medicine degree (Joint Medical Program)

**29. Access to Data**

All principal investigators will be given access to de-identified data sets. This deidentified collated data and analysis will be published within the final report. Identified data will not be shared with any parties.

**30. Ancillary and Post-Trial Care**

Routine post-tonsillectomy follow up and care will be offered to all participants through Gosford Public Hospital and Gosford Private Hospital. Any associated health care costs will be managed by these facilities.

**31. Dissemination Policy**

**1. Trial Results**

Any data obtained within the study will be included. The study results will be released to involved physicians, participants, and the general medical community.

**2. Authorship**

All the researchers involved in the study will be authors of the publication, with the order to be decided in the publication phase.

**3. Reproducible Research**

De-identified data sets will be delivered to appropriate data archives for sharing purposes no later than 3 years after the last survey is completed.

**32. Appendices**

**Appendix A. Information packet**

**Text, letter

Description automatically generated**

**Text, letter

Description automatically generated**

**Text

Description automatically generated with medium confidence**

**Graphical user interface, text, application, email

Description automatically generated**

**Text, letter

Description automatically generated**

**Text, letter

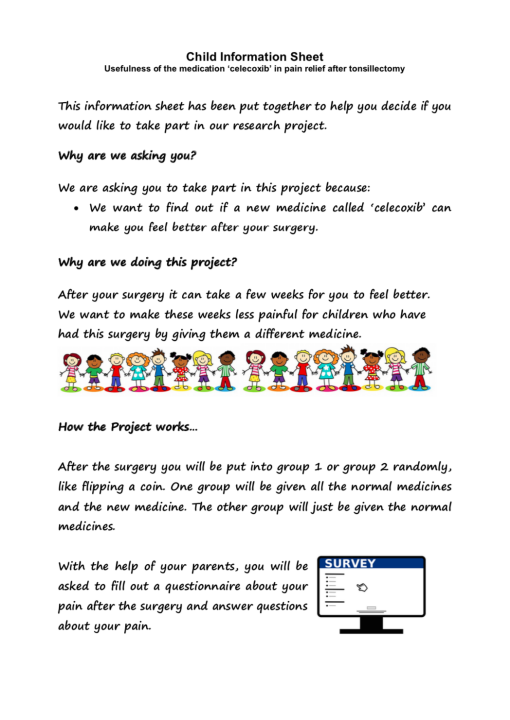
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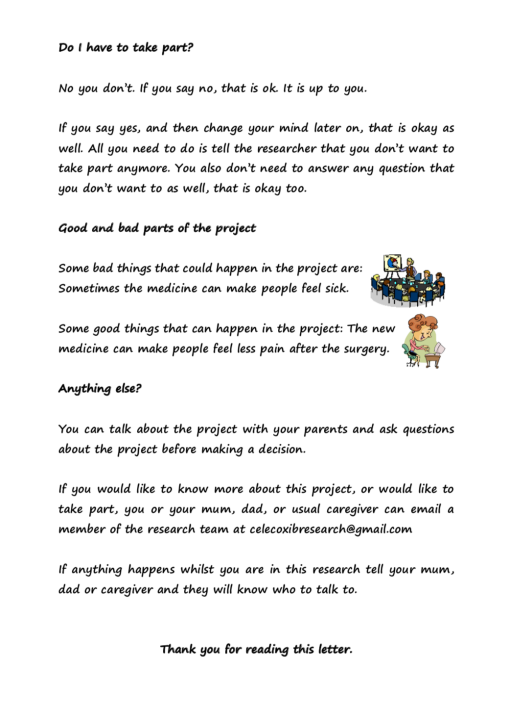
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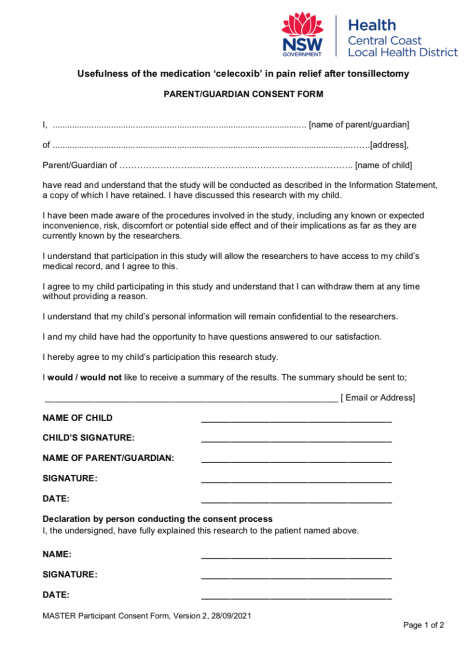
**Graphical user interface, text, application, email

Description automatically generated**





**Appendix B. Consent Form**

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