Queensland Government
West Moreton Health

RESEARCH PROTOCOL

A Randomised Placebo-Controlled Trial: Co-phenylcaine vs. Gel Lubricant vs. Placebo in Flexible Nasendoscopy

Project Summary Researchers

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Background

Flexible nasendoscopy is a routine examination in any otolaryngology outpatient department. It is an important part of the assessment of the nasal airway, pharynx and larynx. Many otolaryngologists are concerned that this examination can be a significant source of discomfort for the patient, especially those patients who require regular screening with nasendoscopy and therefore try to reduce this discomfort by the application of local anaesthetics. There are many different approaches to topicalisation or lubrication in preparation for nasendoscopy. These include lubrication with saline, water-soluble lubricating gel or topical anaesthesia with a lignocaine-based spray such as co-phenylcaine with or without a vasoconstrictor.

There are several studies which have compared some of the varying options for nasal preparation for nasendoscopy. Frosh et al. in 1998 found that the use of xylocaine spray makes the experience worse for the patient compared to no spray and hypothesised that the psychological effect of the spray caused anticipation of the exam and therefore a worse overall experience. Alternatively, they theorised that the anaesthetic agent could be causing a paradoxical hyperaesthesia to the mucosal lining (1). In 2002 Cain et al. conducted a double-blind randomised controlled trial comparing co-phenylcaine topicalisation with placebo and no preparation and concluded that use of co-phenylcaine spray did not give significant advantages over the use of no nasal preparation (2). A multicentre study in the UK and Greece did not find any significant difference in pain or overall discomfort experienced between co-phenylcaine and placebo.

However the sensation of bad taste was significantly worse with cophenylcaine (3). These studies focussed on the patient experience rather than the clinician experience and did not record the ease with which the scope was passed or the quality of the view. Javed et al. found similar results for patient experience, however had significantly better ease of examination scores with the co-phenylcaine than the placebo group (4).

Co-phenylcaine spray is the combination of Lignocaine hydrochloride, a topical anaesthetic, and phenylephrine hydrochloride, a vasoconstrictor and nasal decongestant. The degree to which topical vasoconstrictors alone affect patient discomfort is still unknown. Logically, increasing the nasal aperture by reducing congestion with a vasoconstrictor would improve ease of examination with a nasendoscope. In one study which compared lignocaine and phenylephrine, lignocaine alone and xylometazoline (Otrivin) with no preparation, more than 80% of patients from each group still experienced some degree of unpleasantness. They found that using a vasoconstrictor alone, which is significantly less expensive, was just as effective as using the combined therapy and that pain was not significantly increased in the absence of local anaesthetic. General unpleasantness was significantly reduced by the vasoconstrictor, but not by the local anaesthetic, this is likely due to the taste (5).

In the paediatric population there has been no significant difference found between the discomfort experienced during nasendoscopy after placebo spray, decongestant or topical local anaesthetic with decongestant. Decongestant alone was associated with the least discomfort and the lowest rating of difficulty in performing the procedure (6). A similar study of 53 children comparing lignocaine with oxymetazoline to oxymetazoline alone, found no difference in the duration of endoscopy, quality of view, ease of performance and cooperation of patients. The median pain and anxiety scores were not significantly different (7). This suggests that the addition of lignocaine in the topicalisation does not offer any additional benefits in paediatric nasendoscopy.

Another study aimed to explore the role of patient related and operator related factors in pain perception during flexible nasendoscopy. 532 patients were examined, greater pain was associated with female patients, whereas the pain was less severe in the cases of experienced laryngologists and older patients (8).

Another option for nasendoscopy is lubrication of the scope with water soluble gel, with or without local anaesthetic. Pothier et al. looked at 150 patients and compared the levels of discomfort experienced by patients with or without lubrication of the nasendoscope with KY Jelly. There was no difference between mean pain scores. Scores for difficulty of passing the scope were significantly lower in the lubricant group but loss of image was significantly greater (9). The same author conducted a second study into whether the same advantages of lubrication with KY Jelly could be achieved using water without incurring the same disadvantages of compromised view. Endoscopists found that insertion and image quality was better when water was used rather than KY Jelly and no difference was reported in pain or patient experience (10).

Finally, a systematic review of the literature was conducted by Conlin & McLean 2008, in which eight randomised controlled trials were included, all using visual analogue scales (VAS) to quantify patient's experiences of either pain, discomfort or unpleasantness. Across three studies of 170 subjects there was no significant difference between co-phenylcaine and saline or no treatment, but a higher degree of unpleasantness of taste. Only two studies measured endoscopists outcomes with incongruent results, one finding that co-phenylcaine improved the view, the other finding no difference to placebo and only one study which reported a worse view with a lubricating agent (11).

Further research is needed to confirm or refute the efficacy of lubricating agents and the impact on examiner experience. There are also few studies which consider the impact of examiner experience level on patient outcomes.

Study Objectives

1. To compare no treatment, saline (placebo), co-phenylcaine (local anaesthetic and decongestant) and the use of gel lubricant looking at patient reported outcomes: pain, discomfort, taste, repeatability, and examiner reported outcomes: ease of passing scope and quality of view.
2. To take note of and evaluate differences in patient outcomes when comparing different examiner experience level: resident, principal house officer, registrar, consultant.
3. To determine the best method of topicalization for use in our outpatient clinic for both patient and examiner, and to evaluate cost effectiveness in the context of findings.

Study Design

A double-blind randomised controlled trial

Allocation of participants will be carried out using a computer-generated list of random numbers, participants will be stratified via blocked randomisation with an allocation of 1:1 into the four trial groups. Groups and details of randomisation are as stated below.

The two sprays (saline and co-phenylcaine) will be prepared in identical bottles that are multi-use. One of the research co-ordinators who is not involved in the enrolment, allocation or intervention will prepare the sprays.

The study will be double blinded, apart from the use of lubricant or when no treatment is administered which will be evident to the examiner. The allocation sequence will be concealed from the examiners in sequentially numbered, opaque and sealed envelopes. Patient's will not be privy to the method of topicalisation of any other patient as the procedure will be performed in separate rooms, thus keeping the allocation blinded.

Nasendoscopy will be performed in the outpatient setting in the context of the usual work up and examination of patients. It will be performed by varying levels of examiner including resident, principal

house officer, registrar and consultant. This will be recorded and later used in subgroup analysis, to reflect the variability of examiner in a real clinical environment.

Although principal house officers, registrars and consultants are already proficient in this type of examination, residents regularly rotate through the ENT Department every 10 weeks. It is routine as part of their rotation to learn to perform nasendoscopy and therefore to reflect normal clinical practice in a public hospital, they will be included in this study. However, prior to their participation they will be given a half hour orientation on the use of equipment and technique in performing the examination and will be under the supervision of a senior member of the team for all examinations.

Participants will be over age 16 years and undergoing nasendoscopy as part of their routine clinical assessment in the outpatient clinic where they will be invited to participate in the study. This will include patients who have had previous nasendoscopy, which will be recorded. Any patient with a known allergy to the study medications will be excluded. Pregnant or breast-feeding patients will be excluded (*Table S1*).

By definition nasal endoscopy includes the assessment of the postnasal space, base of tongue, vallecula, pyriform fossae and larynx. This will be conducted using a Storz nasendoscope and video stack available in the ENT outpatient clinic.

Table S1 Inclusion & exclusion criteria

Inclusion criteria	**Exclusion criteria**
Age 16 years and older	Age below 16 years
Any patient requiring routine nasendoscopy	Patients with previous allergy or sensitivity to study medications
Patients who have previously had nasendoscopy examination	Pregnancy or breast-feeding
Patients who present to the ENT outpatient department and who are inpatients and able to give an accurate assessment of their experience	Patient's requiring nasendoscopy in an emergency situation who are unable to give an accurate assessment of their experience

Groups

(I) No treatment
(II) Normal Saline Spray
(III) Co-phenylcaine Spray (lignocaine + phenylephrine hydrochloride)
(IV) Gel Lubricant

Methodology

Patients will be consented by the examiner in the context of their clinical consultation. It is usual for this type of examination to explain the procedure and to get verbal consent, however for the purposes of the study written consent will also be obtained to use the data collected for publication. This will include the option to not have their data included in the study, which will not impact on their care or on the performing of the examination, the method of topicalisation will be at the patient's discretion in this case. See PICF.

For those that choose to take part in the study, they will be randomly assigned to receive either no topicalisation, two puffs of topical nasal spray (or placebo) into each nostril five minutes before examination or gel lubrication on the end of the endoscope. The medication will be delivered using a standardised multi-use pump dispenser, that will be de-identified to the examiner and participant, labelled 'A' and 'B'. In the co-phenylcaine group each spray is equivalent to 6.5mg lignocaine and 0.65mg of phenylephrine hydrochloride.

The two sprays will be directed posteriorly along the floor of the nasal cavity by the examiner, towards the inferior turbinate and nasopharynx. In the group with lubricant, 1cm of gel lubricant will be applied to the end third of the endoscope, taking care not to initially cover the fibreoptic end. The tip of the endoscope may be demisted with an alcohol wipe, as is usual practice. The scope will be passed through the most accommodating nostril as chosen by the examiner. The scope will be passed to the posterior nasal space and down past the oropharynx to fully examine to larynx and hypopharynx.

The patients will then be asked to fill out a short questionnaire in the form of a 100 mm VAS for pain, discomfort, taste and repeatability. Examiners will similarly complete a VAS for ease of examination and quality of view. VASs have been used in all comparable studies in the literature and is a validated method of data collection, it will be used here for ease of comparison to previous literature (Appendix 1).

Sample Size

A power calculation using the equation: Standard Difference = Difference between Means/Population SD; and a 99% confidence Interval. See below *Table S2* for power and sample size calculations for the study outcomes of interest based on available statistics in the published literature (12). We aim to recruit approximately 50 patients per group, with a total of 200 patients.

Table S2 Power calculation of sample sizes based on published studies for each outcome of interest

Outcome measure	Difference in mean	Standard deviation	Standardised difference	Approximate number of patients	Including attrition (30%)
Discomfort cophenylcaine vs placebo (ref: Bonaparte 2011)					
VAS score	18.3	25.8	0.71	54	71
Pain cophenylcaine vs placebo (ref: Bonaparte 2011)					
VAS score	11	23.4	0.47	105	137
Pain (ref: Javed 2017) please note they are using median values					
VAS score	5 (median)	6	0.8	42	55
Discomfort (ref: Javed 2017) please note they are using median values					
VAS score	3.5 (median)	5.5	0.63	74	97
Unpleasantness (ref: Javed 2017) please note they are using median values					
VAS score	3.5 (median)	5	0.7	54	71
Willingness to repeat (ref: Javed 2017) please note they are using median values					
VAS score	1.5 (median)	4	0.4	170	221
Ease of examination (ref: Javed 2017) please note they are using median values					
VAS score	15.5 (median)	10.5	1.48	14	19
Quality of view (ref: Javed 2017) please note they are using median values					
VAS score	2	4	0.5	105	137

Randomisation

Prior to study commencement all examiners, doctors working in the ENT Department, will be briefed on the study protocol and the procedure for allocation and data collection. They will not be privy to the contents of the de-identified spray bottles or to the randomised allocation sequence.

When patients enter the study, they will be given a participant number. Randomisation software will be used to generate a list of numbers in random sequence, a set of 200 numbers ranging from 1 to 4. Patients will be assigned sequentially to this list to determine which group they are allocated to. Blocked randomisation will be performed to ensure an even distribution between groups with the goal of 50 patients per group, with a total of 200 patients recruited (*Figure S2*).

In practical terms the allocation sequence will be available to examiners in the form of individual sealed envelopes in the clinic. So that when a patient is reviewed in clinic, the doctor seeing them can pick up the next sealed envelope which will read one of the following:

(I) No treatment

(II) Bottle A

(III) Bottle B

(IV) Gel

Each clinic room will have two identical spray bottles labelled ‘A’ and ‘B’, one with saline and one with co-phenylcaine. From the allocation card the examiner will then administer the spray or gel in the manner previously described. The allocation card and results form will then be attached together and placed in the results tray for later data entry and analysis. These results will not contain any personal or identifiable patient information.

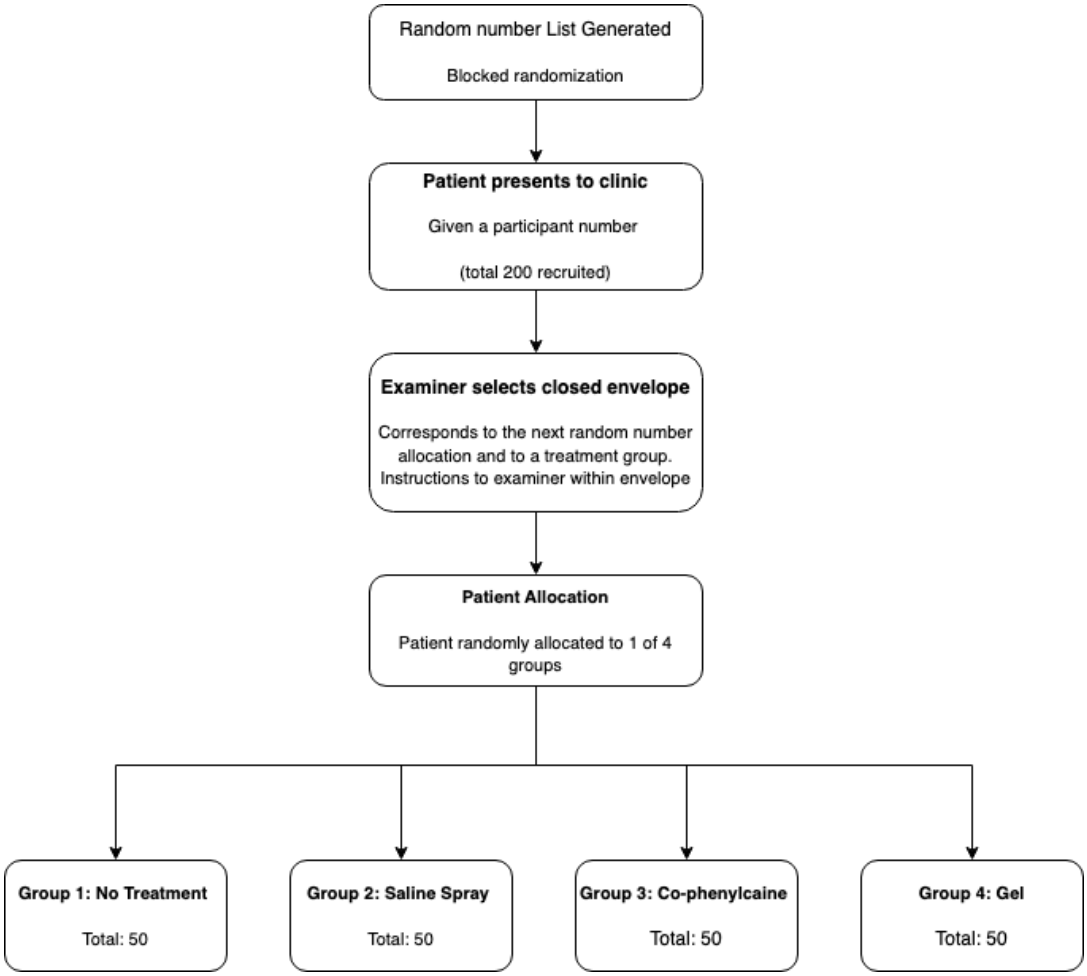

Figure S1 Randomisation and group allocation.

Outcome Measures

- Patient reported outcomes:
  - (I) Pain
  - (II) Discomfort
  - (III) Taste
  - (IV) Willingness to repeat the procedure
- Examiners reported outcomes:
- Ease of scope passage
- Quality of image
- Other data that will be collected: factors which promoted difficulty e.g. anatomy, patient compliance, level of operator, previous experience of patient

Each outcome will be reported on a 100 mm VAS. This method has been used comparatively in similar studies (Appendix 2). Also see Appendix 1 for definitions of outcomes.

Medication Safety Profile
Co-phenylcaine

Co-phenylcaine is a commonly used topical local anaesthetic and nasal decongestion in the ENT outpatient setting to prepare the nose of nasendoscopy. It contains lidocaine hydrochloride (50 mg/mL) and phenylephrine hydrochloride (5 mg/mL). The most common side effect is a burning sensation on application that is temporary. Allergy is rare. Phenylephrine can cause nervousness and excitability, and rarely palpitations, tachycardia and headache (<0.1%) as with all nasal decongestants. The most commonly reported concern of patients is the unpleasant taste, which will be examined as an outcome in this study (13).

Risks

The risks of this study to the patient are negligible. Co-phenylcaine is a safe and routinely used method of nasal topicalisation for nasendoscopy and the most commonly used method in the Ipswich ENT outpatient department. The examination itself does carry with it a small degree of discomfort for the patient that is unavoidable. One of the aims of this study is to determine whether lubrication of the scope improves this discomfort for the patient. There is little to no risk of trauma or bleeding when this procedure is performed correctly by skilled operators working in an ENT Department.

Ethical Considerations

All patients recruited in this trial will be informed that the use of a topical local anaesthetic spray for flexible nasendoscopy, although widely used, is without good evidence to suggest that it reduces discomfort. Only patients who give informed consent and require a nasendoscopy based on standard clinical indications will be eligible to participate. Nasendoscopy will not be performed on patients for the purpose of the study in which it is not clinically indicated.

Expected Outcomes

Based on previous similar studies we expect that patient experience in terms of pain and discomfort will be similar for the co-phenylcaine, saline and no treatment groups. Therefore, we hypothesise that the local anaesthetic agent in the more costly co-phenylcaine spray does not present any added benefit to both patient and examiner experience over saline and that the taste of the co-phenylcaine gives the patient an overall worse experience. We also hypothesise that lubricant gel will significantly improve patient experience but may have some implications for the quality of view from the examiner perspective, but that this will not be significant enough to prevent the routine use of lubricant gel as an alternative to co- phenylcaine.

Significance and Relevance of Study

Currently, there are only a few studies comparing different methods of topicalisation for nasendoscopy examination in the ENT outpatient setting. There are few comprehensive studies including nasal sprays using lignocaine and lubricant gel. There is also a knowledge gap looking at methods of topicalisation and examiner experience. For those of us who work regularly in the ENT outpatient setting there is anecdotal evidence only as to which method is better for both patients and examiners and a variety of opinions. There is no definitive study to support our current methods. This study could also have financial implications for our department; if a cheaper method of topicalisation is shown to be just as good in terms of patient experience and does not compromise examiner view, this could be a more cost-effective alternative to co-phenylcaine.

Cost Analysis

The cost of co-phenylcaine spray is $56.95 per unit and approximate cost of lubricant gel is $4 per unit. This study will not incur any additional costs as all medications and study materials are readily available in the ENT outpatient department. Co-phenylcaine and lubricant gel are available through pharmacy impress, as is normal saline. All examinations carried out would otherwise be carried out in the normal context of the patient's consultation, and therefore additional supplies are not required above what would normally be expected.

Confidentiality/Data Storage

Data will be collected in a de-identified manner (see data collection form). Only simple demographic data will be recorded along with survey answers. No images will be taken. The only identifying documentation that will be kept is the patient consent form. This will be kept in a secure location in a locked draw in the ENT outpatient clinic and at the completion of the trial will be scanned into a secure password protected hard drive and the hard copies shredded.

References

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Appendix 1 Definitions

Term	Definition
Visual Analogue Scale	The **visual analogue scale** (VAS) is a psychometric response **scale** which can be used in questionnaires. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured such as pain. Commonly on a 0–100 mm scale from best to worse response.
Nasendoscopy	Nasendoscopy is a minor procedure that is usually performed in the clinic setting to assess the structures of the nose, sinuses, pharynx, and larynx. It involves using a small camera which is passed through the nostril. The camera is a flexible tube endoscope, that can be manoeuvred to help obtain a good view of the nose and throat. It is placed through the nostril and moved to the back of the nose and throat.
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (From the International Association for the Study of Pain).
Discomfort	the overall unpleasant experience of the procedure including all aspects of the examination other than pain. Any other negative sensations associated with the examination; any side effects associated with the application of the nasal sprays as well as any anxiety associated with the examination.
Taste	The sensation of flavour perceived in the mouth and throat on contact with a substance, in this instance nasal sprays or lubricant.

Appendix 2 Patient & Clinician Survey (example)

Survey of Patient & Clinician Experience: Nasendoscopy

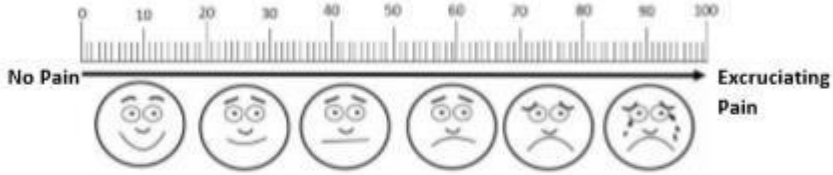
Participant Number:

Age: *Gender: (M/F)*

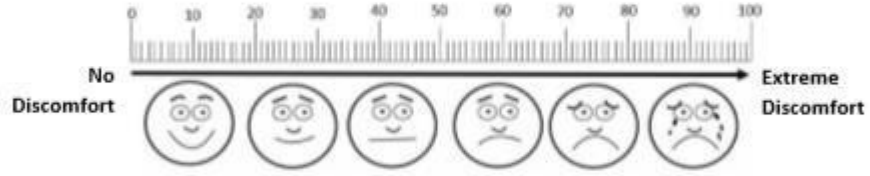
	(Please circle)	
Have you previously had this type of examination?	Yes	No
Have you had any prior nasal surgery?	Yes	No

Instructions: Please place a cross (X) along the scale

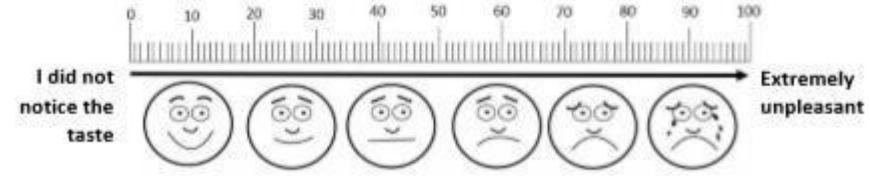
Question 1 – How painful did you find this examination?



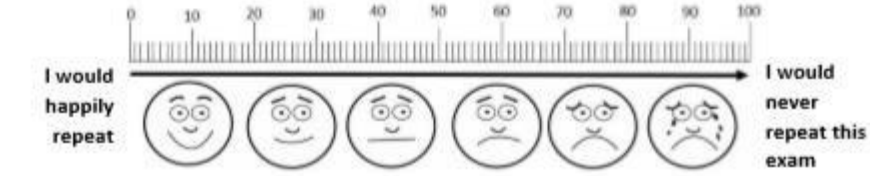
Question 2 – How much discomfort did you experience (other than pain) during this examination?



Question 3 – How unpleasant did you find the taste during this examination?



Question 4 – Would you be willing to repeat this examination again?



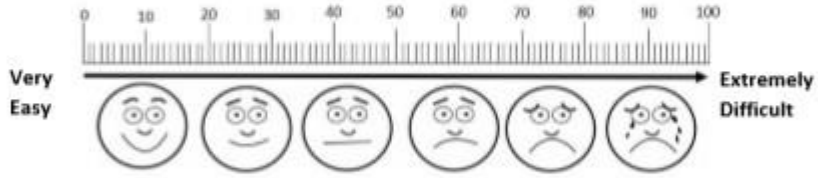
Clinician to Complete

Level of Experience (circle): RMO / PHO/ REG / CONS

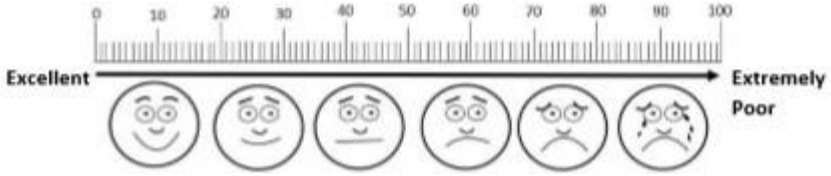
Factors that promoted difficulty
(e.g. anatomy / patient compliance):

Instructions: Please place a cross (X) along the scale

Question 1 – Can you rate the ease with which you were able to pass the scope?



Question 2 – Can you rate the quality of the view?



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