

A double blind placebo-controlled randomised trial to determine the efficacy of Gabapentin in the treatment of adenotonsillectomy pain at Red Cross War Memorial Children's Hospital

Moses Farai Penduka MBChB (UZ)

Registrar, Division of Otolaryngology Head and Neck Surgery, University of Cape Town Medical School

Johannes J Fagan, MBChB (UCT) MMED (UCT)

Professor and Head of Division of Otolaryngology,
University of Cape Town Medical School

Angeline Schrikker

Professional Nurse

Pain Management, Red Cross War Memorial Children's Hospital

Brenda May Morrow

Associate Professor,
Dept. Paediatrics

Hushandre Naiker

Chief Pharmacist

Red Cross War Memorial Children's Hospital

Graeme Copley

Division of Otolaryngology

Red Cross War Memorial Children's Hospital

Jenny Thomas, MBChB (UCT) FFA (SA)

Associate Professor, Department Anaesthesia, Red Cross War Memorial Children's Hospital

University of Cape Town Medical School

Address for correspondence

Dr Moses Farai Penduka

Division of Otolaryngology

Groote Schuur Hospital

Observatory 7925

Cape Town, South Africa

Email: mfpenduka@yahoo.co.uk; Phone +27214066420; Fax +2721448886

Declaration of the Investigator

Title: A double blind placebo-controlled randomized controlled trial to determine the efficacy of Gabapentin in the treatment of Adenotonsillectomy pain at Red Cross War Memorial Children's Hospital.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure (<http://druginfo.nlm.nih.gov>), Case Report Forms, and other scientific data. The study will not be commenced without the prior written approval of the Ethics Committee (EC). No changes will be made to the study protocol without the prior written approval of the EC, except where necessary to eliminate an immediate hazard to the patients. I will abide to all the conditions and instructions contained in this protocol.

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PROTOCOL SYNOPSIS

Title:

A double blind placebo-controlled randomized controlled trial to determine the efficacy of Gabapentin in the treatment of adenotonsillectomy pain at Red Cross War Memorial Children's Hospital

Layperson Title:

A study of oral Gabapentin in the treatment of pain following adenotonsillectomy to see if Gabapentin can reduce the level of pain

Study Centre:

Red Cross Memorial War Children's Hospital, Cape Town, South Africa.

Study Period:

2016-2017

Objectives:

Primary objective

- To determine the efficacy of Gabapentin when administered orally, three times daily, in paediatric patients with post adenotonsillectomy pain, as assessed by difference in mean pain intensity scores (compared to placebo) over 14days, when given in addition to paracetamol and ibuprofen in standard doses.

Secondary objectives

- To evaluate the potential efficacy of Gabapentin using several alternate endpoints.
- To evaluate if there is a change in the trend of post adenotonsillectomy pain.

Design:

Randomized, double blind, placebo controlled, parallel-group comparison (Gabapentin versus a placebo group), proof of therapeutic concept study.

Methodology:

Screening.

Determined by fulfillment of eligibility criteria. Potential participants will be required to provide written informed consent and assent consent.

Treatment Period

72 eligible male and female patients will be randomized to receive either Gabapentin or Placebo in addition to standard analgesia offered to patients following adenotonsillectomy. The on-study treatment period will be a total of 14 days. Patients will be assessed in the hospital pre- and immediately postoperatively for 24hrs and will attend the study center on Days 4, 7, 10 and 14 postoperatively. During the Treatment Period, study medication (Gabapentin or placebo) will be self-administered at home by the caregiver.

Number of patients:

Approximately 72 patients are expected to be enrolled and randomized in a 1:1 ratio to receive Gabapentin or placebo to achieve approximately 36 patients per treatment group completing the study.

[The calculation of the sample size is outlined under Statistical Methods on page 22 of this protocol.](#)

Population:

Patients aged 4 to 13 years undergoing adenotonsillectomy and meeting all other eligibility criteria.

[This age group represents the age at which children are expected to express pain and also the cut off age at which children may be seen at RCWMCH.](#) The investigators will be note immediately as to whether the patient is eligible or ineligible.

Inclusion Criteria

- All patients undergoing (adeno)tonsillectomy between ages 4 and 13 years

Exclusion Criteria

- Bleeding Diathesis
- Renal dysfunction
- Known allergy to Gabapentin
- No consent for participation
- Any comorbidity with contraindication to the use of NSAIDs

Treatment:

Test Product, Dose Mode of Administration

Gabapentin suspension will be administered at a dose of 10mg/kg thrice daily (In addition to standard postoperative analgesia) over 14 days

Reference Therapy, Dose Mode of Administration

Placebo, identical to the active drug in appearance but not containing Gabapentin, will be administered according to the same schedule as described for the Test Product (in addition to standard post-operative analgesia) over 14 days

Criteria for Evaluation

Primary efficacy endpoint:

- Difference in mean pain intensity score (using the visual analogue pain scale) between control and study groups over 14 days.

Note: A patient's daily pain intensity score across the preceding 24 hours will be recorded at a single time point in the evening prior to sleep. The daily pain intensity score will be used to calculate the mean pain intensity score during the Treatment Period.

Secondary efficacy endpoints:

- Weight changes
- Uninterrupted sleep
- Return of appetite
- Revisits to the health facilities with complications related to pain

Statistical Methods:

Approximately 36 patients will be enrolled per group. 72 Patients will be randomized in a 1:1 ratio to receive Gabapentin or placebo. Simple randomization using computer-generated random numbers will be used for simple randomization of subjects

Demographic data will be summarized for all patients.

All tabular summaries of data will be performed using all enrolled patients.

The primary and secondary endpoints will be assessed using the two-sample *t*-test.

Schedule of Assessments

Flow Chart depicted in Appendix A

Conflict of Interest

The study drug and identical placebo will be supplied by a pharmaceutical company that usually supplies medicines to the hospital.

INTRODUCTION

Tonsillectomy or adenotonsillectomy at RCWMCH is commonly performed for the management of obstructive sleep apnoea and recurrent tonsillitis. Although there is a general international consensus about the indications for adenotonsillectomy there are no guidelines on the postoperative management of adenotonsillectomy relating to complications, follow-up and pain management. Post-tonsillectomy oropharyngeal pain is one of the most severe types of pain and is reported by the *American Association of Otolaryngology Head and Neck Surgery (AAO-HNS)* as severe in up to 67% of patients and is the main cause of morbidity after tonsillectomy (5).

Pain following tonsillectomy is the most troublesome aspect of the procedure and can lead to complications including decreased food intake, dehydration, sleep disturbance, weight loss and increased risk of secondary haemorrhage. Post-tonsillectomy pain tends to be continuous with paroxysms on swallowing but also tends to display some of these features and has been noted on Day 4 to be referred to the jaw and ear (6). The evolution/trajjectory of post-tonsillectomy pain has been studied with different profiles identified, but the general trend is that of a significant drop from Day 1-7, with pain levelling off on Day 4 then increasing on Day 5 often doubling on Days 5-7 with the change to a downward trend coinciding with reports of the onset of ear and jaw pain (6, 19).

Researchers have been aware for decades that children's postoperative pain is poorly managed (6,7). A recent study has shown that up to 7.8% of post-tonsillectomy children had a health care revisit within 30 days (8). This is in keeping with an earlier study that showed strong evidence that post-tonsillectomy pain is associated with increased utilisation of health services, in some cases re-hospitalisation, implying considerable costs associated with inadequately managed pain (6). This is tragic given that it is the 2nd most common and 9th most cumulatively expensive reason of care in the

United States children's hospitals (9). Multimodal analgesic treatment has been advocated in postoperative pain management (2, 5,8,11, 14).

Despite this very little research has been done in children with respect to pharmacology and pain control, and we believe this to be an important area for investigation.

Classification of pain

The International Association for the Study of Pain (IASP) defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'(1). Despite the availability of effective pharmacologic treatments, most surgical patients experience acute, often severe, postoperative pain, and some experience pain that continues well beyond the normal healing period (2, 3, 4).

Pain may be classified in a multitude of taxonomies - duration (acute vs. chronic), pathophysiology (nociceptive vs. neuropathic), aetiology (cancer vs. non-cancer) or anatomic. Simplifying the classification of pain blinds us to the multidimensionality of the evolution of pain making treatment by the non-pain specialist inadequate. Healthcare providers may not be adequately trained to diagnose and treat complex pain states in patients who have otherwise recovered from surgery (2). Undertreatment of acute pain is a factor that has been identified as a risk factor for patients to progress from acute to chronic pain (4).

The *IASP* defines neuropathic pain as 'pain due to a primary lesion or dysfunction of the peripheral or central nervous system (1). It is often debilitating and chronic. All forms of neuropathic pain were acute at their inception and it is the passage of time that transforms it from acute through persistent to chronic. It has numerous causes; however the postsurgical causes have received very little attention in the scientific literature (12). The key features of neuropathic pain are a combination of paradoxical pain and sensory loss, the types including allodynia, hyperalgesia, hyperoathia, paroxysms, paraesthesia, dysthaesia, referred pain, abnormal pain radiation and wind up (13).

Post-tonsillectomy pain

Pain following tonsillectomy results from a multitude of factors including muscle spasm of pharyngeal muscles, including the soft palate pillars, nerve irritation and inflammation (11). Numerous techniques may be employed to perform a tonsillectomy including cold steel dissection, electrocautery, coblation, laser dissection and harmonic scalpel dissection. The operative procedure results in tissue damage which stimulates the glossopharyngeal and lesser palatine nerves. Thereafter, afferent nociceptive stimuli arrive in the pain centre of the brain and induce central neuronal sensitization (14). That postoperative pain, including post-tonsillectomy pain, is entirely nociceptive is questionable and studies do show a high prevalence of a neuropathic pain component as high as 68 % (1) with up to 37% of patients having unresolved pain at Day 6 postoperatively (10).

One of the neurotransmitters related to central neuronal sensitization is glutamate which is an excitatory amino acid. The N-methyl-D-aspartate receptor, which is activated by glutamate, transmits a nociceptive stimulus through the central nervous system and also maintains an unusual neuronal discharge leading to central neuronal sensitization of pain. This unusual hyper-reactivity has a major role in the production of pain in the CNS (14-17).

Current Management of Post-tonsillectomy Pain

Emphasis is usually directed toward immediate post-surgery pain, i.e. Day 0 and Day 1, with little attention paid to pain thereafter. The *Scottish Intercollegiate Guidelines (SIGN 117)* do not recommend any particular analgesics but places responsibility of pain control on the medical team and the caregiver; the *AAO-HNS*, though avoiding to recommend specific drugs, also places responsibility of pain management on the clinicians and caregivers. Other practices such as infiltration of the tonsillar fossa with various agents have been discouraged and others such as cryoanalgesia have not been adopted (11, 27, 28). The literature is thus devoid of any research into the optimal treatment of post tonsillectomy pain in children especially after the first 24-48 hours, though advocating for multimodal analgesic regimens for postoperative pain.

GABAPENTIN

Gabapentin is an anticonvulsant structurally related to GABA. It is an alkylated analogue of GABA with a mechanism of action that has not yet been characterised, but is known to modulate voltage-dependent alpha-2-delta calcium channel subunits (20, 22). By reducing calcium influx into nerve terminals it decreases the release of neurotransmitters such as glutamate (recalling that glutamate transmits a nociceptive stimulus through the CNS as well as neuronal sensitization of pain).

Gabapentin was first introduced in the United States in 1994 with anecdotal evidence of its efficacy in neuropathic pain first reported in 1995 (23). It is noted that publications regarding its non-epileptic use account for up to 40% of all reports on Gabapentin. Having the advantages of low toxicity and a favourable side effect profile, it has been used in neuropathic pain syndromes, psychiatric disorders and movement disorders (23). Its favourable effectiveness has been demonstrated in adults for postoperative pain control in abdominal, breast, spinal and thoracic surgery (24, 25, 26), which all advocate the use of multimodal analgesia in the treatment of postoperative pain. Gabapentin is the recommended first line treatment for neuropathic pain states in South africa (43)

Side effects as listed in the United States National Library of Medicine include but may not be limited to

- drowsiness
- tiredness or weakness
- dizziness
- headache
- tremors (uncontrollable shaking of a part of your body)
- double or blurred vision
- unsteadiness
- anxiety
- memory problems
- strange or unusual thoughts

- unwanted eye movements
- nausea
- vomiting
- heartburn
- diarrhea
- dry mouth
- constipation
- increased appetite
- weight gain
- swelling of the hands, feet, ankles, or lower legs
- back or joint pain
- fever
- runny nose, sneezing, cough, sore throat, or flu-like symptoms
- ear pain
- red, itchy eyes (sometimes with swelling or discharge)

Further detailed researcher and layman information relating to Gabapentin including lable information, indications, side effects and precautions, non-clinical and clinical trials may be obtained at The United States National Library of Medicnes with the links which follow:

http://druginfo.nlm.nih.gov/drugportal/ProxyServlet?mergeData=true&objectHandle=DBMaint&APPLICATION_NAME=drugportal&actionHandle=default&nextPage=jsp/drugportal/ResultScreen.jsp&TXTSUPERLISTID=0060142963&QV1=GABAPENTIN

Summary

[Summary of drug information \(MedlinePlusDrug\)](#)

[Summary of consumer health information \(MedlinePlusTopics\)](#)

[Summary of the effect on breastfeeding \(LactMed\)](#)

[Summary of Drug-Induced Liver Injury \(LiverTox\)](#)

[Summary of drug information and clinical research \(PubMed Health\)](#)

[Manufacturers drug label \(DailyMed\)](#)

[Clinical trials \(ClinicalTrials.gov\)](#)

[Drug Identification and Image Display \(Pillbox *beta*\)](#)

Detailed Summary

[Summary of reviewed biological and physical data \(HSDB\)](#)

[References from scientific journals \(Medline/PubMed\)](#)

[References from toxicological journals \(TOXLINE\)](#)

[Biological activities and chemical structures \(PubChem\)](#)

[Toxicological and chemical resources \(ChemID*plus*\)](#)

Additional Resources

[Information from the US Food & Drug Administration \(Drugs@FDA\)](#)

[Search engine for other government resources \(USA.gov\)](#)

RATIONALE

The off label use of gabapentin is wide spread in adults and its use in the paediatric population may be comparable. Neuropathic pain conditions, including postoperative neuropathic pain, are increasingly being recognized in children. However due to a multitude of factors research into paediatric neuropathic pain syndromes is limited. Many of the published studies on interventions of neuropathic pain in children are case reports or clinical series with few or no systemic controls. There is indeed a paucity of research.(38) The published case reports do show a benefit to the use of gabapentin in children with post-operative neuropathic pain(39).The proposed study, Gabapentin, is a double-blind, placebo-controlled, randomized trial designed to prove the efficacy of gabapentin when administered orally, three times daily in patients post Adenotonsillectomy aged 4 to 13 years, for 14 days.

Gabapentin is an Anti-Epilepsy Drug (AED) which has been shown to effectively treat neuropathic pain symptoms.

The safety of Gabapentin is supported in numerous clinical trials done previously.

RISK-BENEFIT ASSESSMENT

Not all pain postoperatively is nociceptive alone. The addition of an adjuvant to conventional treatment is thought to be beneficial. If the results of this study prove to improve pain control and related complications, the current management of not only post-tonsillectomy pain but post-surgical pain in general may be transformed. Recognized side effects of Gabapentin have been outlined above. Gabapentin is recognized as a safe drug. There are no toxic side effects that have been described at the intended dosing regimen to be prescribed for this study. Patients will be followed up and reviewed at

close regular intervals for the total duration of the study and thus provided with optimum level of monitoring for any potential adverse events to ensure adequate safety monitoring during the study.

The readily accessible safety profile of Gabapentin and its well documented efficacy on the treatment of neuropathic pain awards this study an excellent risk-benefit ratio.

STUDY OBJECTIVES

The current post-tonsillectomy treatment employed by our department at the RCWMCH comprises oral Paracetamol and Ibuprofen at standard doses initiated once the patient is awake and ready to tolerate oral intake. The aims of the proposed study are as follows:

Primary Objective:

- Difference in mean pain intensity score (using the Self Report Pain Scale and the FLACC in nonverbal children) between control and study group.

Secondary Objectives:

Is optimal pain control being provided to tonsillectomy patients in the days following Adenotonsillectomy?

- Weight changes
- Uninterrupted sleep
- Return of appetite
- Revisits to health centers with complications due to pain.

METHODOLOGY

This single centre, double-blind, placebo-controlled, randomised, post registration study is designed to investigate the efficacy of Gabapentin when administered orally, three times daily at standard dosing (10mg/kg/day in three divided doses) for 14 days (and a morning dose only on Day 1) in patients with

post Adenotonsillectomy pain. The secondary objectives of the study are to determine any change in the pain trajectory and other outcomes known to be directly related to post Adenotonsillectomy pain control.

The study consists of 14 day period during gabapentin is added to the routine post Adenotonsillectomy analgesia regimen used at RCCWMH. Gabapentin will be administered on the day of surgery 6 hours pre-operatively and post operatively (Day 1 to 14) three times daily. During this period there will be 4 scheduled follow up visits, visit 1(day 3), visit 2(Day 7), visit 3 (Day 10) and visit 4 (Day 14).

Essentially there will be two parallel groups divided as follows:

Group 1

- Gabapentin given preoperatively on the morning of surgery, approximately 6 hours before scheduled starting time, at a dose of 10mg/kg body weight
- Gabapentin in addition to Paracetamol and ibuprofen will be continued postoperatively up to Day14.

Group 2

- Placebo is given preoperatively on the morning of surgery, approximately 6 hours before scheduled starting time.
- Paracetamol, ibuprofen and placebo are given postoperatively up to day 14

Pain assessment

- A pain history is taken by the Principal Investigator (PI) or Pain Management Nurse prior to (adeno)tonsillectomy
- Pain will be assessed while the children are in hospital by the Pain Management Sister or an adequately trained State Registered Nurse in the ward

Tools (see Appendix E)

- Self-Report Pain Scale, Faces Pain Scale – Revised(FPS-R) , for children who can verbalise their pain

- FLACC scale in non-verbal children

In order to manage pain appropriately it is important to objectively assess pain. Numerous pain tools have been devised for this purpose. The validity of the FPS-R has been studied extensively in literature and has been shown to be a highly reliable pain assessment tool. Contrary to previous conceptions FPS-R demonstrates strong psychometric properties in children aged 4-7 years of age despite their age, ethnicity, race, sex or language (40). It has also been compared to other objective pain tools and found to be the most preferable pain scale (41). So accepted is the FPS-R that in numerous other studies it is used as the benchmark scale to validate other pain scales. Mahon et al used the FPS-R to validate the Rainbow pain scale (42). The FLACC was shown to display superior sensitivity and specificity for appropriate pain assessment when compared to the Comfort Behaviour scale for children after cardiac surgery.

Pain will be assessed in hospital immediately post-operatively using the Self-Report Pain Scale and FLACC Pain scales at 4, 8 and 12 hours postoperatively and at discharge. The same pain scales will be used at follow-up on Day 3, Day 7, and Day 10 and on the last postoperative follow up on Day 14. Patients will also be asked to complete a pain/treatment diary while at home

Surgery

- Tonsillectomy by Cold Steel dissection and ligation.
- Adenoidectomy by Curettage

Anaesthesia

- Standard Adenotonsillectomy Anaesthesia as per anaesthetist's preference. The anaesthetic technique will be documented.

It is expected that approximately 72 patients, divided equally between the 2 parallel treatment groups will be enrolled into the study to achieve approximately 36 patients per treatment group completing the study. Patients will be required to attend all study visits (Visit 1 – 4). Once informed consent is obtained, patients will be evaluated for eligibility based on the inclusion and exclusion criteria. A history and physical examination will be taken including measurement of weight. Patients will be instructed to record their daily pain intensity scores, how to complete a treatment diary and follow up schedule. At each visit Pain scores are obtained by the investigators as well as completion of the data

collection forms assessing the secondary end points. Specific enquiry will be done to assess for possible side effects of the treatment. The required consent form is depicted in Appendix B

ENDPOINTS

Primary efficacy endpoint:

Change in mean pain intensity score during the first 14 days post Adenotonsillectomy.

The daily pain intensity score will be used to calculate the mean pain intensity score.

Secondary efficacy endpoints:

- Weight changes over the 14 days postoperatively
- Revisits to health centres with complications related Adenotonsillectomy
- Return of normal appetite as determined by carer
- Time to return of baseline level of activity.

Justification of Study Design

The study is intended to evaluate the efficacy of Gabapentin when added to the standard regime in the treatment of post Adenotonsillectomy pain compared to placebo. The standard methodology for such a comparison is to conduct a double-blind, randomised, comparative study.

- Double-blind: This is to avoid the potential for bias. This is the accepted standard.
- Placebo control: This is to achieve double blinding.
- Continued supply of study medication: Patients will not continue to be supplied with the study medication at completion of the study, however those patients requiring ongoing pain

treatment will be referred to the pain clinic at RCCWMH where gabapentin may be continued to be supplied to the study population.

- Selection of dosage level and regime: This is based on standard dosing of gabapentin for paediatric patients. It is thus considered to be a safe and optimum dosing for patients.

STUDY POPULATION

Inclusion Criteria:

- All patients undergoing (adeno) tonsillectomy between ages 4 and 13 years

Exclusion Criteria

- Bleeding Diathesis
- Renal dysfunction
- Known allergy to Gabapentin
- No consent for participation
- Any co-morbidity with contraindication to the use of NSAIDs

Patient Withdrawal and Replacement:

Patients may exit the study at their own free will without prejudice.

Patients must be withdrawn under the following circumstances:

- The patient withdraws consent
- Severe adverse event(s)
- At the discretion of the investigator
- Violation of eligibility criteria
- Postoperative bleeding requiring surgical control

Any reason for withdrawal from the study will be recorded.

A patient will be considered as having completed the study if he/she has completed all visits through Day 14 of the Treatment Period. Patients who are withdrawn from the study for any reason before completion of the Treatment Period will not be considered to have completed.

Additional patients may be enrolled into the study to achieve approximately 30 completed patients in each group.

Patient Randomisation

Randomisation will occur on Day 0 after all Screening procedures and baseline assessments have been performed and eligibility for the study confirmed. Randomisation will be done using computer-generated random numbers for simple randomization of subjects to achieve a 1:1 ratio to receive Gabapentin or placebo in addition to standard analgesia. To ensure allocation concealment all randomisation will be done at the pharmacy as the patients preoperative medications are issued.

Packaging, Labelling and Storage

Study medication will be labelled and packaged by the supplier and stored in the hospital pharmacy.

Blinding and Breaking the Blind

The study is a double-blind trial hence all drugs supplied will be in similar packaging and colour thereby enabling double-blind conditions.

The study blind should not be broken except in a medical emergency. The reason for unblinding, date and time will be required and recorded.

If anyone is unblinded at any point during the study the patient is withdrawn from the trial and the reason for withdrawal is once again recorded. If the breaking of the blind was due to a severe adverse event the patient should be followed up until the adverse event has resolved or stabilised

PARAMETERS AND STUDY CONDUCT

Efficacy Parameters

- Daily Pain Intensity Score

- Days to uninterrupted sleep
- Weight assessed using a standard scale
- Number of unscheduled visits to a health centre
- Days to return of normal oral intake/appetite

At each visit a pain history will consistently be obtained the above parameters entered into excel tables depicted in Appendix C. The treatment diary (Appendix D) will also be inspected to attain pain scores and analgesic requirements.

STATISTICAL METHODS

All parameters were assumed as follows on a 10 point pain scale: mean pain score of a new drug = 6; mean pain in standard group =8; $\alpha=0.05$; $\beta=0.20$; $\delta=6$; $\delta_0=2$; $s=8$

For statistical superiority design, the formula is:

$$N = 2 \times \left(\frac{z_{1-\frac{\alpha}{2}} + z_{1-\beta}}{\delta} \right)^2 \times s^2$$

For clinical superiority design, the formula is:

$$N = 2 \times \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\delta - \delta_0} \right)^2 \times s^2$$

$$N = \frac{(1.96+0.845)^2}{6} \times 2 \times 8^2 = 27.9752$$

Thus approximately 30 patients will have to be enrolled for each group. However assuming a 20% loss of patients to follow up we will enrol 72 patients.

Study Patients

1. Disposition of Patients.

Patient disposition including the number of patients enrolled by treatment arm and the numbers and percentages of patients in each of the Full Analysis Set and Per-protocol Set will be summarised. In addition, the number and frequency of patients discontinuing the study will be summarised, along with the reasons

2. Protocol Deviations.

Investigators will apply due diligence to avoid protocol deviations. Deviations from the protocol, including violations of inclusion/exclusion criteria, will be assessed as “minor” or “major”. Major deviations from the protocol will lead to the exclusion of a patient from the Per-Protocol Set. Deviations will be defined prior to unblinding.

3. Analysis Populations

- The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomisation. According to the intent to treat principle, patients will be analysed according to the treatment they have been assigned to during the randomisation procedure.
- The Per-Protocol Set (PPS) consists of the subset of the patients in the FAS that are compliant with requirements of the Clinical Study Protocol. This population is defined for use in supportive analyses for the primary and secondary efficacy endpoints.
- The primary and secondary efficacy analyses will be based on the Full Analysis Set, although a secondary analysis will also be performed based upon the Per-Protocol Set, to assess the sensitivity of the analysis to the choice of analysis population.

Treatment Compliance

A patient will be considered sufficiently compliant with study treatment if they have taken at least 50% of their prescribed study treatment.

ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

Data Collection Quality Assurance

- Only the principal investigator and other investigators on the research team will be responsible for data capturing.
- Information collected will be recorded on an Excel spread sheet and kept on the principal investigators personal computer
- The study staff will review all data on an ongoing basis for data completeness and accuracy.
- Data on adherence to treatment protocol will be reviewed monthly research team.

The Investigators will ensure adequate and correct documentation, maintaining accurate data and capturing of all information and maintaining medical records. The investigators will enter the data required by the protocol into the forms shown in the appendix additional information entered into the patients' medical records when required.

Archiving Study Records

No personal identifiable data will be collected, apart from the patient's hospital number. The information obtained from the study will be published such that patients' identities will remain anonymous. This confidential information will remain in a secure place that is locked up, and only be accessed by the investigators. Researchers from this institution in future, however, may examine the results of the study. All essential documents will be maintained as per RCCWMH policy but may be retained for longer if so required.

Good Clinical Practice

During the entire duration of this study principles of the South African Good Clinical Practice guidelines second edition will be adhered to.

Informed Consent/Assent Consent

Before each patient is admitted to the study, informed consent will be obtained from the legal guardian/parents along with assent consent for children over seven years or younger if they are of an appropriate developmental level. The investigator will not undertake any study-related assessments until valid consent has been obtained. A sample of the consent form is included in this protocol (Appendix B).

- The parent/guardian will be asked to review the consent form

- The PI/ co-investigators will meet with the guardian and subject to review the form and confirm their understanding of the study

Protocol Approval and Amendment

Before the start of the study, the Ethics Committee will have to approve the study protocol and/or other relevant documents.

Duration of the Study

For an individual patient, the duration of the study will be up to 14 days. The study will close when all patients have completed the Follow-up.

Premature Termination of the Study

If the Investigators or the managers of RCCWMH become aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties.

Stopping Rules

This study will be stopped prior to completion if:

- If there is associated adverse effects that question the safety of the intervention.
- Difficulty in study recruitment or retention will significantly affect the ability to study the endpoints
- Any new information becomes available during the trial that necessitates stopping the trial
- Other situations arise that would compel stopping the trial

Confidentiality

All study findings and documents will be regarded as confidential. The investigators and members of the research team must not disclose such information without prior written approval from the

RCCWMH and the University of Cape Town ethics committee. The anonymity of participating patients must be maintained.

Designation of a monitoring committee

An Independent Monitoring Committee (IMC) to perform independent review of on going study progress and safety has been designated. The IMC includes Dr Shazia Peer, a paediatric otolaryngologist and Dr Janieke Van Nugteren, an anaesthetist with a particular interest in pain management, they are qualified to review the patient safety data because of their unique expertise in Paediatric Otolaryngology, Paediatric Anaesthetics and Pain Management , Pharmacology and Research.

Safety Review Plan

Though this study is not powered sufficiently to study safety, study progress and safety will be reviewed monthly(and more frequently if needed). Reports will be submitted to the independent monitors as frequently.

Budget

See appendix H for the budget summary.

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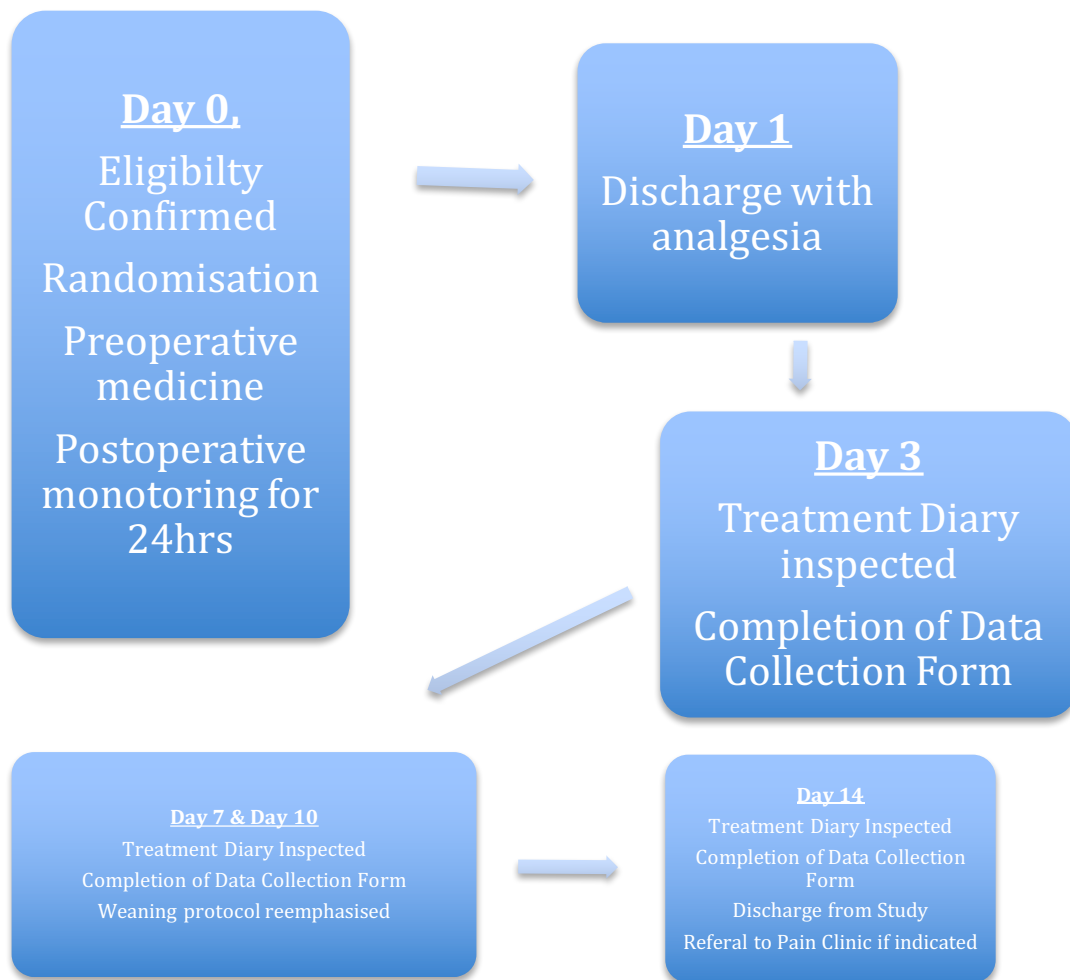
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APPENDIX

Appendix A

Flow Diagram



- **Day 0,**
 - Eligibility confirmed
 - Randomisation
 - Preoperative medicine
 - Postoperative monitoring for 24hrs
- **Day 1**
 - Discharge with analgesia
- **Day 3**
 - Treatment Diary inspected
 - Completion of Data Collection Form
- **Day 7 & Day 10**
 - Treatment Diary Inspected

- Completion of Data Collection Form
- Weaning protocol reemphasised
- **Day 14**
 - Treatment Diary Inspected
 - Completion of Data Collection Form
 - Discharge from Study
 - Referral to Pain Clinic if indicated

Appendix B

Consent/Assent form

Gabapentin Post-adenotonsillectomy Pain Study

CONSENT FORM

Introduction

We invite you to consider your child taking part in this research study which aims to identify a better way of treating pain after Adenotonsillectomy surgery. Taking part in this study is entirely voluntary. We urge you discuss any questions about this study with our staff members. Take your time to make your decision. If you decide to allow your child to participate, you must sign this form to show that you understand the study and are happy for him/her to take part.

Purpose of study

The purpose of this study is to compare the effects of giving an extra medicine to your child on top of the usual medicines given after Adenotonsillectomy to control the pain. The standard treatment for pain after this operation is Paracetamol (Panadol) and Ibuprofen. The study will determine whether adding Gabapentin improves pain control after the operation. In this study, your child will receive either Gabapentin or Placebo in addition to Paracetamol and Ibuprofen. A placebo is something that looks, tastes and smells like the real medicine (Gabapentin), but has no effect on the human body.

Procedures

Your child will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance, like throwing a coin. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

Depending on which group you are in your child will be receiving either gabapentin or a medicine that appears to be gabapentin but has no effects on the human body, also called a Placebo. Whichever group your child is placed he/she will be followed up to assess if the pain control is adequate.

Duration of study

Your child will be involved in the study for 14 days during which he/she will be followed up four times after the operation.

Risks of participating in the study

Gabapentin is a safe drug with low toxicity and favourable side effect profile if taken at prescribed doses. You will be monitored for side effects on your follow up visits. The known side effects of gabapentin, though uncommon include somnolence, dizziness ataxia, headache, nystagmus, tremor, fatigue, visual disturbances, peripheral oedema, nausea and vomiting, dysarthria, confusion, skin reactions, dyspepsia, vasodilation, impotence and haematological reactions

Benefits of participating in this study The possible benefit your child may experience from gabapentin is optimal pain control. However, there is no guarantee that you will get this benefit. The results of this research may guide the future treatment of post-operative pain.

Confidentiality Your child's identity will be kept secret and will not be published along with the outcomes of this study. We will keep your child's participation in this research study confidential to the extent permitted by law.

Costs for participation

At the end of the study you will be reimbursed for the transport costs incurred for the follow up visits at a rate of R50.00 per visit.

What if Something Goes Wrong?

The University of Cape Town (UCT) has insurance cover for the event that research-related injury or harm results from your participation in the trial. The insurer will pay all reasonable medical expenses in accordance with the South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI) in the event of an injury or side effect resulting directly from your participation in the trial. You will not be required to prove fault on the part of the University.

The University will not be liable for any loss, injuries and/or harm that you may sustain where the loss is caused by

- The use of unauthorised medicine or substances during the study
- Any injury that results from you not following the protocol requirements or the instructions that the study doctor may give you
- Any injury that arises from inadequate action or lack of action to deal adequately with a side effect or reaction to the study medication *
- An injury that results from negligence on your part *

[* Researchers must bear in mind that it is unacceptable to impose a burden on participants who may not recognize symptoms or have the ready means to take action.]

“By agreeing to participate in this study, you do not give up your right to claim compensation for injury where you can prove negligence, in separate litigation. In particular, your right to pursue such a claim in a South African court in terms of South African law must be ensured. Note, however, that you will usually be requested to accept that payment made by the University under the SA GCP guideline 4.11 is in full settlement of the claim relating to the medical expenses. “

An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. It is important to tell the study doctor if you are thinking about stopping so that he/she can evaluate any risks from the treatment. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Contact Information for Questions or Concerns

You have the right to ask any questions you may have about this research. If you have questions, complaints, or concerns or believe you may have developed an injury related to this research, contact Dr M Penduka at 0781341811 and Ethics Board Professor Blockmann on 021406492

Participants Authorisation

Your signature below means that you have received this information, have asked the questions you currently have about the research, and have received answers to those: By signing this consent form, you indicate that you are voluntarily choosing for your child to take part in this research study. You will receive a copy of the signed and dated form to keep for future reference.

By signing this consent form, you indicate that you are voluntarily choosing to take part in this research

Signature of legal guardian: _____ Date: - -20_____

Witness signature: _____ Date: - -20_____

Assent Consent

This assent consent is for children aged between 7 and 13 who are eligible to take part in the Gabapentin Post Adenotonsillectomy study.

Introduction

My name is _____. We are doing research to test pain medications to see which works best to make pain better after an operation. We want to know if another medication makes the operation less painful.

I am going to give you information and invite you to be part of a research study. You can choose whether or not you want to participate. We have discussed this research with your parent(s)/guardian and they know that we are also asking you for your agreement. But if you do not wish to take part in the research, you do not have to, even if your parents have agreed.

There may be some words you don't understand or things that you want me to explain more about because you are interested or concerned. Please ask me to stop at anytime and I will take time to explain).

Why are you doing this research?

We want to find better ways to make operations less painful. We are going to use a medicine that is known to make certain types of pain better.

Why are you asking me?

We are giving it to children who have had an operation like you are having because it can be very painful and we believe this drug can make the pain better.

Do I have to do this?

You do not have to take part in the research. It is up to you. Even if you say yes, you are allowed to change your mind later.

I have checked with the child and they understand that participation is voluntary _____ (initial)

What is going to happen to me?

We are going to test this medicine by giving some children and giving others another medicine, which looks like it to see who feels better after the operation. Neither you nor us will know who has been given the medicine.

If you decide you want to do this you will be given the medicine of one that looks like the medicine and you will have to take it every day for two weeks. During those two weeks we will see you three or four times after the operation to see how well your pain is controlled.

Is this bad or dangerous for me?

The medicine is considered safe. There maybe some side effects of the medicine but these are quite uncommon and we have explained to your guardian. But you must tell your guardian if you are not feel well at any time so that they can bring you to the hospital.

I have checked with the child and they understand the risks and discomforts _____(initial)

Is there anything good that happens to me?

If what we believe is true, then if you are getting the study medicine you will feel less pain than you would if you had not taken it.

I have checked with the child and they understand the benefits_____ (initial)

Is everybody going to know about this?

We will not tell anyone that you are in this research project and we will not share information about it with any one who is not involved in this research.

What happens if I get hurt?

If you become sick during the we will look after you. We have given your parents information about what to do if you are hurt or sick.

Who can I talk to or ask questions to?

You can ask me questions now or later.

Certificate of Assent

I have read this information (or had the information read to me) I have had my questions answered and know that I can ask questions later if I have them.

I agree to take part in the research.

OR

I do not wish to take part in the research and I have not signed the assent below. _____(initialled by child/minor)

Only if child assents:

Print name of child _____

Signature of child: _____

Date: _____
day/month/year

If illiterate:

A literate witness must sign (if possible, this person should be selected by the participant, not be a parent, and should have no connection to the research team). Participants who are illiterate should include their thumb print as well.

I have witnessed the accurate reading of the assent form to the child, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness (not a parent) _____ AND Thumb print of participant

Signature of witness _____

**Date _____
Day/month/year**



I have accurately read or witnessed the accurate reading of the assent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given assent freely.

Print name of researcher _____

Signature of researcher _____

**Date _____
Day/month/year**

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the child understands that the following will be done:

- 1.
- 2.
- 3.

I confirm that the child was given an opportunity to ask questions about the study, and all the questions asked by him/her have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this assent form has been provided to the participant.

Print Name of Researcher/person taking the assent _____

Signature of Researcher /person taking the assent _____

**Date _____
Day/month/year**

Copy provided to the participant _____(initialed by researcher/assistant)

Parent/Guardian has signed an informed consent ___Yes ___No _____(initialed by researcher/assistant)

Appendix C

Data Collection Form

Hospital Number	Day 0	Day 1	Day 4	Day 7	Day 10	Day 14
Pain Scores	4hrs					
	8hrs					
	12hrs					
Weight Change/kg						
Uninterrupted sleep						
Health Centre Visits						
Normal Eating						

Appendix D

Treatment diary

Hospital Number	Day 1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
Medications														
Panado	Time													
brufen	Time													
Gaba	Time													
Pain Score														

Appendix E Pain Scales

The FLACC Scale

Recommended when a child cannot verbalise if they have pain (or in children between 1 and 3 years old)

Observe a child for 1-5 minutes to obtain a pain score.

Rate the child in each of the five categories between 0 and 2 (select the number that most closely matches the observed behaviour), add together and document total pain score 0-10.

What to do: A score equal or greater than '5' indicates pain.

If so, contact the doctor, registered nurse or pain management team to assess pain treatment or prescribe alternative analgesia. Continue to assess pain until you are assured that the child is pain free.

Categories	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, with-drawn, disoriented	Frequent to constant frown, quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whispers; occasional complaints	Crying steadily, screams or sobs, frequent complaints
Consolability	No cry (awake or asleep)	Reassured by occasional touching, hugging or being talked to; distractible	Difficult to console or comfort

Ref: Merkel, S., Voepel-Lewis, T., Malviya, S. 2002. Pain Control: Pain Assessment in Infants and Young Children: The FLACC Scale. Journal of Nursing, 102 (10):55-56.

Collaborators: A. Schrikker; Child Nurse Practice Development Initiative; Prof. J. Thomas & IIC/WCUI Nursing Management

Faces Pain Scale

Recommended when a child is old enough to verbalise their pain (usually age 4 – 16 yrs)

This scale measures how children feel inside (pain) not how their face looks.

Explain to the child that you want to assess their pain and not emotions, avoid words like 'happy' and 'sad'.

Explain the following to the child:

- These faces show how much something can hurt.
- The face on the left shows no pain.
- The faces show more and more pain from left to right up to the one on the far right, it shows lots of pain.
- Ask the child to point to the face that shows how much they hurt or are in pain [right now].

Score the chosen face 0, 2, 4, 6, 8, or 10, counting left to right, so '0' = 'no pain' and '10' = 'lots of pain.'

What to do:

A score equal or greater than '5' indicates pain.

If so, contact the doctor, registered nurse or pain management team to assess pain treatment or prescribe alternative analgesia.

Continue to assess pain until you are assured that the child is pain free.



NO PAIN → LOTS OF PAIN

Ref: Hicks, C.L., von Baeyer, C.L., Spafford, P., van Kortlaar, J. & Goodenough, B. 2001. The Faces Pain Scale - Revised: Toward a common metric in pediatric pain measurement. Pain 93(2):173-183.

Appendix F

Demographics table (Excel)

Characteristics		N	N%
Gender			
	Male		
	Female		
Ethnicity			
	Coloured		
	Black		
	White		
Age			
	Mean(se)		
	Median(min/max)		

Appendix G

Enrollment data (Excel)

Hosp#	date enrolled	Date completed	Status	Reason for withdrwal	

Appendix H

University of Cape Town, Dept. of					
otolaryngology					
Budget Proposal					
Title: A double blind placebo-controlled randomised controlled trial to determine the efficacy of Gabapentin in the treatment of Adenotonsillectomy pain at Red cross War memorial Children's Hospital					
Principal Investigator: Jenny Thomas					
Study Coordinator: Moses F Penduka					
Per Subject Budget		Cost Per Unit		Units	Total Cost
Placebo		x		40	40x
Study drug		y		40	40y
Hospital Visits		200		72	14400
Total					14400+40x +40y
Fixed Study Budget		Cost Per Visit		Units	Total Cost
Research Nurse Overtime		0.00		10	0.00
Variable Costs					
SAE					