Oral Sucrose for Pain Management During Flexible Nasolaryngoscopy

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Study Site(s): *Hospital for Sick Children*
Funded By: *Gnat/Bastable-Potts Chair in Otolaryngology*

Statement of Compliance

The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Research Ethics Board (REB) of Record, except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB of Record for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol or consent materials will require review and approval by the REB of Record before the changes are implemented to the study. All changes to the consent form will be REB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

This page should be signed by the Principal Investigator at each site. If this is a single center study conducted only at SickKids, delete the site address below.

Principal Investigator:

Name: Nikolaus Wolter

Signed:  Date: 06/08/2024

<DD Month YYYY>

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1 PROTOCOL SUMMARY

1.1 Synopsis

Title	Oral Sucrose for Pain Management during Flexible Nasolaryngoscopy
Short Title	Be Sweet to Babies during Flexible Nasolaryngoscopy
Study Description	This study aims to evaluate the impact of oral sucrose on pain or distress in outpatient infants undergoing flexible nasolaryngoscopy during a scheduled appointment at the SickKids Pediatric Otolaryngology Clinic.
Objectives	The primary objective of this study is to determine the impact of using oral sucrose solutions on clinical pain scores after FNL in infants under 12 months of age. The secondary objectives of this study are to evaluate the impact of oral sucrose on crying times, maximum heart rate, and skin conductance during FNL in infants under 12 months of age.
Study Design	This is double-blinded randomized controlled trial. The intervention in this study is the provision of 0.5 ml 0.24% oral sucrose solution, which is a standard procedure for acute painful procedures in infants and widely available, compared to a control group of 0.5 ml water. The practice of giving sucrose during FNL has not yet been established, with inconsistent use across sites due to a lack of data, which this study aims to provide. Approximately 30 participants will be randomized into each arm.
Participant Population, Selection Criteria	**Inclusion criteria:** ● Patient <12 months of age; ● Scheduled for an appointment with Dr. Nikolaus Wolter, Dr. Evan Propst or Dr. Jennifer Siu, who are Staff Pediatric Otolaryngologists at the Hospital for Sick Children, or Meghan Tepsich, a complex airway Nurse Practitioner at SickKids; ● Requiring flexible nasolaryngoscopy for diagnostic purposes; ● Accompanied by caregivers who provided consent. **Exclusion criteria***:* ● Patient ≥12 months of age ● Infants <37 weeks corrected gestational age ● Infants with decreased level of consciousness or delayed neuromuscular development with limited pain response ● Infants with the following conditions, where oral sucrose is contraindicated or ineffective (detailed under *Exclusion Criteria*). ● Infants whose parents did not consent to enrolling their child in the study, including randomization into either arm of the study due to preference for a given intervention ● Any other circumstance in which consent for participation in the study was not obtained prior to the scope Infants will also be excluded from the study if they present with conditions in which FNL is contraindicated (detailed under *Exclusion Criteria)*.
Study Sites	Sickkids Pediatric Otolaryngology Clinic

Participant Duration	All participant observations will be completed on one day, during their scheduled appointment.
Number of participants	The goal is to enroll approximately 30 participants into arm of the study for a total of 60 participants.
Study Phases (Screening, Study Treatment, Follow-Up)	1) **Screening:** Screening will be completed by a member of the research team prior to a given clinic day, and eligible patients will be flagged on Epic. (2) **Enrollment and Consent:** Consent and study intervention will be completed on the same day. Prior to their scheduled appointment, parents or guardians of the potential participant will be approached by a member of the circle of care to introduce the study. If they are interested in participating, a member of the research team will obtain informed consent. (3) **Study Treatment:** For consenting participants, patients will be randomized into intervention (sucrose) or control (water) prior to undergoing nasolaryngoscopy. The administration of intervention or control will be integrated into their appointment and data will be collected concurrently by an independent observer. (4) **Follow-up:** No follow-up of patients will be required for the study purposes. (5) **Data analysis** will be completed once the target number of randomized patients (n=60) is reached.
Efficacy Evaluations	EVENDOL scale, heart rate, duration of cry, and skin conductance will be used to evaluate the analgesic efficacy of oral sucrose.
Safety Evaluations	Children will be undergoing flexible nasolaryngoscopy which is a part of a routine physical exam. Children will be administered sucrose which is recommended by the Hospital for Sick Children for any non-sedated painful procedures in infants. No safety evaluations are required
Statistical Analysis	The primary and secondary outcome measures will be assessed for normalcy and compared by Student's T test or Kruskal Wallace test as appropriate.
Data and Safety Monitoring Plan	As the principal investigator, Dr. Nikolaus Wolter will be responsible for data quality management and ongoing assessment of the study conduct.

1.2 Schedule of Activities (SOA)

The study will take place during previously scheduled outpatient visits requiring routine diagnostic flexible nasolaryngoscopy (FNL) at the Hospital for Sick Children Otolaryngology Clinic. Screening patients for eligibility may occur up to 2 months prior to their appointment dates and on a rolling basis until study objectives are met. Consent will be obtained on the scheduled appointment day, while patients wait to see the clinician. FNL is a routine part of the pediatric otolaryngological exam but will only be initiated if clinically indicated for the patient. A routine visit will include: visiting with the otolaryngologist and or nurse practitioner, team review, physical exam including endoscopy, review of findings and formulation of a plan. A visit takes approximately 30-45 minutes and participation in the study will not alter the duration. For the purposes of gaining consent to participate in the study, the clinical indication must already be ascertained prior to the encounter. The study intervention and data collection will occur during

the clinical encounter. Incoming data will be reviewed for completeness and study acceptability after the appointments, at least every 2-4 weeks for the duration of the study.

1.3 Key Roles

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No other sites will be involved in the study.

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Flexible nasolaryngoscopy (FNL) is a common, painful procedure performed as a routine part of the upper airway exam in children. FNL is used to examine the nose, nasopharynx, oropharynx and supraglottis for a wide range of presenting complaints in the Otolaryngologist's office. As these areas cannot be examined with the naked eye and are poorly captured on x-ray and static cross-sectional images, FNL is essential. It must be done in the awake, spontaneously breathing child to observe the dynamic airway changes that occur actively and passively with airflow.

Although it is felt to be safe and is generally short in duration, it is a painful procedure and can be quite distressing for the infant. A clinical nurse typically assists with the procedure, with the infant sitting in their lap and holding their head and hands to minimize movement (Figure 1). It is not uncommon for children to require multiple FNL examinations over time to assess the evolution of their underlying condition or recovery. In addition, the painful nature of the procedure often limits the visualization of these structures due to poor compliance and the anatomical limitations of the pediatric airway often obscures distal structures (narrow nasal aperture, obstructing adenoids, hooding of the vocal cords by the supraglottis, etc.) Friedman noted that a single FNL was inadequate for diagnosis in 20% of children under the age of 3 years.[1] It is now well established that untreated or undertreated pain can lead to infant and parental distress during procedures.[2] Repeated exposures to pain early in life can alter long term pain responses and negatively impact a child's future relationship with the healthcare system.[3-6] Similarly, watching an infant go through a painful procedure can be quite distressing for caregivers. Although FNL is an essential part of the evaluation of the

Figure 1. Infant undergoing awake flexible nasolaryngoscopy. An assistant holds the child and supports the head and arms during the procedure. Botma *et al. 2000 IJPORL. 55. 17-20*

pediatric airway, it is the responsibility of the health care team to prevent or minimize the pain involved with this procedure whenever possible.[7,8]

Attempts to anesthetize the nasal and oral mucosa have been considered but are quite unpalatable, often making the experience worse. Participants who have received topical anesthesia (topical decongestant/anesthetic spray) will not be included in this research study. This effect can last up to two hours and patients must be kept fasting during this time which can be problematic for infants who must feed frequently, particularly in our population, where caloric demands are increased due to increased work of breathing. As painful procedures for young children are not uncommon in the inpatient setting, e.g. venipuncture, heel sticks, eye exams, nasogastric tube insertion; various non-pharmacological pain management methods have been studied. Strategies include breastfeeding, non-nutritive sucking, kangaroo care, and oral sucrose.[2,4,12] None of these interventions have been assessed for FNL in infants. Of these options, considering the limitations imposed by patient positioning during FNL and need for access to the nasal cavity, oral sucrose is the only feasible option.

Oral sucrose is an easily accessible, non-pharmacological molecule given by syringe or pacifier prior to painful procedures in children less than 12 months of age in various clinical settings[13] at the Hospital for Sick Children.[14] A recent Cochrane review did not find any serious side effects associated with oral sucrose in infants.[15] Multiple mechanisms of action for oral sucrose have been proposed. The sweet taste of sucrose may cause the release of endogenous opioids that may sufficiently attenuate nociceptive stimuli from painful procedures.[13] The nearly immediate response of intraoral administration suggests that stimulation of gustatory cells may also simply temporarily divert the infant's attention from painful stimuli.[16,17] Despite its widespread use and positive safety profile, randomized control trials and meta-analyses have shown only variable results of oral sucrose on pain owing to the inherent challenges of measuring pain in infants but also the varying degrees of pain that are caused by the procedures. A Cochrane review showed effective pain management for heel lance and venipuncture in infants.[12,15] For other painful procedures such as circumcision and ocular exams, however, oral sucrose alone did not seem to sufficiently reduce pain on a consistent basis.[18] The use of oral sucrose for nasogastric tube insertion has also been studied and may be the closest correlate to FNL as they stimulate similar structures upon entry. Results here are similarly variable but encouraging[2]. In contrast to a nasogastric tube, upon insertion a FNL is visually guided through the nose and can be steered away from sensitive anatomical structures. Additionally, the FNL sits above the larynx to examine it from a distance and does not collide with it like a nasogastric tube. For these reasons, oral sucrose may be even more effective in FNL than nasogastric tube insertion.

We have recently started using oral sucrose in clinic for some infants less than 12 months of age undergoing routine diagnostic FNL. While oral sucrose may have a positive safety profile and demonstrated efficacy in some contexts, its effectiveness specially for FNL has not been conclusively established, thus there is equipoise to randomize patients to not receive the oral sucrose solution to determine whether it provides significant benefits

Our objective is to understand the analgesic efficacy of oral sucrose on pain in infants undergoing FNL compared to placebo (water). Our hypothesis is that oral sucrose will reduce pain and crying duration in infants undergoing FNL compared to placebo.

Our primary outcome measure will be the impact on infant pain measured by: validated infant pain scores, vital signs, time to cessation of crying, and skin conductance algesimetry (SCA). In order to evaluate the analgesic efficacy of oral sucrose in this context, procedural pain must be reliably and consistently assessed. Numerous pain scales have been validated for the assessment and management of pain in pre-verbal children. In a position statement by the Canadian Pediatric Society, the Evaluation Enfant Douleur (EVENDOL) scale was noted to carry a lower risk of bias compared to other frequently employed behavioral pain scales.[19] Initially designed for evaluating pain in the emergency department, components of the EVENDOL scale are simple to assess in the outpatient setting. Five measures are each rated between 0-3 for a total out of 15 points at rest, during the procedure, and at interval reassessments depending on the context. The measures are vocal or verbal expression, facial expression, movements, postures, and interactions with the environment. The EVENDOL scale is appropriate for evaluating acute, procedural, and chronic pain in children aged 0-7.[20]

The SCA is a safe and noninvasive validated tool that uses electrodermal activity to complement behavioral pain scale data in infants. The SCA uses surface electrodes on the skin, which can be easily applied and removed in the outpatient setting. Driven by cholinergic muscarinic receptors, the autonomic response to pain causes bursts of increased skin conductance due to increased perspiration. Measuring these changes in peaks per second on the algesimeter provides an objective, physiologic marker of pain or distress. In contrast to vital signs such as heart rate and oxygen saturation, skin conductance changes per second are not influenced by respiratory rhythm, vasoactive drugs, or environmental temperature.[21,22] The SCA will be used as a physiologic counterpart to the EVENDOL scale.

2.2 Rationale

This study aims to address the question: *does oral sucrose reduce pain in infants undergoing flexible laryngoscopy (FNL)?*

FNLs are essential to evaluating a pediatric airway and provide rapid, diagnostic information in an outpatient setting. Addressing procedural pain and distress is a key component of providing developmentally appropriate and family-centered care.

While there is substantial evidence to support the use of oral sucrose for venipuncture or heel lances, to our knowledge, there is no research published on the analgesic efficacy of sucrose in infants undergoing FNL. There is limited and variable but encouraging evidence for the use of oral sucrose during nasogastric tube insertion, which may be the closest clinical correlate. A pilot retrospective analysis of use of sucrose in FNL in our clinic demonstrated improvements in scores and parental satisfaction but was limited by imperfect blinding and lack of placebo.

The results of this study could inform clinical practice with respect to minimizing infant distress during FNL.

2.3 Potential Risks & Benefits

2.3.1 Potential Risks

One potential risk to conducting the study is that randomization and pain assessment may lengthen the duration of the appointment and/or FNL procedure. Consent would be obtained while patients are waiting for endoscopy, study solutions will be made readily available, and both the EVENDOL and SCA are designed for rapid assessment. Nevertheless, the cumulative effect of these study components could alter clinical workflow and increase waiting times. A pilot retrospective study done in our clinic demonstrated no significant increase in clinic visit time.

The procedure for both groups would involve administering a few drops of study solution onto the tip of the baby's tongue. This is standard practice throughout the Hospital for Sick Children where sucrose is used routinely used in the ED, on the ward and in the critical care unit for acute painful procedures such as heel lances. This method carries a low risk of aspiration compared to breast or bottle feeding.

The risk of being randomized into the intervention group is related to the potential risks of oral sucrose solution. Oral sucrose solutions have been used for a variety of other indications in reducing pain during acute minor painful procedures among newborns and young infants. These procedures include heel lances, vaccinations, venipuncture, frenuloplasty, NG tube insertion etc. Several studies, including a Cochrane systematic review have shown that there is no evidence to support that administration of sucrose prior to painful procedures causes any significant side effects.[15] Although not impossible, it is highly unlikely that infants in an outpatient setting would present with an undiagnosed contraindication to sucrose such as a rare metabolic condition. The risk is no higher in the inpatient or ED setting where sucrose use is routinely used. All children undergo thorough systematic review including review of perinatal genetic testing prior to assessment in our clinic and screening for eligibility will include these precautions.

The risk of being randomized into the control group is that an infant who may have otherwise received oral sucrose may experience more pain or parental distress if they were given water instead. Provision of oral sucrose is not currently the standard of care and its analgesic efficacy in this context is unknown. Therefore, there is sufficient clinical equipoise to justify randomization into either group.

As the intervention (FNL) is a routine part of our clinical exam, there are no foreseeable long-term risks to participating in this study.

2.3.2 Potential Benefits

All infants who participate in this study will be directly observed for signs of pain and distress, prompting caregivers to respond accordingly when FNL is completed. Additionally, caregivers will learn about the potential applications of oral sucrose for procedural pain in other contexts, such as heel lances or immunizations. Consequently, they may be more likely to advocate for appropriate non-pharmacological measures aimed at reducing distress during future painful procedures.

If our hypothesis is correct, then infants who are randomized to the intervention group may experience less procedural pain or distress during the FNL compared to routine practice.

Although there will be no financial compensation, families may benefit from learning more about initiatives to make FNL less distressing for our youngest patients. Long term, the results of this study could justify the practice of providing oral sucrose to infants undergoing FNL. Conclusions drawn from this study could then inform future policies regarding procedural pain management for infants.

3 Objectives and Purpose

The purpose of this study is to determine the analgesic effect of oral sucrose in infants undergoing FNL. The data from this study will help inform our potential future use of oral sucrose for FNL in clinical practice. The data may also help guide future studies.

The primary objective of this study is to determine the impact of using oral sucrose solutions on clinical pain scores after FNL in infants under 12 months of age.

Objective	Brief Description / Justification of Outcome Measure	Outcome Measured By	Time Frame
Determine the impact of using oral sucrose solutions on clinical pain scores after FNL in infants under 12 months of age.	Pain scores are used to quantitatively evaluate infant distress and tolerance of procedures. There is little data on infant pain or distress during FNL, which often forms the basis of physical examination in pediatric otolaryngology clinics.	Blinded research team member (not the clinical MD) will directly observe participants during the procedure and assign a pain score using the EVENDOL scale.*	Scores obtained during the scheduled appointment for each participant.

**** The EVENDOL scale is a validated 15-point scale developed for children with presenting, prolonged, or procedural pain. Infant pain observations are ranked from 0-3 based on 5 different observations: (1) vocal or verbal expression, (2) facial expression, (3) movements, (4) postures, and (5) interactions with the environment.***

3.1 Secondary Objectives

The secondary objective(s) of this study are to:

1. Determine the impact of using oral sucrose solutions on crying time after FNL in infants under 12 months of age.
2. Determine the impact of using oral sucrose solutions on the infant's maximum heart rate and time to return to baseline as measured by a pulse oximeter during FNL.
3. Determine the impact of using oral sucrose solutions on the infant's palmar or plantar skin conductance during FNL as measured by maximum peaks per second.
4. Determine if the administration of oral sucrose prolongs clinic visits.

5. Determine the impact of using oral sucrose on caregiver impression of infant discomfort.

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Determine the impact of oral sucrose solutions on crying time after flexible nasolaryngoscopy in children under 12 months of age.	Crying time is another measurable indicator of infant pain and distress. It may provide additional data points when evaluating the impact of oral sucrose solutions.	The crying time will be defined as the time from cessation of FNL to when the infant stops crying for a period of 10 consecutive seconds. Crying will be measured for a maximum of 5 minutes.	Will be assessed and documented at the same time as the primary outcome.
Determine the impact of using oral sucrose solutions on the infant's maximum heart rate during FNL.	Changes in the baby's heart rate is an additional indicator of infant pain or distress frequently employed in pain scales. This may provide additional data when evaluating the impact of oral sucrose solutions.	The heart rate will be measured using a portable pulse oximeter for a maximum of 5 minutes.	Will be assessed and documented at the same time as the primary outcome.
Determine the impact of using oral sucrose on the infant's palmar or plantar skin conductance during FNL.	Painful stimuli trigger the release of norepinephrine, which stimulates muscarinic cholinergic receptors to increase perspiration. Perspiration improves local skin conductance, which is a sensitive measure for pain. This may provide additional data when evaluating the analgesic effect of oral sucrose solutions.	Skin conductance is measured through electrodes attached to the baby's hand or foot and recorded on the algesimeter.	Will be assessed and documented at the same time as the primary outcome.
Determine if administration of oral sucrose prolongs clinic visits.	Whether or not oral sucrose prolongs the length of the encounter helps evaluate the feasibility and acceptability of implementing oral sucrose into FNL procedures.	The length of the clinical encounter will be assessed in both arms of the study.	The duration of the clinical encounter will be assessed at the same time as the primary outcome.
Determine the impact of using oral sucrose on caregiver impression of infant discomfort.	Watching an infant go through a painful procedure can be distressing for caregivers. This can impact their relationship with the healthcare team.	Wong-Baker FACES pain rating scale	After the FNL is completed, caregivers will be given the FACES scale to rate their child's pain.

4 Study Design and Endpoints

4.1 Description of Study Design

This is a double-blinded randomized controlled trial evaluating the analgesic effect of oral sucrose on pain scores in outpatient infants undergoing FNL during a scheduled appointment. These appointments take place at the Pediatric Otolaryngology Clinic at SickKids. There are no other study sites. Recruitment will continue on a rolling basis from the above clinics with the goal of recruiting thirty patients in each arm. This is anticipated to take place over the course of approximately 12 months. As such, recruitment is anticipated to occur between May 2024-2025.

The intervention in this study is the provision of 0.5 ml 0.24% oral sucrose solution, which is a standard procedure at SickKids for acute painful procedures in infants and widely available, compared to a control group of 0.5 ml water. The practice of giving sucrose during FNL has not yet been established, with inconsistent use across sites due to a lack of data, which this study aims to provide.

Following evaluation for eligibility, the clinical team will introduce the study to the patient's caregivers and introduce the study coordinator. Informed consent will be obtained by the study coordinator during team review. The study coordinator will randomize the participant to sucrose or water using an open-source random number generator. Sucrose or water will be hand-delivered to the clinical team immediately prior to endoscopy in identical, unmarked syringes prepared and provided by the study coordinator who performs consent. The clinical team, parents, and a separate evaluator will be blinded to sucrose vs. water.

Pain assessment will involve validated infant pain scores, vital signs, time to cessation of crying, and skin conductance algesimetry (SCA). EVENDOL is an excellent pain scale for non-verbal children noted to carry a lower risk of bias compared to other frequently employed behavioral pain scales and is recommended by the Canadian Pediatric Society.[19] Initially designed for evaluating pain in the emergency department, components of the EVENDOL scale are simple to assess in the outpatient setting. Five measures are each rated between 0-3 for a total out of 15 points at rest, during the procedure, and at interval reassessments depending on the context. The measures are vocal or verbal expression, facial expression, movements, postures, and interactions with the environment. The EVENDOL scale is appropriate for evaluating acute, procedural, and chronic pain in children aged 0-7.[20]

We will also measure time to cessation of crying or "settling" which is defined as a period of 10 consecutive seconds of no crying. Finally, the infant's maximum heart rate will be measured by a pulse oximeter. These outcome measures will be recorded by a member of the research team during the participant's appointment along with the identification number of the study solution they were given. Crying will be measured to a maximum of 5 minutes after the procedure.

The SCA is a safe and noninvasive validated tool that uses electrodermal activity to complement behavioral pain scale data in infants. The SCA uses surface electrodes on the skin, which can be easily applied and removed in the outpatient setting. Driven by cholinergic muscarinic receptors, the autonomic response to pain causes bursts of increased skin conductance due to increased

perspiration. Measuring these changes in peaks per second on the algesimeter provides an objective, physiologic marker of pain or distress. In contrast to vital signs such as heart rate and oxygen saturation, skin conductance changes per second are not influenced by respiratory rhythm, vasoactive drugs, or environmental temperature.[21,22] The SCA will be used as a physiologic counterpart to the EVENDOL scale.

We will compare the pain scores of infants from each study arm. We will also compare the time spent during the appointment to determine the impact of sucrose administration in the clinic. Finally, we will compare the caregiver's impression of their child's pain using the Wong-Baker FACES scale.

4.2 Duration of Study Participation

Potential participants will be screened prior to each clinic day and approached for consent after introduction by the clinical team while they are waiting for their physician or nurse practitioner during the team review. Participants will be observed by the evaluator for up to 5 minutes following FNL during their scheduled appointment time. The duration of patient participation is limited to their scheduled appointment at the clinic. No follow-up is required from the participants for this study. As such, participation is limited to the day of their appointment. Although some participants will be followed for clinical reasons, participation in the study will not impact their next visit. Caregivers will be given the option to opt out of being approached for re-enrollment at future appointments if the patient is still eligible.

4.3 Total Number of Participants and Sites

Recruitment will end when approximately 30 participants are enrolled to each arm.

5 Study Enrollment and Withdrawal

5.1 Participant Inclusion Criteria

- Patient <12 months of age;
- Scheduled for an appointment with Dr. Nikolaus Wolter or Dr. Jennifer Siu, who are Staff Pediatric Otolaryngologists at the Hospital for Sick Children, or Meghan Tepsich, a complex airway Nurse Practitioner at SickKids;
- Requiring flexible nasolaryngoscopy for diagnostic purposes;
- Accompanied by caregivers who provided consent.

5.2 Participant Exclusion Criteria

- Patient ≥12 months of age
- Infants <37 weeks corrected gestational age
- Infants with decreased level of consciousness or delayed neuromuscular development with limited pain response
- Infants who have received acute/urgent /emergent airway assessment such as respiratory distress or a foreign body, etc.

- Infants who have received topical anesthesia (topical decongestant/anesthetic spray)
- Infants with the following conditions, where oral sucrose is contraindicated or ineffective:
    - Carbohydrate intolerance
    - Decreased level of consciousness or heavy sedation
    - Absent gag reflex
    - Non-functional gastrointestinal tract
    - History of aspiration, tracheoesophageal fistula
    - Necrotizing enterocolitis
- Infants whose parents did not consent to enrolling their child in the study, including randomization into either arm of the study due to preference for a given intervention
- Any other circumstance in which consent for participation in the study was not obtained prior to the scope

Infants will also be excluded from the study if they present with conditions in which FNL is contraindicated:

- Severe respiratory distress
- Post-palliative systemic artery to pulmonary artery shunt
- Single ventricle congenital heart disease

5.3 Strategies for Recruitment and Retention

Potential participants are the patients scheduled to see Dr. Wolter, Dr. Propst, Dr. Siu, or Meghan Tepsich NP at the SickKids Pediatric Otolaryngology clinic. The clinic schedule of these practitioners will be reviewed on Epic prior to the appointment date, and patients <12 months old will be screened for eligibility. Specifically, the provider's referral note and clinical chart for the patient may be reviewed to determine whether FNL is indicated during their appointment, and whether the patient has any medical conditions impacting their eligibility. Parents of potential participants will be introduced to the study by someone in the circle of care and consent will be obtained by the study coordinator prior to seeing their physician or nurse practitioner during team review. As such, the consent process should not interfere with the clinic's scheduled patient care. All patients will be seen as scheduled and the intervention will be integrated into the clinical visit to minimize inconvenience to the patient and caregivers.

Parents of potential participants will be asked to confirm whether their child has any of the medical conditions listed in the exclusion criteria. Demographic information (age, sex, birth weight, current weight, history of previous endoscopy, history of previous surgery, and reason for clinic appointment) will be obtained using Epic after obtaining participant consent. A member of the research team will accompany consenting participants for the duration of the FNL; however, the research team will not be present for the remainder of the appointment.

An overview of the study including the primary objective, inclusion criteria, and implications on clinical flow (i.e. speaking with parents of eligible patients in the clinic room prior to being seen

by the doctor or nurse practitioner) will be provided to nurses working at the SickKids Pediatric Otolaryngology Clinic. No marketing or media services will be required. If the FNL is interrupted for any reason, the consenting participant's data will not be included in the data analysis. No data will be stored for non-consenting patients; however, the number of non-consenting patients will be tracked to review study acceptability and participant flow. The patient's participation in the study ends once their clinic appointment is over. Participating will not impact any future visits, and they are not committing to participating again even if the next visit will also include FNL as part of the baby's evaluation.

5.4 Participant Withdrawal or Termination

5.4.1 Reasons for Withdrawal or Termination

Parents or caregivers are free to withdraw their infant from participating in this study at any time upon request. Additionally, an investigator may terminate a patient's participation in the study if:

- The participant meets an exclusion criterion, either newly developed or not previously recognized
- A clinical adverse event (AE) occurs when administering the intervention such that it would not be advisable to proceed with the scoping procedure
- A situation occurs such that continued participation in the study would not be in the best interest of the participant

No participant data will be included in the analysis if FNL needs to be interrupted for any reason.

5.4.2 Handling of Participant Withdrawals or Termination

If a caregiver withdraws consent for their child to participate, or if participation is terminated due to meeting any criteria described in 5.4.1, then all participant data will be removed from study documentation. Efforts will be made to document reasons for study withdrawal in the interest of periodically assessing the acceptability of the study. Likewise, the reason for termination will be documented in the participant flow sheet.

6 Study Assessments and Procedures

Participants will be screened for eligibility by a REB-approved research team member no more than 28 days prior to their appointment at the Outpatient Otolaryngology Clinic. The appointment schedules for Dr. Wolter, Dr. Siu, or Meghan Tepsich NP on a given clinic day will be reviewed to screen for participant eligibility. Patients who are less than 12 months of age will be further screened using the Chart Review and Summary views on Epic to look for inclusion and exclusion criteria. Potential participants will be flagged accordingly to be approached by a member of the research team.

No pre-consenting process for screening is indicated. Parents of eligible infants will be approached in the clinic, while they are waiting to see their doctor or nurse practitioner. The nature of the study, anticipated risks or benefits, and possible outcomes of randomization will be reviewed. Questions will be answered to their satisfaction, and parents will be able to withdraw consent at any time without impacting their child's care. This consent process will occur in a

private clinic room to respect confidentiality. The consent form will be stored in a locked file cabinet for the duration of the study. Information from patients who decline participation in the study will not be recorded; however, the number of eligible patients who declined will be recorded for the purpose of evaluating study acceptability and participant flow.

7 Study Procedures/Evaluations

7.1 Procedures / Evaluations

Consented participants will be given the randomized solution and observed during FNL. Collection of EVENDOL pain scores and crying time is part of routine standard procedure.

Randomization:
Each participant will be randomized into the intervention or control group by an online random number generator (https://www.random.org/)

Intervention:
Each participant will be administered a previously prepared 1cc syringe containing either the sucrose solution or sterile water depending on their randomization. The expiry dates of sucrose solutions will be verified prior to drawing-up 0.5mL of the solution into a 0.5 mL syringe. The control group will receive 0.5 mL of sterile water via syringe in the mouth, which will be prepared in identical syringes to maintain the blinded nature of this study. An equal number of intervention and control syringes will be prepared prior to initiating the study, and each syringe will each be labeled using an identification number. A log of the solution contained in each syringe will be kept in a separate folder, which will not be opened until after completion of study activities. During the study, each participant's study solution identification number will be recorded along with their pain scores. The log will then be accessed and participants will be matched into the intervention or control group for data analysis.

Study Solution Administration:
We will follow the standard procedure for oral sucrose administration in infants undergoing other acute painful procedures, such as heel lances. Approximately 0.5 mL of either solution is placed on the tip of the baby's tongue, or on their pacifier. The solution is administered within 2 minutes prior to FNL.

Outcome Data Collection:
A member of the research team will apply the non-invasive skin algesimeter stickers and portable pulse oximeter prior to the procedure. A blank printed EVENDOL scale and a timer will be used to obtain the pain scores and crying times, respectively. Maximum heart rate during the procedure will also be documented. This data will be collected on a printed paper (Appendix A) with the participant's study ID and study solution number. It will be shredded after transferring the data to the password-protected Excel spreadsheet.

Flexible Endoscopy:
This procedure will be performed by a single endoscopist for all eligible participants to reduce potential provider-dependent variations. The research team member obtaining the data will not

comment, interfere, or interact with the participant during this procedure. This single endoscopist will be blinded to the randomization.

8 Statistical Considerations

8.1 Study Hypotheses

The study hypothesis is that oral sucrose administration in infants undergoing FNL will result in lower pain and distress as measured by the EVENDOL pain score, heart rate, crying time, and skin conductance as compared to infants who receive sterile water instead.

8.2 Sample Size Determination

Based on our retrospective review completed earlier in 2023, we anticipate needing 30 participants per study arm for a total of 60 participants. This sample size should be sufficiently powered to evaluate both primary and secondary outcomes. This sample size is also comparable to similar studies that sought to evaluate the analgesic efficacy of oral sucrose for nasogastric tube insertions.[23] Participants who withdraw from the study will be replaced.

8.3 Statistical Methods

Demographic data including sex, age, birthweight, current weight, and history of endoscopy/surgery will be summarized using means and proportions where appropriate. Chi-squared test will be used to ensure balanced arms after randomization, and study arms will be compared statistically by Wilcoxon rank sum tests or Student's T-test as appropriate.

To evaluate the study hypothesis the pain scores, vital signs, cry duration, algesimetry, and parent Wong-Baker FACES scores will be assessed for normalcy and compared by Student's T-test or Kruskal Wallace depending on whether the data is parametric. These are all continuous variables. Analysis of data will be done using SPSS statistical analysis software (Version 24.0 for Macintosh; SPSS, Chicago, Illinois).

9 Source Documents and Access to Source Data/Documents

Access to study records will be limited to REB-approved members of the study team. The PI will permit study-related monitoring, audits, and inspections by the REB and/or University compliance and quality assurance groups of all study related documents (e.g. source documents, data collection instruments, study data etc.). Participation as a PI in this study implies acceptance of potential inspection by REB and/or applicable University compliance and quality assurance offices.

10 Study Oversight

Study oversight will primarily be done by the principal investigator and the Otolaryngologist in Chief at SickKids, Dr. Blake Papsin.

Preliminary data will be reviewed every month. If a clear difference in pain scores is observed

between the two groups, the study will be terminated on the basis of lacking clinical equipoise to continue. No other sites are involved in the study. As such, there will be no dissemination of data outside of the SickKids Otolaryngology Clinic.

11 Ethics/Protection of Human Participants

11.1 Ethical Standard

Respect for persons – Consent will be obtained in a way that respects their rights to self-advocacy and privacy. There will be no coercion to participate in this study. The decision to participate or decline participation will not affect their present or future care at the Otolaryngology Clinic. If the parent would like their child to receive sucrose during FNL rather than a blinded study solution, their preference will be respected and the patient will not be enrolled in the study.

Concern for welfare – This study was designed to minimize the inconvenience and time burden on participants. Participant safety and wellbeing must be prioritized over recruitment.

Social and clinical value – the intent of this study is to evaluate a potential method to reduce infant pain and distress during FNL, which is often a central component of the physical exam when assessing the airway and nasal passages. While there are no direct benefits for study participants, the data from this study may improve the future quality of care and inform future research on pain management strategies during FNL.

11.2 Informed Consent Process and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. A clinic nurse or another member of the patient's circle of care will introduce the study before any member of the research team gets involved. The research coordinator or an appointed member of the research team will be responsible for obtaining consent in a private clinic room to respect patient privacy. Extensive discussion of study's purpose, possible risks, and alternative choices will be provided to the participant's decision-maker. A language line or translation iPad may be used for translation if needed; the need for translation would be documented as well. As all study participants will be infants, consent will be obtained from their parent, guardians, or appointed clinical decision-maker. Consent forms will be REB approved and the potential participant's decision-maker will be asked to read and review the document. The study coordinator will explain the research study to the potential participant and answer any questions that may arise. The family will be given sufficient time to carefully review the written consent form and ask questions about the study. Their decision to participate or decline will be respected. The parent will sign the informed consent document prior to any procedures being done specifically for the study. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the participant's decision-maker for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline participation in this study.

A copy of the signed informed consent document will be stored in the participant's research record. The consent process, including the name of the individual obtaining consent, will be documented in the participant's research record. Any alteration to the standard consent process (ex. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

11.3 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms detailing the study intervention, procedure, potential risks, and the option to decline without affecting their care are given to the participant's decision-maker. Written documentation of informed consent is required prior to administering the intervention. The Parent Consent Form is provided with this protocol for review. No further materials will be produced for the study.

12 Data Handling and Record Keeping

12.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Consent forms will be stored in a locked cabinet for the duration of the study. Any paper data obtained during research activities (for example, an EVENDOL pain scoring tool) will be shredded on site after entering data into a password-protected Excel file. Each participant will be assigned a Study ID, and data will be stored on a password-protected Excel file using the SickKids Microsoft 365 Sharepoint. All data entered into this Excel file will be de-identified and will not contain any identifiable information. We will be responsible for creating and maintaining a log that links the Study ID of the patient to the patient's identifiable information (i.e., name, hospital MRN) for auditing purposes. The master linking log will be kept separately from the study data.

12.2 Study Records Retention

Paper records of the consent forms will be retained in a locked cabinet for 7 years from the last publication prior to disposal in SickKids confidential disposal bins. All electronic records will be stored in a password-protected file for the same duration, and destroyed by contacting the SickKids IS help desk.

13 Protocol Deviations

Research activities will be reviewed and an informal debriefing will occur after each clinic day to ensure compliance with the approved protocol. Any deviations that were detected will be reported to the Research Ethics Board for approval.

If evidence of information dissemination is discovered, our team would contact the Otolaryngology – Head and Neck Surgery Chief along with the SickKids Hospital Research Ethics office and the SickKids Privacy Office. We would also contact the participants that may be affected by the data breach.

14 Publication and Data Sharing Policy

Dr. Wolter is the Principal Investigator and as such, he will be responsible for resolving any authorship issues that may arise. This is a single site study, and data will not be shared with outside institutions. The final analysis will be summarized in a manuscript for publication. A summary of the data analyzed from this study may also be presented at national and international meetings.

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