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External Cold and Vibration for Pain Management of Children Undergoing Needle-Related Procedures in the Emergency Department: A Randomized Controlled Non-Inferiority Trial Protocol

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ABSTRACT

Introduction: Needle-related procedures are considered as the most important source of pain and distress in children in hospital settings. Considering the physiological and psychological consequences resulting from these procedures, management of pain and distress through pharmacological and non-pharmacological methods is essential. Therefore, it is important to have interventions that are rapid and easy-to-use and implement. The aim of this study will be to determine whether a device combining cold and vibration (Buzzy®) is non-inferior to a topical anesthetic (liposomal lidocaine 4% cream) for pain management of children undergoing needle-related procedures in the Emergency Department. Non-inferiority would be demonstrated if the mean procedural pain scores of the experimental group is not worse than the mean procedural pain scores of the control group by a non-inferiority margin of 0.70 on the Color Analogue Scale (CAS).

Methods and analysis: This study is a randomized controlled non-inferiority trial comparing the Buzzy® device to liposomal lidocaine 4% cream for needle-related pain management. A total of 346 participants will be randomly assigned in a 1:1 ratio to one of these two interventions. The primary outcome will be the mean difference in pain intensity between groups during needle-related procedures. The secondary outcomes will be the level of distress during the procedure, the success of the procedure at first-attempt, the occurrence of adverse events, the satisfaction of both interventions and the memory of pain 24 hours after the procedure. The primary outcome will be assessed for non-inferiority and the secondary outcomes for superiority.

Ethics and dissemination: This study protocol was reviewed and approved by the institutional review board of the study setting. Findings of this trial will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number: NCT02616419

Keywords: Buzzy, Topical Anesthetic, Procedural pain, Children, Non-pharmacological intervention

Article summary

Strengths and limitations of this study

- This is the first study to assess the efficacy of the Buzzy® device in Canada.
- The large sample size of 346 participants will provide enough power to demonstrate the non-inferiority of the Buzzy® device compared to a topical anesthetic.
- The non-inferiority margin is justified on both clinical and statistical grounds.
- This study presents potential clinical implications for nursing and medical practices in the emergency department.
- The main limitation of this trial is the impossibility to blind participants and personnel to treatment/intervention allocation.

INTRODUCTION

Background and rationale

Needle-related procedures, such as venipuncture and intravenous (IV) catheter insertions, are considered as the most important source of pain and distress in children in hospital settings[1-4]. The intensity of pain and distress caused by these procedures can vary from mild to moderate for some, while for others, it may be severe[4-7]. It is now recognized that even a minor procedure, such as venipuncture, can result in numerous physiological, psychological and emotional consequences[8 9]. Among these, needle phobia is the most important and prevalent consequence with more than 60% of children reporting an extreme fear of needles following a bad needle experience[10]. Children with needle phobia are more likely to report higher levels of pain and distress from subsequent procedures[11 12] and they can experience physiological symptoms, such as increased heart rate and blood pressure and vasovagal reactions[13 14]. Further, children with needle-phobia can develop healthcare avoidance behaviors in adulthood, such as delays in care, non-compliance of immunization requirements and avoidance of treatment[10 14]. Nurses play a critical role in the assessment and management of children's pain and distress, and the use of pharmacological and non-pharmacological interventions must be an integrant part of nursing practice[15].

Procedural pain management represents a major challenge for nurses, specifically for those working in the Emergency Department (ED). Consequently, children are at high risk for undertreatment of their pain during needle-related procedures[16]. Although healthcare professionals recognize the importance of providing adequate procedural pain relief, pain management is still suboptimal[8 17-19]. Several studies have identified different barriers to using available pharmacological and non-pharmacological interventions for pain management in the ED[8 17-19]. Barriers most frequently identified by nurses are time constraints, heavy workload, staffing limitations, space limitations, lack of knowledge, and interruptions in the continuity of care[15 20-22].

Currently, the current gold standard intervention for needle-related procedural pain is the application of a topical anesthetic prior to the procedure and several systematic reviews and meta-analysis have supported this intervention demonstrating its efficacy extensively[23-26]. However, topical anesthetics require an application time ranging from 30 to 60 minutes, making their implementation for routine use difficult in the rapid and busy setting of the ED[27 28]. Indeed, a study led by Papa & Zempsky[27] showed that only 28% of ED nurses used a topical anesthetic during painful procedures. They reported that main barriers to using this pharmacological intervention were the onset of action

of the drug, treatment delays caused by application time and the vasoconstriction of blood vessels[27]. Consequently, topical anesthetics do not seem to be the most feasible intervention for procedural pain management in an acute care setting where time is critical[21 29]. Also, the use of topical anesthetics may also be associated with local side effects such as redness, itching, edema and vasoconstriction in 25 to 50% of cases[24 25 29 30].

Other pharmacological and non-pharmacological interventions have also been evaluated for their efficacy on children's pain management and distress during needle-related procedures. Among these, there are sweet tasting solutions[31 32], needle-free injection systems[33 34], vapocoolant sprays[35], and distraction[36 37]. However, most of these interventions involve delays in treatment, or require a lot of time, specific training, or additional staff. Moreover, they are not tailored to the specific setting of the ED.

The limited applicability of both pharmacological and non-pharmacological interventions to manage procedural pain and distress in the ED setting demonstrates a need for innovation in this domain. The optimal intervention for needle-related procedural pain management in the ED would need to be rapid, easy-to-use, and without side effects. To answer this problem, Dr. Amy Baxter, an emergency pediatrician and pain researcher in the United States, developed a pain blocker device called Buzzy® (MMJ Labs, Atlanta, GE, USA) specifically for pain management of children undergoing needle-related procedures. The Buzzy® is a bee-shaped device combining vibration (body of the bee) and cold (removable ice wings)[38]. The theoretical bases explaining the action of the device are the Gate Control Theory[39] and the diffuse noxious inhibitory control theory, which both involve modulation of the transmission of pain[38]. Therefore, it is theorized that the simultaneous use of vibration and cold would provide optimal pain management.

To date, there have been some randomized controlled trials that have investigated the efficacy of the Buzzy® device on pain management in children undergoing needle-related procedures in various medical settings[40-48]. However, these studies present several limitations such as the absence of an active comparator[40 42 43 45-47], the lack of prior power analyses or sample size calculation[42 43], lack or unclear allocation concealment[40-43 46 47], among others. Of those studies, only two have been conducted in the ED setting[44 48] and none have been done in Canada. The Buzzy® device seems to be a promising method to reduce and control procedural pain in the ED and it would be interesting to determine if the Buzzy device is at least as efficacious as a topical anesthetic for pain management in children and adolescents during needle-related procedures.

Study Objectives

Primary objective

To determine if a device combining cold and vibration (Buzzy®) is non-inferior (no worse) to a topical anesthetic (liposomal lidocaine 4% cream) for pain management in children undergoing needle-related procedures in the emergency department.

Secondary objectives

To determine if, in comparison to a topical anesthetic (liposomal lidocaine 4% cream), the Buzzy® device will:

- decrease the level of distress during the needle-related procedure
- improve the success of the needle-related procedure at first attempt
- decrease pain memories 24 hours after the needle-related procedure.

Other secondary objectives

- To determine the occurrence of adverse events in each study group.
- To evaluate the satisfaction of parents, children and nurses regarding the use of the Buzzy® device and the topical anesthetic (liposomal lidocaine 4% cream).

METHOD

This study protocol is developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendation[49].

Trial design and study setting

The study design is a randomized, controlled, non-inferiority trial with two parallel groups and a 1:1 allocation ratio. This study design is of interest when a new intervention seems to present some advantages over the reference intervention[50]. Considering that the Buzzy® device seems to be less expensive, faster and easier to use than the topical anesthetic, which is the current reference intervention, the choice of a non-inferiority trial design is justified. As recommended for a non-inferiority trial[50], a study demonstrating the superiority of the reference intervention compared to a placebo in a similar context should be used as rationale to support this study design[50]. For this purpose, the study by Taddio et al.[51] which aimed to determine the efficacy of

the liposomal lidocaine 4% cream over a placebo for managing pain resulting from venipuncture in children in the ED, was used as a reference trial to the current study.

This single center study will take place in the ED of the CHU Sainte-Justine (Montreal, Qc, Canada), a university pediatric tertiary hospital center with a census of more than 80 000 ED visits per year.

Participants

Participants will be deemed eligible if they meet all of the following inclusion criteria: (a) aged between 4 and 17 years old, (b) presenting to the ED and requiring a needle-related procedure (venipuncture or IV catheter insertion), (c) having the ability to communicate in either French or English, and (d) accompanied by at least one parent/legal guardian who can understand, read and speak French or English. We will exclude children with (a) a neuro-cognitive disability that precludes them from assenting and participating to the study, (b) an inability to self-report pain, (c) a critical or unstable health status (<3 on the Canadian Triage and Acuity Scale), (d) a Reynaud's syndrome or sickle cell disease with extreme sensitivity to cold; (e) a break or abrasion on the skin where the device would be installed, and (f) a nerve damage or limited sensation in the extremity where the needle-related procedure will be performed. We will not exclude patients who received analgesics, including acetaminophen or ibuprofen, within the four hours prior to presentation to the ED, but we will document this co-intervention.

Interventions

Experimental group: Buzzy® device

Participants in the experimental group will receive the Buzzy® device® intervention. The Buzzy® is a palm-sized device with two components: 1) body of the bee (vibration) and, 2) removable and reusable ice wings (ice). The body of the bee is a vibrating motor powered by two alkaline AAA batteries and it lasts for about 20 hours. The vibration component is activated by a manual switch on the top part of the device. The removable set of wings contain a total of 18 grams of ice. Each set of ice wings can stay frozen for about 10 minutes at room temperature and they are reusable up to 100 times. Dimensions of the device are 8 cm x 5 cm x 2.5 cm. Enrolled children will have the opportunity to hold and get familiarized with the Buzzy® device before the needle-related procedure.

Use and Placement for the needle-related procedure. The research nurse will follow the following steps, as recommended by the manufacturer' instructions (MMJ Labs, Atlanta, GE, USA): 1) Immediately before the needle-related procedure, a set of ice wings will be retrieved directly from the freezer of the ED unit. For optimal efficacy, the wings must be frozen solid; 2) The ice wings will be inserted through the elastic bands fixed on the back of the Buzzy® device; 3) When the staff nurse is ready to clean the site and perform the needle-related procedure, the research nurse will install the Buzzy® device on the child's arm, above and as close as possible to the insertion site (about 3-5 cm) with a reusable tourniquet, and the vibration will be activated. The Buzzy® device will be installed for about 30 to 60 seconds prior the needle-related procedure; 4) The device has to be maintained on the child's arm throughout the procedure, at least until the needle is removed; 5) When the procedure is over, the two components of the device will be cleaned with a disinfectant cleaner based on proprietary accelerated hydrogen peroxide (Virox™) as per the Infection Prevention and Control guidelines at the study setting; 6) The ice wings will then be put back in the freezer of the unit for a subsequent procedure.

Physiological basis of the Buzzy® device. The Gate Control Theory[39] and the Descending Noxious Inhibitory Controls (DNIC) are the theoretical bases of the Buzzy® device. More specifically, the Gate Control Theory stipulates that the vibration component of the device blocks the A-delta and C nociceptive fibers by stimulating the A-beta non-nociceptive fibers. It activates an inhibitory interneuron and results in a reduction of the pain signal transmitted to the spinal cord[48 52]. The cold component (prolonged cold application 30-60 seconds) stimulates the C nociceptive fibers and further blocks the A-delta nociceptive pain transmission signal when applied close to the needle insertion site[48]. The second theory behind the Buzzy® device is the DNIC. More specifically, intense cold application stimulates the nociceptive C fibers and activates a supraspinal modulation which, in turn, increases the body's overall pain threshold and therefore produces a generalized hypoalgesia at the insertion site[38 53].

Control group: topical anesthetic (liposomal lidocaine 4% cream)

Participants in the control group will receive an application of liposomal lidocaine 4% cream (Maxilene™, RGR Pharma Ltd., LaSalle, ON) over the insertion site 30 minutes before the needle-related procedure. The topical anesthetic cream will be applied by the research nurse according to the manufacturer's recommendation and the site will be covered by a Tegaderm™

dressing (3M Canada Company, London, ON). The topical anesthetic cream and the Tegaderm™ dressing will be removed just before the procedure. This intervention was chosen as an active control intervention as it has been shown to be the most effective for pain management regarding needle-related procedures[23-26] and it is also the standard care currently established in the study setting.

The liposomal lidocaine 4% cream has been chosen over other topical anesthetics because of its shorter application time (30 minutes) and its minimal vasoactive properties that minimize potential interference with the success of the needle-related procedure[51]. Currently, the gold standard topical anesthetic cream is a combination of lidocaine 2.5% and prilocaine 2.5% cream (EMLA), but it requires an application time of 60 minutes and is frequently associated with vasoconstriction of blood vessels[51 54]. The liposomal lidocaine 4% cream has also been chosen due to the lower occurrence of rash reactions after its application, which is often observed with the amethocaine 4% gel[55]. The ametocaine 4% gel has also been associated with vasodilatation and a risk of hypersensitivity with repeated use[51].

Mechanism of action. The mechanism of action of topical anesthetics relies on the reversible interruption of nerve conduction near the application site by inhibiting sodium influx through the voltage-gated sodium channels[30 56-58]. This inhibition of sodium influx decreases the ability to generate action potentials decreasing or blocking hereby pain signals conduction. Following the application, a temporary loss of sensation in the limited area of application is produced[57 58].

Study proceedings

Recruitment

Eligible participants will be recruited consecutively in the ED by two research nurses during study enrolment hours (approximately 25 hours/weeks, depending on research nurses' availability). Potentially eligible patients will be initially assessed upon arrival to the ED by triage nurses, staff nurses and physicians. Then, when the treating physician determines that a child requires a venipuncture or catheter IV insertion, the research nurse will approach the patient and his or her family to confirm study eligibility per the inclusion and exclusion criteria, to explain the study in greater details, and to answer all questions before seeking consent for study participation. Informed written consent will be obtained from parents or legal guardians and

assent will be obtained from children over 7 years old. Research nurses will maintain and complete a Screening and Enrollment Log to provide a comprehensive list of all children who were screened for eligibility. Recruited children will be randomly allocated to either the experimental (Buzzy® device intervention) or the control group (liposomal lidocaine 4% cream).

Data collection and outcomes measures

Data collection will start following consent and enrolment. All data will be collected by one of the two research nurses using a paper case report form (CRF) developed and designed for this study. In addition to the primary and secondary outcomes, socio-demographic and clinical data and covariates will be also recorded. Data will be collected at different end points: before randomization (T-0), 5 minutes before the needle-related procedure (T-1), during the needle-related procedure (T-2), immediately after the needle-related procedure (T-3) and 24 hours after the needle-related procedure (T-4). Of note, the needle-related procedure will be performed by the staff nurse and not the research nurse.

Socio-demographic and clinical data

Before randomization of participants (T-0), socio-demographic and clinical data will be collected by the research nurse. This includes data on age, sex, reason for consultation, previous experience(s) of needle-related procedures, and analgesia received in the last 4 hours prior de procedure. Contact preference and information will also be obtained for a follow up 24 hours after the needle-related procedure.

Primary outcome measure

The primary outcome will be the mean difference in pain scores during the needle-related procedure between experimental and control groups. It will be assessed immediately after the first the needle-related procedure attempt using the Color Analogue Scale (CAS) (T-3). The chosen end point evaluation time aligns with recommendations on standard assessment of post-needle pain[37]. The CAS is a self-reported pediatric pain scale consisting of a plastic ruler with a mechanical slider and showing a wedge-shape figure gradually changing in color from white to red. The white end means “no pain” and the red end means the “worst pain”. The reverse side of

the scale is numbered from 0 to 10 cm with 0.25 increments, allowing investigators to quantify children's pain[59-61]. The CAS has shown excellent psychometric properties in children with acute pain in the ED[60 62]. The child will be shown the side with the wedge-shape figure with the mechanical slider in the middle position and will be asked to move the slider to the place that corresponds to the pain he or she experienced during the needle-relate procedure. The meaning of each anchor will also be explained to the child prior to using the scale. The research nurse will record the corresponding pain score on the reversed side of the scale.

Secondary outcomes measures

The secondary outcomes will be the pain intensity during the needle-related procedure (T-3), the level of distress during the needle-related procedure (T-2, T-3), the success of the procedure at first attempt (T-3), the satisfaction with both interventions (T-3), the occurrence of adverse events, and the memory of pain 24 hours after the needle-related procedure (T-4).

Pain intensity. Mean difference in procedural pain scores between groups will also be assessed using the Faces Pain Scales – Revised (FPS-R)[63] immediately after the first needle-related procedure attempt (T-3). This self-report pain scale is the revised version of the original scale previously developed by Bieri et al[64]. The FPS-R consists of 6 faces and each of them represents a greater intensity of pain than the previous one. The face on the far-left shows "no pain" and the face on the far-right shows "very much pain". On the reversed side of the scale, each face is associated with a score ranging from 0 to 10 (0, 2, 4, 6, 8, 10)[63]. This scale is the most recommended to evaluate procedural pain intensity in children, particularly in children aged from 4 to 12 years old[65]. Immediately after the procedure, the research nurse will ask the child to point the face that shows how much pain he or she felt during the needle-related procedure. The research nurse will document the pain score associated with the face identified by the child.

Level of distress. Mean differences between groups on distress scores during the needle-related procedure will be assessed using the Procedure Behavior Check List (PBCL)[66] (T-2) and the Children's Fear Scale (CFS)[67] (T-3). The PBCL is an observational scale specifically developed to evaluate pain-related fear and anxiety during painful procedures. This scale consists of a checklist with 8 behavioral items: muscle tension, screaming, crying, restraint used, pain verbalized, anxiety verbalized, verbal stalling and physical resistance. The observer has to rate the intensity of each behavior on a scale from 1 to 5 (1=very mild distress; 5=extremely intense

distress)[66]. The research nurse will record the PBCL during the first needle-related procedure attempt (T-2). The CFS is a self-reported scale developed to measure fear of children during painful experiences. This scale has 5 faces with a range of scores from 0 to 4 as each face shows an increasing amount of being scared moving from left to right[67]. Immediately after the first needle-related procedure attempt (T-3), the child will be asked to choose the face that best shows how much he was scared during the procedure. The child will be informed that the first face is "not scared at all" and the last face is "the most scare possible"[67].

Success of the procedure at first attempt. The proportion of participants achieving a successful procedure at first attempt will be recorded as a binary outcome (yes/no) (T-3). If the procedure is not successful at first attempt, the research nurse will document the number of attempts in the CRF.

Satisfaction. Satisfaction of both interventions will be evaluated using three questionnaires tailored for children, parents and nurses and including Likert scale questions and dichotomized (yes/no) questions. It will be assessed immediately after the needle-related procedure with parents and children (T-3) and when reaching 50% of the targeted recruitment for nurses.

Adverse events. The proportion of participants experiencing an adverse event will be recorded as a binary outcome. An adverse event will be defined as an unexpected medical occurrence in a participant which may or may not be necessarily causally related to one of the two interventions. Adverse events will be recorded after enrolment of the participant until hospital discharge.

Memory of pain. The memory of pain will be assessed by comparing pain scores between groups 24 hours after the needle-related procedure using the FPS-R phrased in terms of recall[63] (T-4). After the needle-related procedure, the research nurse will give a paper copy of the FPS-R to each parent or legal guardian with the corresponding instructions. They will be informed that they will be contacted in the next 24 hours (±6 hours) by telephone, text message or email, depending on their preference. The research nurse will then ask the child to point at face that corresponds with how much pain they remember feeling during the needle-related procedure at the ED. The child/parent will report by telephone, text message or email the chosen face (first, second, third, fourth, fifth, sixth) and the research nurse will record the answer.

Covariates

Data will be collected from participants and their parents for potential covariates. Pre-procedural pain (CAS) and pre-procedural level of distress (PBCL, CFS) will be assessed 5 minutes before the needle-related procedure (T-1). Clinical data will also be recorded during the needle-related procedure (T-2), including: type of procedure (venipuncture, IV catheter insertion), healthcare professional performing the procedure (nurse, nursing assistant, phlebotomist), presence of parent/legal guardian during the procedure (one parent, two parents, none), position of the child during the procedure (sitting position, on a parent's lap, dorsal decubitus, dorsal decubitus against his will), restraints used during the procedure (yes/no) and use of other non-pharmacological interventions during the procedure.

Data management

All data collected with the CRFs will be manually entered into an electronic database statistical software and the original CRFs will be kept on file at the participating site. Data entry and coding will be performed by the same person. A verification will be done by a second person to compare with the original CRFs. Each participant's file will be assigned an identification number to preserve participant confidentiality. Files will be stored in numerical order in a locked file cabinet in the principal investigator's office at the research center. Files will be maintained in storage for a period of minimum 25 years after completion of the study, according to Health Canada regulations for Health Canada Regulated Clinical Trials.

Randomization and allocation

An independent biostatistician of the Applied Clinical Research Unit (Unité de Recherche Clinique Appliquée - URCA) will generate the sequence of randomization as per a computer-generated random listing of interventions applying a permuted block design with random blocks stratified by age (4-7 years; 8-12 years; 13-17 years). The SAS software version 9.3 (SAS Institute Inc, Cary, NC) will be used to generate the randomization list using a pre-specified seed to ensure reproducibility and proof of random allocation. To ensure concealment, the block size will not be disclosed. Enrolled participants will be randomly assigned, in a 1:1 allocation ratio, to

receive either the experimental intervention (Buzzy® device intervention) or the control intervention (liposomal lidocaine 4% cream).

The allocation concealment will be ensured by the use of sequentially numbered, opaque and sealed envelopes previously prepared by the URCA. The randomization sequence will be stored at the URCA for the whole duration of the study in order to keep the investigators and blinded from the study conditions. After the enrolled participant completed all baseline measurements, the appropriate numbered envelope will be opened by the research nurse. Each envelope will contain the randomization number and the allocated intervention.

Due to the major differences between the two interventions in appearance and timing of application, it will not be possible to blind participants, parents, healthcare providers and outcome assessors (research nurses) to the participant's allocation.

Data analyses

Sample Size

The primary aim of this trial is to demonstrate the non-inferiority of the Buzzy device compared to a topical anesthetic (liposomal lidocaine 4% cream) for procedural pain management during needle-related procedures in the ED. To determine the non-inferiority margin, an electronic survey was sent to 34 pediatric emergency physicians working in ED settings from Quebec and Ontario. The following scenario and question were presented: "You are seeing a four-year old female requiring an IV catheter for drug delivery. You are considering two interventions for pain management during the needle-related procedure: a topical anesthetic application (liposomal lidocaine 4% cream) or the Buzzy® device. You need to assume that both of these interventions have the potential for reducing needle-related pain." "What is the greatest difference in mean pain reduction, on a numerical scale from 0 to 10, between the topical anesthetic (liposomal lidocaine 4% cream) and the Buzzy® device you are willing to accept to routinely adopt the use of the Buzzy® device over the topical anesthetic (liposomal lidocaine 4% cream) for needle-related procedures?". Respondents had to choose a difference ranging from 0.1 to 1.5 with 0.1 increments. The mean answer was 0.70, consequently, this value was chosen as the non-inferiority margin. Considering that the minimal clinically significant difference (MCSD) on the CAS in children with acute pain is 1.0 on a scale from 0 to 10[68], the choice of a 0.70 non-

inferiority margin is considered conservative and insures that a minimally important difference would not be missed. Therefore, a sample size of 346 participants would be necessary to provide the trial with 90% power to show the non-inferiority of the Buzzy® device compared to a topical anesthetic at a one-sided alpha level of 0.025 with the use of a non-inferiority margin of 0.70 for the per-procedural pain intensity. We anticipate no loss to follow-up considering the short time frame between the intervention and the assessment of the primary outcome. The sample size was calculated using the G*Power software version 3.0.10.

Statistical methods

The primary analysis was designed to test whether the Buzzy® device is non-inferior to a topical anesthetic (4% liposomal lidocaine) for procedural pain management during needle-related procedures, as evaluated by performing a Student's t-test for the mean differences in pain scores between groups and calculating its confidence interval (CI). Non-inferiority would be declared if the upper limit of the two-sided 95% CI (1-2α x100%CI) (or equivalently, the upper limit of the one-sided 97.5% CI) for the between-group difference (experimental group – control group) is less than the predetermined non-inferiority margin of Δ 0.70. In this case, the null hypothesis of inferiority will be rejected in favor of the alternative hypothesis of non-inferiority and the non-inferiority of the Buzzy® device over the topical anesthetic (liposomal lidocaine 4% cream) will be established. A two-sided 95%CI will be applied because it will provide additional information if the superiority of the experimental intervention is demonstrated[50]. In the case where the non-inferiority is met, superiority testing will be performed using a two-sided alpha of 0.05 and in looking if the upper limit of the confidence interval is less than zero. Non-inferiority analysis will be evaluated according to the intention-to-treat principle (participants who had undergone randomization) as well as to the per-protocol principle (participants who received the assigned intervention) to examine for consistency and avoid bias[50].

The secondary analysis was designed to test the superiority of the Buzzy® device over the liposomal lidocaine 4% cream for secondary outcomes. The Student's t-test will be performed to compare the between-group mean differences in pre-procedural and procedural distress scores. The memory of pain 24 hours after the needle-related procedure will also be evaluated by the Student's t-test to compare the mean differences in pain scores between the experimental and

control groups. The proportion of participants achieving the success of the procedure at first attempt will be calculated in each group and compared using the Chi-square test. Descriptive statistics will be used to report data collected on satisfaction, as well as socio-demographic and clinical data. Means and standard deviation will be reported for continuous variables and proportions will be calculated for categorical and nominal variables. Potentially relevant pre-procedural and procedural variables will be included in covariate model (ANCOVA) in an attempt to determine predictors of pain scores reduction. All secondary analysis will be carried out according to the intention-to-treat principle. For superiority testing, a p value <0.05 will be considered as indicating statistical significance.

Preplanned subgroups non-inferiority analyses will be carried out for the primary outcomes based on age group (4-7 years vs. 8-12 years vs. 13-17 years). As we will not have the statistical power in each subgroup to conclude to non-inferiority, the results will be considered as exploratory and will primarily serve for hypothesis generation for future studies. Subgroups superiority analyses will be also performed by age group for secondary outcomes. Multiple imputation methods and sensitivity analysis will be used when possible and appropriate to handle the missing data.

No formal interim analysis is planned for this non-inferiority trial for different reasons. First, there is no necessity to conduct interim analysis for futility reasons in non-inferiority trials considering that even if non-inferiority is established before the completion of the trial, the data collection should be pursued in hope of demonstrating superiority[50]. Second, considering that we do not expect potentially serious adverse events, interim analysis for safety reasons and stoppings rules are not required[49 69]. There is also no need to implement a data monitoring committee (DMC) as the known risks are minimal for both interventions[49 70 71].

DISCUSSION

This study protocol provides the rational and methods associated with a randomized controlled non-inferiority trial comparing the Buzzy® device to a topical anesthetic with the aim of improving procedural pain and distress management in children undergoing needle-related procedures. To our knowledge, this is the first study assessing the efficacy of the Buzzy® device in Canada in any clinical setting. A systematic review currently in preparation by our team has

identified several limitations in the studies previously conducted on the Buzzy® device (PROSPERO ID: CRD42017076531). The present study is carefully designed to overcome these limitations and provide rigorous evidence on its efficacy. The large sample size will allow to determine if the Buzzy® device is at least as efficacious as the liposomal lidocaine 4% cream in decreasing procedural pain. Therefore, this study has the potential to improve clinical care and outcomes of children undergoing needle-related procedures in the ED. More specifically, findings from this trial could potentially prevent pain and distress experienced by children, as well as improve nurses pain management practices. In addition, this study could determine the efficacy of the Buzzy® device intervention across age ranges and developmental differences. If the non-inferiority of the Buzzy® is demonstrated, steps will be taken to eventually obtain a Medical Device Licence from Health Canada to make this device available in the EDs across Canada.

This study presents some limitations which are important to recognize. First, considering the nature and the major differences between both interventions, blinding of participants and personnel is not possible. Consequently, they are aware of the intervention allocation once the randomized envelop is opened. This lack of blinding could influence their behaviour and responses to outcomes, particularly subjective ones like pain and distress creating therefore a potential performance bias[72]. However, the use of an active comparator (anesthetic) could potentially reduce or overcome this bias. Indeed, a recent study[73] has demonstrated that randomized controlled trials using an active comparator reported similar expectation ratings from participants between groups. Second, it is not possible to blind the secondary outcome assessors (research nurses) as it requires observing the behavior of the participant during the procedure. However, the primary outcome assessment is by self-report, which is considered as a primary source of evidence for pediatric pain intensity[74]. This could increase the magnitude of the detection bias as pain is a subjective measure[75]. However, some have argued that self-report assessment could be considered as equivalent to blinding of outcome assessors considering that self-report is not associated with an overestimated intervention effects, as is the case in psychotherapy meta-analyses[76 77]. Third, we expect a variability related to the nurses performing the needle-related procedure and their approach to the child and the family. This could positively or negatively influence the pain and distress experienced. However, it could also increase the generalization of results and optimize implementation in clinical settings as it resembles daily clinical practice.

Finally, although there is an increase in use and development of pharmacological and non-pharmacological interventions in research, pain management is still suboptimal. It suggests that evidence is not being translated and implemented in clinical practice or that it is underused by healthcare providers[37 78]. Therefore, it is important to provide healthcare professionals with interventions that are likely to be translated into clinical practice for routine use. The Buzzy® device is an easy-to-use and fast intervention that seems to be a promising option in the ED setting.

ETHICS AND DISSEMINATION

Ethics and safety consideration

This study has been reviewed and approved by the Research Ethics Board (REB) of the study setting (CHU Sainte-Justine Research Centre, University of Montreal; #2017-1405). This approval covers the protocol, informed consent forms and the data collection forms. To date, no important protocol modification has been made after the initial ethics approval. As recommended by the International Committee of Medical Journal Editors (ICMJE)[79], this clinical trial was registered in a public trials registry prior to the beginning of the recruitment (ClinicalTrials.gov: NCT02616419). An Investigational Testing Authorization from the Medical Device Bureau of Health Canada was also granted (#272708). Finally, this study will be conducted in accordance with the principles of the Declaration of Helsinki[80] and all REB policies and guidelines. Written informed consent will be obtained from parents or legal guardians and assent will be obtained from children over 7 years old. Consent involve a follow-up 24 hours after the needle-related procedure.

Dissemination

The research protocol has been already presented to local clinicians and stakeholders, as well as at national and international conferences. Scientific results will be disseminated at regional, national and international conferences targeting nurses, emergency physicians and pediatric researchers. A manuscript will be submitted to a high impact peer-reviewed journal.

Trial status

Recruitment for this study is ongoing.

Acknowledgement

The authors would like to acknowledge the research nurses (Maryse Lagacé and Ramona Cook) who are currently collecting data for this study. They also thank all the recruited and future participants and their families, as well as the ED staff, for their continuous support. They are particularly grateful to Céline Pinard and Jessie Laflamme, two nurses working in the ED, for their collaboration on this project. The authors also want to acknowledge the Applied Clinical Research Unit of the CHU Sainte-Justine, specifically Aude-Christine Guédon for assistance with biostatistical analyses. AB would like to acknowledge the financial support received from the following organizations: Quebec's Healthcare Research Fund, Quebec's Ministry of Higher Education, Quebec Network on Nursing Intervention Research.

Authors' contribution

AB conceptualized and designed the study and wrote the first draft of this research protocol. CK, EDT, BB, NP, JT and SLM provided feedback to refine the research methodology. SA, EDT and BB contributed to the implementation of the study. SA is involved in the data collection process. All authors read, critically revised and approved the final version of this research protocol.

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Competing interests statement

None declared.

Ethics approval

Research Ethics Board (REB) of the CHU Sainte-Justine (# 2017-1405)

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**2, 18**
	2b	All items from the World Health Organization Trial Registration Data Set	**n/a**
Protocol version	3	Date and version identifier	**n/a**
Funding	4	Sources and types of financial, material, and other support	**19**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1**
	5b	Name and contact information for the trial sponsor	**n/a**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**n/a**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**n/a**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4**
	6b	Explanation for choice of comparators	**4**
Objectives	7	Specific objectives or hypotheses	**6**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**6**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**7**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**7**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**n/a**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**n/a**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**n/a**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**10**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**9**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**14**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**9**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**13**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**14**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**13**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**14**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**n/a**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**10**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**n/a**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**13**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**15**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**16**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**15**

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**16**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**16**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**n/a**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**n/a**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**18**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**18**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**9, 18**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**n/a**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**13, 18**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**19**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**n/a**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**n/a**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**18**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**n/a**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**n/a**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**n/a**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**n/a**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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External Cold and Vibration for Pain Management of Children Undergoing Needle-Related Procedures in the Emergency Department: A Randomized Controlled Non-Inferiority Trial Protocol

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Title: External Cold and Vibration for Pain Management of Children Undergoing Needle-Related Procedures in the Emergency Department: A Randomized Controlled Non-Inferiority Trial Protocol

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ABSTRACT

Introduction: Needle-related procedures are considered as the most important source of pain and distress in children in hospital settings. Considering the physiological and psychological consequences resulting from these procedures, management of pain and distress through pharmacological and non-pharmacological methods is essential. Therefore, it is important to have interventions that are rapid and easy-to-use and implement. The aim of this study will be to determine whether a device combining cold and vibration (Buzzy®) is non-inferior to a topical anesthetic (liposomal lidocaine 4% cream) for pain management of children undergoing needle-related procedures in the Emergency Department.

Methods and analysis: This study is a randomized controlled non-inferiority trial comparing the Buzzy® device to liposomal lidocaine 4% cream for needle-related pain management. A total of 346 participants will be randomly assigned in a 1:1 ratio to one of these two interventions. The primary outcome will be the mean difference in pain intensity between groups during needle-related procedures. Non-inferiority would be demonstrated if the mean procedural pain scores of the experimental group is not worse than the mean procedural pain scores of the control group by a non-inferiority margin of 0.70 on the Color Analogue Scale (CAS). The secondary outcomes will be the level of distress/anxiety during the procedure, the success of the procedure at first-attempt, the occurrence of adverse events, the satisfaction of both interventions and the memory of pain 24 hours after the procedure. The primary outcome will be assessed for non-inferiority and the secondary outcomes for superiority.

Ethics and dissemination: This study protocol was reviewed and approved by the institutional review board of the study setting. Findings of this trial will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number: NCT02616419

Keywords: Buzzy, Topical Anesthetic, Procedural pain, Children, Non-pharmacological intervention

Article summary

Strengths and limitations of this study

- This is the first study to assess the efficacy of the Buzzy® device in Canada.
- The large sample size of 346 participants will provide enough power to demonstrate the non-inferiority of the Buzzy® device compared to a topical anesthetic.
- The non-inferiority margin is justified on both clinical and statistical grounds.
- This study presents potential clinical implications for nursing and medical practices in the emergency department.
- The main limitation of this trial is the impossibility to blind participants and personnel to treatment/intervention allocation.

INTRODUCTION

Background and rationale

Needle-related procedures, such as venipuncture and intravenous (IV) catheter insertions, are considered as the most important source of pain and distress in children in hospital settings[1-4]. The intensity of pain and distress caused by these procedures can vary from mild to moderate for some, while for others, it may be severe[4-7]. It is now recognized that even a minor procedure, such as venipuncture, can result in numerous physiological, psychological and emotional consequences[8 9]. Among these, needle phobia is the most important and prevalent consequence with more than 60% of children reporting an extreme fear of needles following a bad needle experience[10]. Children with needle phobia are more likely to report higher levels of pain and distress from subsequent procedures[11 12] and they can experience physiological symptoms, such as increased heart rate and blood pressure and vasovagal reactions[13 14]. Further, children with needle-phobia can develop healthcare avoidance behaviors in adulthood, such as delays in care, non-compliance of immunization requirements and avoidance of treatment[10 14]. Nurses play a critical role in the assessment and management of children's pain and distress, and the use of pharmacological and non-pharmacological interventions must be an integrant part of nursing practice[15].

Procedural pain management represents a major challenge for nurses, specifically for those working in the Emergency Department (ED). Consequently, children are at high risk for undertreatment of their pain during needle-related procedures[16]. Although healthcare professionals recognize the importance of providing adequate procedural pain relief, pain management is still suboptimal[8 17-19]. Several studies have identified different barriers to using available pharmacological and non-pharmacological interventions for pain management in the ED[8 17-19]. Barriers most frequently identified by nurses are time constraints, heavy workload, staffing limitations, space limitations, lack of knowledge, and interruptions in the continuity of care[15 20-22].

Currently, the current gold standard intervention for needle-related procedural pain is the application of a topical anesthetic prior to the procedure and several systematic reviews and meta-analysis have supported this intervention demonstrating its efficacy extensively[23-26]. However, topical anesthetics require an application time ranging from 30 to 60 minutes, making their implementation for routine use difficult in the rapid and busy setting of the ED[27 28]. Indeed, a study led by Papa & Zempsky[27] showed that only 28% of ED nurses used a topical anesthetic during painful procedures. They reported that main barriers to using this pharmacological intervention were the onset of action

of the drug, treatment delays caused by application time and the vasoconstriction of blood vessels[27]. Consequently, topical anesthetics do not seem to be an optimal intervention for procedural pain management in an acute care setting where time constraints represent an important barrier to adequate pain control[21 29]. Also, topical anesthetics had a minimal side effect profile, including minor local reactions, such as mild irritation, redness, itching, edema or rash of the skin site following the application in 25 to 50% of cases[24 25 29-31].

Other pharmacological and non-pharmacological interventions have also been evaluated for their efficacy on children's pain management and distress during needle-related procedures. Among these, there are sweet tasting solutions[32 33], needle-free injection systems[34 35], vapocoolant sprays[36], and distraction[37 38]. However, even if the efficacy of most of these interventions is well demonstrated, their use remains limited in clinical practice, and this may be due to time constraints and limited resources of the ED setting[15 20-22]. These interventions may require specific training for healthcare professionals, preparation time, or excessive cost, which represent barriers to their implementation in a busy, fast-paced environment of the ED setting[15 20-22].

The limited applicability of both pharmacological and non-pharmacological interventions to manage procedural pain and distress in the ED setting demonstrates a need for innovation in this domain. The optimal intervention for needle-related procedural pain management in the ED would need to be rapid, easy-to-use, and without side effects. To answer this problem, Dr. Amy Baxter, an emergency pediatrician and pain researcher in the United States, developed a pain blocker device called Buzzy® (MMJ Labs, Atlanta, GE, USA) specifically for pain management of children undergoing needle-related procedures. The Buzzy® is a bee-shaped device combining vibration (body of the bee) and cold (removable ice wings)[39]. The theoretical bases explaining the action of the device are the Gate Control Theory[40] and the diffuse noxious inhibitory control theory, which both involve modulation of the transmission of pain[39]. Therefore, it is theorized that the simultaneous use of vibration and cold would provide optimal pain management.

To date, there have been some randomized controlled trials that investigated the efficacy of the Buzzy® device on pain management in children undergoing needle-related procedures in various medical settings[41-49]. However, these studies present several limitations such as the absence of an active comparator[41 43 44 46-48], the lack of prior power analyses or sample size calculation[43 44], lack or unclear allocation concealment[41-44 47 48], among others. Of those studies, only two have been conducted in the ED setting[45 49] and none have been done in Canada. The Buzzy® device seems to be

a promising intervention to decrease and control procedural pain in the ED and it would be interesting to determine if it is at least as efficacious as a topical anesthetic for pain management in children and adolescents during needle-related procedures.

Study Objectives

Primary objective

To determine if a device combining cold and vibration (Buzzy®) is non-inferior (no worse) to a topical anesthetic (liposomal lidocaine 4% cream) for pain management in children undergoing needle-related procedures in the emergency department.

Secondary objectives

To determine if, in comparison to a topical anesthetic (liposomal lidocaine 4% cream), the Buzzy® device will:

- decrease the level of distress/anxiety during the needle-related procedure
- improve the success of the needle-related procedure at first attempt
- decrease pain memories 24 hours after the needle-related procedure.

Other secondary objectives

- To determine the occurrence of adverse events in each study group.
- To evaluate the satisfaction of parents, children and nurses regarding the use of the Buzzy® device and the topical anesthetic (liposomal lidocaine 4% cream).

METHOD

This study protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendation[50].

Trial design and study setting

The study design is a randomized, controlled, non-inferiority trial with two parallel groups and a 1:1 allocation ratio. This study design is of interest when a new intervention seems to present some advantages over the reference intervention[51]. Considering that the Buzzy® device seems to be less expensive, faster and easier to use than the topical anesthetic, which is the current reference intervention, the choice of a non-inferiority trial design is justified. As recommended for a non-inferiority trial[51], a study demonstrating the superiority of the reference intervention

compared to a placebo in a similar context should be used as rationale to support this study design[51]. For this purpose, the study by Taddio et al.[52] which aimed to determine the efficacy of the liposomal lidocaine 4% cream over a placebo for managing pain resulting from venipuncture in children in the ED, was used as a reference trial to the current study.

This single center study will take place in the ED of the CHU Sainte-Justine (Montreal, Qc, Canada), a university pediatric tertiary hospital center with a census of more than 80 000 ED visits per year.

Participants

Participants will be deemed eligible if they meet all of the following inclusion criteria: (a) aged between 4 and 17 years old, (b) presenting to the ED and requiring a needle-related procedure (venipuncture or IV catheter insertion), (c) having the ability to communicate in either French or English, and (d) accompanied by at least one parent/legal guardian who can understand, read and speak French or English. We will exclude children with (a) a neuro-cognitive disability that precludes them from assenting and participating to the study, (b) an inability to self-report pain, (c) a critical or unstable health status (<3 on the Canadian Triage and Acuity Scale), (d) a Raynaud's syndrome or sickle cell disease with extreme sensitivity to cold; (e) a break or abrasion on the skin where the device would be installed, and (f) a nerve damage or limited sensation in the extremity where the needle-related procedure will be performed. We will not exclude patients who received analgesics, including acetaminophen or ibuprofen, within the four hours prior to presentation to the ED, but we will document this co-intervention.

Interventions

Experimental group: Buzzy® device

Participants in the experimental group will receive the Buzzy® device® intervention. The Buzzy® is a palm-sized device with two components: 1) body of the bee (vibration) and, 2) removable and reusable ice wings (ice). The body of the bee is a vibrating motor powered by two alkaline AAA batteries and it lasts for about 20 hours. The vibration component is activated by a manual switch on the top part of the device. The removable set of wings contain a total of 18 grams of ice. Each set of ice wings can stay frozen for about 10 minutes at room temperature and they are reusable up to 100 times. Dimensions of the device are 8 cm x 5 cm x 2.5 cm. Enrolled

children will have the opportunity to hold and get familiarized with the Buzzy® device before the needle-related procedure.

Use and Placement for the needle-related procedure. The research nurse will follow the following steps, as recommended by the manufacturer' instructions (MMJ Labs, Atlanta, GE, USA): 1) Immediately before the needle-related procedure, a set of ice wings will be retrieved directly from the freezer of the ED unit. For optimal efficacy, the wings must be frozen solid; 2) The ice wings will be inserted through the elastic bands fixed on the back of the Buzzy® device; 3) When the staff nurse is ready to clean the site and perform the needle-related procedure, the research nurse will install the Buzzy® device on the child's arm, above and as close as possible to the insertion site (about 3-5 cm) with a reusable tourniquet, and the vibration will be activated. The Buzzy® device will be installed for about 30 to 60 seconds prior the needle-related procedure; 4) The device has to be maintained on the child's arm throughout the procedure, at least until the needle is removed; 5) When the procedure is over, the two components of the device will be cleaned with a disinfectant cleaner based on proprietary accelerated hydrogen peroxide (Virox™) as per the Infection Prevention and Control guidelines at the study setting; 6) The ice wings will then be put back in the freezer of the unit for a subsequent procedure.

Physiological basis of the Buzzy® device. The Gate Control Theory[40] and the Descending Noxious Inhibitory Controls (DNIC) are the theoretical bases of the Buzzy® device. More specifically, the Gate Control Theory stipulates that the vibration component of the device blocks the A-delta and C nociceptive fibers by stimulating the A-beta non-nociceptive fibers. It activates an inhibitory interneuron and results in a reduction of the pain signal transmitted to the spinal cord[49 53]. The cold component (prolonged cold application 30-60 seconds) stimulates the C nociceptive fibers and further blocks the A-delta nociceptive pain transmission signal when applied close to the needle insertion site[49]. The second theory behind the Buzzy® device is the DNIC. More specifically, intense cold application stimulates the nociceptive C fibers and activates a supraspinal modulation which, in turn, increases the body's overall pain threshold and therefore produces a generalized hypoalgesia at the insertion site[39 54].

Control group: topical anesthetic (liposomal lidocaine 4% cream)

Participants in the control group will receive an application of liposomal lidocaine 4% cream (Maxilene™, RGR Pharma Ltd., LaSalle, ON) over the insertion site 30 minutes before the needle-related procedure. The topical anesthetic cream will be applied by the research nurse according to the manufacturer's recommendation and the site will be covered by a Tegaderm™ dressing (3M Canada Company, London, ON). The topical anesthetic cream and the Tegaderm™ dressing will be removed just before the procedure. This intervention was chosen as an active control intervention as it has been shown to be the most effective for pain management regarding needle-related procedures[23-26] and it is also the standard care currently established in the study setting.

The liposomal lidocaine 4% cream has been selected over other topical anesthetics because of its shorter application time (30 minutes) and its minimal vasoactive properties that minimize potential interference with the success of the needle-related procedure[52]. Currently, the gold standard topical anesthetic cream is a combination of lidocaine 2.5% and prilocaine 2.5% cream (EMLA), but it requires an application time of 60 minutes and is frequently associated with vasoconstriction of blood vessels[55-57]. The liposomal lidocaine 4% cream has also been chosen due to the lower occurrence of rash reactions after its application, which is often observed with the amethocaine 4% gel[58]. The taller has also been associated with vasodilatation and a risk of hypersensitivity with repeated use[26].

Mechanism of action. The mechanism of action of topical anesthetics relies on the reversible interruption of nerve conduction near the application site by inhibiting sodium influx through the voltage-gated sodium channels[30 59-61]. This inhibition of sodium influx decreases the ability to generate action potentials decreasing or blocking hereby pain signals conduction. Following the application, a temporary loss of sensation the limited area of application is produced[60 61].

Study proceedings

Recruitment

Eligible participants will be recruited consecutively in the ED by two research nurses during study enrolment hours (approximately 25 hours/weeks, depending on research nurses' availability). Potentially eligible patients will be initially assessed upon arrival to the ED by triage nurses, staff nurses and physicians. Then, when the treating physician determines that a

child requires a venipuncture or catheter IV insertion, the research nurse will approach the patient and his or her family to confirm study eligibility per the inclusion and exclusion criteria, to explain the study in greater details, and to answer all questions before seeking consent for study participation. Informed written consent will be obtained from parents or a legal guardian and assent will be obtained from children over 7 years old. Research nurses will complete and maintain a Screening and Enrollment Log to provide a comprehensive list of all children who were screened for eligibility. Recruited children will be randomly allocated to either the experimental (Buzzy® device intervention) or the control group (liposomal lidocaine 4% cream).

Data collection and outcomes measures

Data collection will start following consent and enrolment. All data will be collected by one of the two research nurses using a paper case report form (CRF) developed and designed for this study. In addition to the primary and secondary outcomes, socio-demographic and clinical data and covariates will be also recorded. Data will be collected at different end points: before randomization (T-0), 5 minutes before the needle-related procedure (T-1), during the needle-related procedure (T-2), immediately after the needle-related procedure (T-3) and 24 hours after the needle-related procedure (T-4). Of note, the needle-related procedure will be performed by the staff nurse and not the research nurse.

Socio-demographic and clinical data

Before randomization of participants (T-0), socio-demographic and clinical data will be collected by the research nurse. This includes data on age, sex, reason for consultation, previous experience(s) of needle-related procedures, and analgesia received in the last 4 hours prior to the procedure. Contact preference and information will also be obtained for a follow up 24 hours after the needle-related procedure.

Primary outcome measure

The primary outcome will be the mean difference in pain scores during the needle-related procedure between experimental and control groups. It will be assessed immediately after the first the needle-related procedure attempt using the Color Analogue Scale (CAS) (T-3). The

selected end point evaluation time aligns with recommendations on standard assessment of post-needle pain[38]. The CAS is a self-reported pediatric pain scale consisting of a plastic ruler with a mechanical slider and showing a wedge-shape figure gradually changing in color from white to red. The white end means "no pain" and the red end eans the "worst pain". The reverse side of the scale is numbered from 0 to 10 cm with 0.25 increments, allowing investigators to quantify children's pain[62-64]. The CAS has shown excellent psychometric properties in children with acute pain in the ED[63 65]. The child will be shown the side with the wedge-shape figure with the mechanical slider in the middle position and will be asked to move the slider to the place that corresponds to the pain he or she experienced during the needle-relate procedure. The meaning of each anchor will also be explained to the child prior to using the scale. The research nurse will record the corresponding pain score on the reversed side of the scale.

Secondary outcomes measures

The secondary outcomes will be the pain intensity during the needle-related procedure (T-3), the level of distress/anxiety during the needle-related procedure (T-2, T-3), the success of the procedure at first attempt (T-3), the level of satisfaction of both interventions (T-3), the occurrence of adverse events, and memory of pain 24 hours after the needle-related procedure (T-4).

Pain intensity. Mean difference in procedural pain scores between groups will also be assessed using the Faces Pain Scales – Revised (FPS-R)[66] immediately after the first needle-related procedure attempt (T-3). This self-report pain scale is the revised version of the original scale previously developed by Bieri et al[67]. The FPS-R consists of 6 faces and each of them represents a greater intensity of pain than the previous one. The face on the far-left shows "no pain" and the face on the far-right shows "very much pain". On the reversed side of the scale, each face is associated with a score ranging from 0 to 10 (0, 2, 4, 6, 8, 10)[66]. This scale is the most recommended to evaluate procedural pain intensity in children, particularly in children aged from 4 to 12 years old[68]. Immediately after the procedure, the research nurse will ask the child to point the face that shows how much pain he or she felt during the needle-related procedure. The research nurse will document the pain score associated with the face selected by the child.

Level of distress/Anxiety. Mean differences between groups on distress/anxiety scores during the needle-related procedure will be assessed using the Procedure Behavior Check List

(PBCL)[69] (T-2) and the Children's Fear Scale (CFS)[70] (T-3). The PBCL is an observational scale specifically developed to evaluate pain-related fear and anxiety during painful procedures. This scale consists of a checklist with 8 behavioral items: muscle tension, screaming, crying, restraint used, pain verbalized, anxiety verbalized, verbal stalling and physical resistance. The observer has to rate the intensity of each behavior on a scale from 1 to 5 (1=very mild; 5=extremely intense)[69]. The research nurse will record the PBCL during the first needle-related procedure attempt (T-2). The CFS is a self-reported scale developed to measure fear of children during painful experiences. This scale has 5 faces with a range of scores from 0 to 4 as each face shows an increasing amount of being scared moving from left to right[70]. Immediately after the first needle-related procedure attempt (T-3), the child will be asked to choose the face that best shows how much he was scared during the procedure. The child will be informed that the first face is "not scared at all" and the last face is "the most scare possible"[70].

Success of the procedure at first attempt. The proportion of participants achieving a successful procedure at first attempt will be recorded as a binary outcome (yes/no) (T-3). If the procedure is not successful at first attempt, the research nurse will document the number of attempts in the CRF.

Satisfaction. Level of satisfaction of both interventions will be evaluated using three questionnaires tailored for children, parents and nurses and including Likert scale questions and dichotomized (yes/no) questions. This variable will be assessed immediately after the needle-related procedure for parents and children (T-3) and when reaching 50% of the targeted recruitment for nurses.

Adverse events. The proportion of participants experiencing an adverse event will be recorded as a binary outcome. An adverse event will be defined as an unexpected medical occurrence in a participant which may or may not be necessarily caused by one of the two interventions. Adverse events will be recorded following enrolment of participants until hospital discharge.

Memory of pain. Memory of pain will be assessed by comparing pain scores between groups 24 hours after the needle-related procedure using the FPS-R phrased in terms of recall[66] (T-4). After the needle-related procedure, the research nurse will give a plastified copy of the FPS-R to each parent or legal guardian with the corresponding instructions. They will be

informed that they will be contacted in the next 24 hours (±6 hours) by telephone, text message or email, depending on their preference. The research nurse will then ask the child to point to the face corresponding to the level of pain they remember feeling during the needle-related procedure while they were in the ED. The child/parent will report by telephone, text message or email the selected face (first, second, third, fourth, fifth, sixth) and the research nurse will record the answer.

Covariates

Data will be collected from participants and their parents for potential covariates. Pre-procedural pain (CAS) and pre-procedural level of distress/anxiety (PBCL, CFS) will be assessed 5 minutes before the needle-related procedure (T-1). Clinical data will also be recorded during the needle-related procedure (T-2), including: type of procedure (venipuncture, IV catheter insertion), healthcare professional performing the procedure (nurse, nursing assistant, phlebotomist), presence of parent/legal guardian during the procedure (one parent, two parents, none), position of the child during the procedure (sitting position, on a parent's lap, dorsal decubitus, dorsal decubitus against his will), restraints used during the procedure (yes/no) and use of other non-pharmacological interventions during the procedure.

Data management

All data collected with the CRFs will be manually entered into an electronic database statistical software and the original CRFs will be kept on file at the participating site. Data entry and coding will be performed by the same person. A verification will be done by a second person to compare with the original CRFs. Each participant's file will be assigned an identification number to preserve participant confidentiality. Files will be stored in numerical order in a locked file cabinet in the principal investigator's office at the research center. Files will be maintained in storage for a period of minimum 25 years after completion of the study, according to Health Canada regulations for Health Canada Regulated Clinical Trials.

Randomization and allocation

An independent biostatistician of the Applied Clinical Research Unit (Unité de Recherche Clinique Appliquée - URCA) will generate the sequence of randomization as per a computer-

generated random listing of interventions applying a permuted block design with random blocks stratified by age (4-7 years; 8-12 years; 13-17 years). The SAS software version 9.3 (SAS Institute Inc, Cary, NC) will be used to generate the randomization list using a pre-specified seed to ensure reproducibility and proof of random allocation. To ensure concealment, the block size will not be disclosed. Enrolled participants will be randomly assigned, in a 1:1 allocation ratio, to receive either the experimental intervention (Buzzy® device intervention) or the control intervention (liposomal lidocaine 4% cream).

Allocation concealment will be ensured by the use of sequentially numbered, opaque and sealed envelopes previously prepared by the URCA. The randomization sequence will be stored at the URCA for the whole duration of the study in order to keep the investigators and blinded from the study conditions. After the enrolled participant completed all baseline measurements, the appropriate numbered envelope will be opened by the research nurse. Each envelope will contain the randomization number and the allocated intervention.

Due to the major differences between the two interventions in appearance and timing of application, it will not be possible to blind participants, parents, healthcare providers and outcome assessors (research nurses) to the participant's allocation.

Data analyses

Sample size

The primary aim of this trial is to demonstrate the non-inferiority of the Buzzy device compared to a topical anesthetic (liposomal lidocaine 4% cream) for procedural pain management during needle-related procedures in the ED. To determine the non-inferiority margin, an electronic survey was sent to 34 pediatric emergency physicians working in ED settings located within the provinces of Quebec and Ontario in Canada. The following scenario and question were presented: "You are seeing a four-year old female requiring an IV catheter for drug delivery. You are considering two interventions for pain management during the needle-related procedure: a topical anesthetic application (liposomal lidocaine 4% cream) or the Buzzy® device. You need to assume that both of these interventions have the potential for reducing needle-related pain." "What is the greatest difference in mean pain reduction, on a numerical scale from 0 to 10, between the topical anesthetic (liposomal lidocaine 4% cream) and the Buzzy® device you are

willing to accept to routinely adopt the use of the Buzzy® device over the topical anesthetic (liposomal lidocaine 4% cream) for needle-related procedures?". Respondents had to choose a difference ranging from 0.1 to 1.5 with 0.1 increments. The mean answer was 0.70, consequently, this value was chosen as the non-inferiority margin. Considering that the minimal clinically significant difference (MCSD) on the CAS in children with acute pain is 1.0 on a scale from 0 to 10[71], the choice of a 0.70 non-inferiority margin is considered conservative and insures that a minimally important difference would not be missed. Therefore, a sample size of 346 participants would be necessary to provide the trial with 90% power to show the non-inferiority of the Buzzy® device compared to a topical anesthetic at a one-sided alpha level of 0.025 with the use of a non-inferiority margin of 0.70 for the per-procedural pain intensity. We anticipate no loss to follow-up considering the short time frame between the intervention and the assessment of the primary outcome. The sample size was calculated using the G*Power software version 3.0.10.

Statistical methods

The primary analysis was designed to test whether the Buzzy® device is non-inferior to a topical anesthetic (4% liposomal lidocaine) for procedural pain management during needle-related procedures, as evaluated by calculating the confidence interval (CI) for the mean differences in pain score between groups. Non-inferiority would be declared if the upper limit of the two-sided 95% CI (1-2α x100%CI), or equivalently, the upper limit of the one-sided 97.5% CI, for the between-group difference (experimental group – control group) is less than the predetermined non-inferiority margin of Δ 0.70. In this case, the null hypothesis of inferiority will be rejected in favor of the alternative hypothesis of non-inferiority and the non-inferiority of the Buzzy® device over the topical anesthetic (liposomal lidocaine 4% cream) will be established. A two-sided 95%CI will be applied because it will provide additional information if the superiority of the experimental intervention is demonstrated[51]. In the case where the non-inferiority is met, superiority testing will be performed using a two-sided alpha of 0.05 and in looking if the upper limit of the confidence interval is less than zero. Non-inferiority analysis will be evaluated according to the intention-to-treat principle (primary analysis) as well as to the per-protocol principle (secondary analysis) to examine for consistency and avoid bias[51].

The secondary analysis was designed to test the superiority of the Buzzy® device over the liposomal lidocaine 4% cream for secondary outcomes. The Student's t-test will be performed to compare the between-group mean differences in pre-procedural and procedural distress/anxiety scores. The memory of pain 24 hours after the needle-related procedure will also be evaluated by the Student's t-test to compare the mean differences in pain scores between the experimental and control groups. The proportion of participants achieving the success of the procedure at first attempt will be calculated in each group and compared using the Chi-square test. Descriptive statistics will be used to report data collected on satisfaction, as well as socio-demographic and clinical data. Means and standard deviation will be reported for continuous variables and proportions will be calculated for categorical and nominal variables. Potentially relevant pre-procedural and procedural variables will be included in covariate model (ANCOVA) in an attempt to determine predictors of pain scores reduction. All secondary analysis will be carried out according to the intention-to-treat principle. For superiority testing, a p value <0.05 will be considered statistically significant.

Preplanned subgroups non-inferiority analyses will be carried out for the primary outcomes based on age group (4-7 years vs. 8-12 years vs. 13-17 years). As we will not have the statistical power in each subgroup to conclude to non-inferiority, the results will be considered as exploratory and will primarily serve for hypothesis generation for future studies. Subgroups superiority analyses will be also performed by age group for secondary outcomes. Multiple imputations methods and sensitivity analysis will be used when possible and appropriate to handle the missing data.

No formal interim analysis is planned for this non-inferiority trial for different reasons. First, there is no necessity to conduct interim analysis for futility reasons in non-inferiority trials considering that even if non-inferiority is established before the completion of the trial, the data collection should be pursued in hope of demonstrating superiority[51]. Second, considering that we do not expect potentially serious adverse events, interim analysis for safety reasons and stoppings rules are not required[50 72]. There is also no need to implement a data monitoring committee (DMC) as the known risks are minimal for both interventions[50 73 74].

Patient and Public Involvement

Patients and public were not involved in the design, recruitment and conduct of this study.

DISCUSSION

This study protocol provides the rational and methods associated with a randomized controlled non-inferiority trial comparing the Buzzy® device to a topical anesthetic with the aim of improving procedural pain and distress/anxiety management in children undergoing needle-related procedures. To our knowledge, this is the first study assessing the efficacy of the Buzzy® device in Canada in any clinical setting. A systematic review currently in preparation by our team has identified several limitations in the studies previously conducted on the Buzzy® device (PROSPERO ID: CRD42017076531). The present study is carefully designed to overcome these limitations and provide rigorous evidence on its efficacy. The large sample size will allow to determine if the Buzzy® device is at least as efficacious as the liposomal lidocaine 4% cream in decreasing procedural pain. Therefore, this study has the potential to improve clinical care and outcomes of children undergoing needle-related procedures in the ED. More specifically, findings from this trial could potentially prevent pain and distress/anxiety experienced by children, as well as improve nurses pain management practices. In addition, this study could determine the efficacy of the Buzzy® device intervention across age ranges and developmental differences. If the non-inferiority of the Buzzy® is demonstrated, steps will be taken to eventually obtain a Medical Device Licence from Health Canada to make this device available in hospital settings across Canada.

This study presents some limitations which are important to recognize. First, considering the nature and the major differences between both interventions, blinding of participants and personnel is not possible. Consequently, they are aware of the intervention allocation once the randomized envelop is opened. This lack of blinding could influence their behaviour and responses to outcomes, particularly subjective ones like pain and distress/anxiety creating therefore a potential performance bias[75]. However, the use of an active comparator (anesthetic) could potentially reduce or overcome this bias. Indeed, a recent study[76] has demonstrated that randomized controlled trials using an active comparator reported similar expectation ratings from participants between groups. Second, it is not possible to blind the secondary outcome assessors (research nurses) as it requires observing the behavior of the participant during the procedure. However, the primary outcome assessment is by self-report, which is considered as a primary source of evidence for pediatric pain intensity[77]. This could increase the magnitude of the

detection bias as pain is a subjective measure[78]. However, some have argued that self-report assessment could be considered as equivalent to blinding of outcome assessors considering that self-report is not associated with an overestimated intervention effects, as is the case in psychotherapy meta-analyses[79 80]. Third, we decided to exclude children under the age of four years old as the large majority of blood samples done in this population are performed via micro-method (blood collected in capillary tubes from finger sticks) and the use of the Buzzy device is not applicable for this procedure. The inability Iof children under 4 years to self-report pain was also a reason for exclusion.

Finally, although there is an increase in use and development of pharmacological and non-pharmacological interventions in research, pain management is still suboptimal. It suggests that evidence is not being translated and implemented in clinical practice or that it is underused by healthcare providers[38 81]. Therefore, it is important to provide healthcare professionals with interventions that are likely to be translated into clinical practice for routine use. The Buzzy® device is an easy-to-use and fast intervention that seems to be a promising option in the ED setting.

ETHICS AND DISSEMINATION

Ethics and safety considerations

This study has been reviewed and approved by the Research Ethics Board (REB) of the study setting (CHU Sainte-Justine Research Centre, University of Montreal; #2017-1405). This approval covers the protocol, informed consent forms and the data collection forms. To date, no important protocol modification has been made after the initial ethics approval. As recommended by the International Committee of Medical Journal Editors (ICMJE)[82], this clinical trial was registered in a public trials registry prior to the beginning of the recruitment (ClinicalTrials.gov: NCT02616419). An Investigational Testing Authorization from the Medical Device Bureau of Health Canada was also granted (#272708). Finally, this study will be conducted in accordance with the principles of the Declaration of Helsinki[83] and all REB policies and guidelines. Written informed consent will be obtained from parents or legal guardians and assent will be obtained from children over 7 years old. Consent involved a follow-up 24 hours after the needle-related procedure. Only the principal investigators (AB, CK and SLM) will be given access to the

complete final data sets. Other investigators will have access to the complete final data set if a formal request is formulated and approved by the principal investigators.

Dissemination

The research protocol has already been presented to local clinicians and stakeholders, as well as at national and international conferences. Scientific results will be disseminated at regional, national and international conferences targeting nurses, emergency physicians and pediatric researchers and clinicians. A manuscript will be submitted to a high impact peer-reviewed journal.

Trial status

Recruitment for this study is ongoing.

Acknowledgement

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Authors' contribution

AB conceptualized and designed the study and wrote the first draft of this research protocol. CK, EDT, BB, NP, JT and SLM provided feedback to refine the research methodology. SA, EDT and BB contributed to the implementation of the study. SA is involved in the data collection process. All authors read, critically revised and approved the final version of this research protocol.

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Competing interests statement

None declared.

Ethics approval

Research Ethics Board (REB) of the CHU Sainte-Justine (# 2017-1405)

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**2, 18**
	2b	All items from the World Health Organization Trial Registration Data Set	**n/a**
Protocol version	3	Date and version identifier	**n/a**
Funding	4	Sources and types of financial, material, and other support	**19**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1**
	5b	Name and contact information for the trial sponsor	**n/a**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**n/a**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**n/a**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4**
	6b	Explanation for choice of comparators	**4**
Objectives	7	Specific objectives or hypotheses	**6**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**6**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**7**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**n/a**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**n/a**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**n/a**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**10**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**9**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**14**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**9**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**13**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**14**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**13**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**14**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**n/a**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**10**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**n/a**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**13**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**15**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**16**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**16**

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**16**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**16**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**n/a**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**n/a**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**18**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**18**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**9, 18**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**n/a**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**13, 18**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**19**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**18**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**n/a**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**18**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**n/a**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**n/a**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**n/a**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**n/a**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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External Cold and Vibration for Pain Management of Children Undergoing Needle-Related Procedures in the Emergency Department: A Randomized Controlled Non-Inferiority Trial Protocol

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Title: External Cold and Vibration for Pain Management of Children Undergoing Needle-Related Procedures in the Emergency Department: A Randomized Controlled Non-Inferiority Trial Protocol

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ABSTRACT

Introduction: Needle-related procedures are considered as the most important source of pain and distress in children in hospital settings. Considering the physiological and psychological consequences resulting from these procedures, management of pain and distress through pharmacological and non-pharmacological methods is essential. Therefore, it is important to have interventions that are rapid and easy-to-use and implement. The aim of this study will be to determine whether a device combining cold and vibration (Buzzy®) is non-inferior to a topical anesthetic (liposomal lidocaine 4% cream) for pain management of children undergoing needle-related procedures in the Emergency Department.

Methods and analysis: This study is a randomized controlled non-inferiority trial comparing the Buzzy® device to liposomal lidocaine 4% cream for needle-related pain management. A total of 346 participants will be randomly assigned in a 1:1 ratio to one of these two interventions. The primary outcome will be the mean difference in pain intensity between groups during needle-related procedures. Non-inferiority would be demonstrated if the mean procedural pain scores of the experimental group is not worse than the mean procedural pain scores of the control group by a non-inferiority margin of 0.70 on the Color Analogue Scale (CAS). The secondary outcomes will be the level of distress during the procedure, the success of the procedure at first-attempt, the occurrence of adverse events, the satisfaction of both interventions and the memory of pain 24 hours after the procedure. The primary outcome will be assessed for non-inferiority and the secondary outcomes for superiority.

Ethics and dissemination: This study protocol was reviewed and approved by the institutional review board of the study setting. Findings of this trial will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number: NCT02616419

Keywords: Buzzy, Topical Anesthetic, Procedural pain, Children, Non-pharmacological intervention

Article summary

Strengths and limitations of this study

- This is the first study to assess the efficacy of the Buzzy® device in Canada.
- The large sample size of 346 participants will provide enough power to demonstrate the non-inferiority of the Buzzy® device compared to a topical anesthetic.
- The non-inferiority margin is justified on both clinical and statistical grounds.
- This study presents potential clinical implications for nursing and medical practices in the emergency department.
- The main limitation of this trial is the impossibility to blind participants and personnel to treatment/intervention allocation.

INTRODUCTION

Background and rationale

Needle-related procedures, such as venipuncture and intravenous (IV) catheter insertions, are considered as the most important source of pain and distress in children in hospital settings[1-4]. The intensity of pain and distress caused by these procedures can vary from mild to moderate for some, while for others, it may be severe[4-7]. It is now recognized that even a minor procedure, such as venipuncture, can result in numerous physiological, psychological and emotional consequences[8 9]. Among these, needle phobia is the most important and prevalent consequence with more than 60% of children reporting an extreme fear of needles following a bad needle experience[10]. Children with needle phobia are more likely to report higher levels of pain and distress from subsequent procedures[11 12] and they can experience physiological symptoms, such as increased heart rate and blood pressure and vasovagal reactions[13 14]. Further, children with needle-phobia can develop healthcare avoidance behaviors in adulthood, such as delays in care, non-compliance of immunization requirements and avoidance of treatment[10 14]. Nurses play a critical role in the assessment and management of children's pain and distress, and the use of pharmacological and non-pharmacological interventions must be an integrant part of nursing practice[15].

Procedural pain management represents a major challenge for nurses, specifically for those working in the Emergency Department (ED). Consequently, children are at high risk for undertreatment of their pain during needle-related procedures[16]. Although healthcare professionals recognize the importance of providing adequate procedural pain relief, pain management is still suboptimal[8 17-19]. Several studies have identified different barriers to using available pharmacological and non-pharmacological interventions for pain management in the ED[8 17-19]. Barriers most frequently identified by nurses are time constraints, heavy workload, staffing limitations, space limitations, lack of knowledge, and interruptions in the continuity of care[15 20-22].

Currently, the current gold standard intervention for needle-related procedural pain is the application of a topical anesthetic prior to the procedure and several systematic reviews and meta-analysis have supported this intervention demonstrating its efficacy extensively[23-26]. However, topical anesthetics require an application time ranging from 30 to 60 minutes, making their implementation for routine use difficult in the rapid and busy setting of the ED[27 28]. Indeed, a study led by Papa & Zempsky[27] showed that only 28% of ED nurses used a topical anesthetic during painful procedures. They reported that main barriers to using this pharmacological intervention were the onset of action

of the drug, treatment delays caused by application time and the vasoconstriction of blood vessels[27]. Consequently, topical anesthetics do not seem to be an optimal intervention for procedural pain management in an acute care setting where time constraints represent an important barrier to adequate pain control[21 29]. Also, topical anesthetics had a minimal side effect profile, including minor local reactions, such as mild irritation, redness, itching, edema or rash of the skin site following the application in 25 to 50% of cases[24 25 29-31].

Other pharmacological and non-pharmacological interventions have also been evaluated for their efficacy on children's pain management and distress during needle-related procedures. Among these, there are sweet tasting solutions[32 33], needle-free injection systems[34 35], vapocoolant sprays[36], and distraction[37 38]. However, even if the efficacy of most of these interventions is well demonstrated, their use remains limited in clinical practice, and this may be due to time constraints and limited resources of the ED setting[15 20-22]. These interventions may require specific training for healthcare professionals, preparation time, or excessive cost, which represent barriers to their implementation in a busy, fast-paced environment of the ED setting[15 20-22].

The limited applicability of both pharmacological and non-pharmacological interventions to manage procedural pain and distress in the ED setting demonstrates a need for innovation in this domain. The optimal intervention for needle-related procedural pain management in the ED would need to be rapid, easy-to-use, and without side effects. To answer this problem, Dr. Amy Baxter, an emergency pediatrician and pain researcher in the United States, developed a pain blocker device called Buzzy® (MMJ Labs, Atlanta, GE, USA) specifically for pain management of children undergoing needle-related procedures. The Buzzy® is a bee-shaped device combining vibration (body of the bee) and cold (removable ice wings)[39]. The theoretical bases explaining the action of the device are the Gate Control Theory[40] and the diffuse noxious inhibitory control theory, which both involve modulation of the transmission of pain[39]. Therefore, it is theorized that the simultaneous use of vibration and cold would provide optimal pain management.

To date, there have been some randomized controlled trials that have investigated the efficacy of the Buzzy® device on pain management in children undergoing needle-related procedures in various medical settings[41-49]. However, these studies present several limitations such as the absence of an active comparator[41 43 44 46-48], the lack of prior power analyses or sample size calculation[43 44], lack or unclear allocation concealment[41-44 47 48], among others. Of those studies, only two have been conducted in the ED setting[45 49] and none have been done in Canada. The Buzzy® device seems to be

a promising method to reduce and control procedural pain in the ED and it would be interesting to determine if the Buzzy device is at least as efficacious as a topical anesthetic for pain management in children and adolescents during needle-related procedures.

Study Objectives

Primary objective

To determine if a device combining cold and vibration (Buzzy®) is non-inferior (no worse) to a topical anesthetic (liposomal lidocaine 4% cream) for pain management in children undergoing needle-related procedures in the emergency department.

Secondary objectives

To determine if, in comparison to a topical anesthetic (liposomal lidocaine 4% cream), the Buzzy® device will:

- decrease the level of distress during the needle-related procedure
- improve the success of the needle-related procedure at first attempt
- decrease pain memories 24 hours after the needle-related procedure.

Other secondary objectives

- To determine the occurrence of adverse events in each study group.
- To evaluate the satisfaction of parents, children and nurses regarding the use of the Buzzy® device and the topical anesthetic (liposomal lidocaine 4% cream).

METHOD

This study protocol is developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendation[50].

Trial design and study setting

The study design is a randomized, controlled, non-inferiority trial with two parallel groups and a 1:1 allocation ratio. This study design is of interest when a new intervention seems to present some advantages over the reference intervention[51]. Considering that the Buzzy® device seems to be less expensive, faster and easier to use than the topical anesthetic, which is the current reference intervention, the choice of a non-inferiority trial design is justified. As recommended for a non-inferiority trial[51], a study demonstrating the superiority of the reference intervention

compared to a placebo in a similar context should be used as rationale to support this study design[51]. For this purpose, the study by Taddio et al.[52] which aimed to determine the efficacy of the liposomal lidocaine 4% cream over a placebo for managing pain resulting from venipuncture in children in the ED, was used as a reference trial to the current study.

This single center study will take place in the ED of the CHU Sainte-Justine (Montreal, Qc, Canada), a university pediatric tertiary hospital center with a census of more than 80 000 ED visits per year.

Participants

Participants will be deemed eligible if they meet all of the following inclusion criteria: (a) aged between 4 and 17 years old, (b) presenting to the ED and requiring a needle-related procedure (venipuncture or IV catheter insertion), (c) having the ability to communicate in either French or English, and (d) accompanied by at least one parent/legal guardian who can understand, read and speak French or English. We will exclude children with (a) a neuro-cognitive disability that precludes them from assenting and participating to the study, (b) an inability to self-report pain, (c) a critical or unstable health status (<3 on the Canadian Triage and Acuity Scale), (d) a Reynaud's syndrome or sickle cell disease with extreme sensitivity to cold; (e) a break or abrasion on the skin where the device would be installed, and (f) a nerve damage or limited sensation in the extremity where the needle-related procedure will be performed. We will not exclude patients who received analgesics, including acetaminophen or ibuprofen, within the four hours prior to presentation to the ED, but we will document this co-intervention.

Interventions

Experimental group: Buzzy® device

Participants in the experimental group will receive the Buzzy® device® intervention. The Buzzy® is a palm-sized device with two components: 1) body of the bee (vibration) and, 2) removable and reusable ice wings (ice). The body of the bee is a vibrating motor powered by two alkaline AAA batteries and it lasts for about 20 hours. The vibration component is activated by a manual switch on the top part of the device. The removable set of wings contain a total of 18 grams of ice. Each set of ice wings can stay frozen for about 10 minutes at room temperature and they are reusable up to 100 times. Dimensions of the device are 8 cm x 5 cm x 2.5 cm. Enrolled

children will have the opportunity to hold and get familiarized with the Buzzy® device before the needle-related procedure.

Use and Placement for the needle-related procedure. The research nurse will follow the following steps, as recommended by the manufacturer' instructions (MMJ Labs, Atlanta, GE, USA): 1) Immediately before the needle-related procedure, a set of ice wings will be retrieved directly from the freezer of the ED unit. For optimal efficacy, the wings must be frozen solid; 2) The ice wings will be inserted through the elastic bands fixed on the back of the Buzzy® device; 3) When the staff nurse is ready to clean the site and perform the needle-related procedure, the research nurse will install the Buzzy® device on the child's arm, above and as close as possible to the insertion site (about 3-5 cm) with a reusable tourniquet, and the vibration will be activated. The Buzzy® device will be installed for about 30 to 60 seconds prior the needle-related procedure; 4) The device has to be maintained on the child's arm throughout the procedure, at least until the needle is removed; 5) When the procedure is over, the two components of the device will be cleaned with a disinfectant cleaner based on proprietary accelerated hydrogen peroxide (Virox™) as per the Infection Prevention and Control guidelines at the study setting; 6) The ice wings will then be put back in the freezer of the unit for a subsequent procedure.

Physiological basis of the Buzzy® device. The Gate Control Theory[40] and the Descending Noxious Inhibitory Controls (DNIC) are the theoretical bases of the Buzzy® device. More specifically, the Gate Control Theory stipulates that the vibration component of the device blocks the A-delta and C nociceptive fibers by stimulating the A-beta non-nociceptive fibers. It activates an inhibitory interneuron and results in a reduction of the pain signal transmitted to the spinal cord[49 53]. The cold component (prolonged cold application 30-60 seconds) stimulates the C nociceptive fibers and further blocks the A-delta nociceptive pain transmission signal when applied close to the needle insertion site[49]. The second theory behind the Buzzy® device is the DNIC. More specifically, intense cold application stimulates the nociceptive C fibers and activates a supraspinal modulation which, in turn, increases the body's overall pain threshold and therefore produces a generalized hypoalgesia at the insertion site[39 54].

Control group: topical anesthetic (liposomal lidocaine 4% cream)

Participants in the control group will receive an application of liposomal lidocaine 4% cream (Maxilene™, RGR Pharma Ltd., LaSalle, ON) over the insertion site 30 minutes before the needle-related procedure. The topical anesthetic cream will be applied by the research nurse according to the manufacturer's recommendation and the site will be covered by a Tegaderm™ dressing (3M Canada Company, London, ON). The topical anesthetic cream and the Tegaderm™ dressing will be removed just before the procedure. This intervention was chosen as an active control intervention as it has been shown to be the most effective for pain management regarding needle-related procedures[23-26] and it is also the standard care currently established in the study setting.

The liposomal lidocaine 4% cream has been chosen over other topical anesthetics because of its shorter application time (30 minutes) and its minimal vasoactive properties that minimize potential interference with the success of the needle-related procedure[52]. Currently, the gold standard topical anesthetic cream is a combination of lidocaine 2.5% and prilocaine 2.5% cream (EMLA), but it requires an application time of 60 minutes and is frequently associated with vasoconstriction of blood vessels[55-57]. The liposomal lidocaine 4% cream has also been chosen due to the lower occurrence of rash reactions after its application, which is often observed with the amethocaine 4% gel[58]. The ametocaine 4% gel has also been associated with vasodilatation and a risk of hypersensitivity with repeated use[26].

Mechanism of action. The mechanism of action of topical anesthetics relies on the reversible interruption of nerve conduction near the application site by inhibiting sodium influx through the voltage-gated sodium channels[30 59-61]. This inhibition of sodium influx decreases the ability to generate action potentials decreasing or blocking hereby pain signals conduction. Following the application, a temporary loss of sensation in the limited area of application is produced[60 61].

Study proceedings

Recruitment

Eligible participants will be recruited consecutively in the ED by two research nurses during study enrolment hours (approximately 25 hours/weeks, depending on research nurses' availability). Potentially eligible patients will be initially assessed upon arrival to the ED by triage nurses, staff nurses and physicians. Then, when the treating physician determines that a

child requires a venipuncture or catheter IV insertion, the research nurse will approach the patient and his or her family to confirm study eligibility per the inclusion and exclusion criteria, to explain the study in greater details, and to answer all questions before seeking consent for study participation. Informed written consent will be obtained from parents or legal guardians and assent will be obtained from children over 7 years old. Research nurses will maintain and complete a Screening and Enrollment Log to provide a comprehensive list of all children who were screened for eligibility. Recruited children will be randomly allocated to either the experimental (Buzzy® device intervention) or the control group (liposomal lidocaine 4% cream).

Data collection and outcomes measures

Data collection will start following consent and enrolment. All data will be collected by one of the two research nurses using a paper case report form (CRF) developed and designed for this study. In addition to the primary and secondary outcomes, socio-demographic and clinical data and covariates will be also recorded. Data will be collected at different end points: before randomization (T-0), 5 minutes before the needle-related procedure (T-1), during the needle-related procedure (T-2), immediately after the needle-related procedure (T-3) and 24 hours after the needle-related procedure (T-4). Of note, the needle-related procedure will be performed by the staff nurse and not the research nurse.

Socio-demographic and clinical data

Before randomization of participants (T-0), socio-demographic and clinical data will be collected by the research nurse. This includes data on age, sex, reason for consultation, previous experience(s) of needle-related procedures, and analgesia received in the last 4 hours prior the procedure. Contact preference and information will also be obtained for a follow up 24 hours after the needle-related procedure.

Primary outcome measure

The primary outcome will be the mean difference in pain scores during the needle-related procedure between experimental and control groups. It will be assessed immediately after the first the needle-related procedure attempt using the Color Analogue Scale (CAS) (T-3). The

chosen end point evaluation time aligns with recommendations on standard assessment of post-needle pain[38]. The CAS is a self-reported pediatric pain scale consisting of a plastic ruler with a mechanical slider and showing a wedge-shape figure gradually changing in color from white to red. The white end means "no pain" and the red end means the "worst pain". The reverse side of the scale is numbered from 0 to 10 cm with 0.25 increments, allowing investigators to quantify children's pain[62-64]. The CAS has shown excellent psychometric properties in children with acute pain in the ED[63 65]. The child will be shown the side with the wedge-shape figure with the mechanical slider in the middle position and will be asked to move the slider to the place that corresponds to the pain he or she experienced during the needle-relate procedure. The meaning of each anchor will also be explained to the child prior to using the scale. The research nurse will record the corresponding pain score on the reversed side of the scale.

Secondary outcomes measures

The secondary outcomes will be the pain intensity during the needle-related procedure (T-3), the level of distress during the needle-related procedure (T-2, T-3), the success of the procedure at first attempt (T-3), the satisfaction with both interventions (T-3), the occurrence of adverse events, and the memory of pain 24 hours after the needle-related procedure (T-4).

Pain intensity. Mean difference in procedural pain scores between groups will also be assessed using the Faces Pain Scales – Revised (FPS-R)[66] immediately after the first needle-related procedure attempt (T-3). This self-report pain scale is the revised version of the original scale previously developed by Bieri et al[67]. The FPS-R consists of 6 faces and each of them represents a greater intensity of pain than the previous one. The face on the far-left shows "no pain" and the face on the far-right shows "very much pain". On the reversed side of the scale, each face is associated with a score ranging from 0 to 10 (0, 2, 4, 6, 8, 10)[66]. This scale is the most recommended to evaluate procedural pain intensity in children, particularly in children aged from 4 to 12 years old[68]. Immediately after the procedure, the research nurse will ask the child to point the face that shows how much pain he or she felt during the needle-related procedure. The research nurse will document the pain score associated with the face identified by the child.

Level of distress. Mean differences between groups on distress scores during the needle-related procedure will be assessed using the Procedure Behavior Check List (PBCL)[69] (T-2) and the Children's Fear Scale (CFS)[70] (T-3). The PBCL is an observational scale specifically

developed to evaluate pain-related fear and anxiety during painful procedures. This scale consists of a checklist with 8 behavioral items: muscle tension, screaming, crying, restraint used, pain verbalized, anxiety verbalized, verbal stalling and physical resistance. The observer has to rate the intensity of each behavior on a scale from 1 to 5 (1=very mild distress; 5=extremely intense distress)[69]. The research nurse will record the PBCL during the first needle-related procedure attempt (T-2). The CFS is a self-reported scale developed to measure fear of children during painful experiences. This scale has 5 faces with a range of scores from 0 to 4 as each face shows an increasing amount of being scared moving from left to right[70]. Immediately after the first needle-related procedure attempt (T-3), the child will be asked to choose the face that best shows how much he was scared during the procedure. The child will be informed that the first face is "not scared at all" and the last face is "the most scare possible"[70].

Success of the procedure at first attempt. The proportion of participants achieving a successful procedure at first attempt will be recorded as a binary outcome (yes/no) (T-3). If the procedure is not successful at first attempt, the research nurse will document the number of attempts in the CRF.

Satisfaction. Satisfaction of both interventions will be evaluated using three questionnaires tailored for children, parents and nurses and including Likert scale questions and dichotomized (yes/no) questions. It will be assessed immediately after the needle-related procedure with parents and children (T-3) and when reaching 50% of the targeted recruitment for nurses.

Adverse events. The proportion of participants experiencing an adverse event will be recorded as a binary outcome. An adverse event will be defined as an unexpected medical occurrence in a participant which may or may not be necessarily causally related to one of the two interventions. Adverse events will be recorded after enrolment of the participant until hospital discharge.

Memory of pain. The memory of pain will be assessed by comparing pain scores between groups 24 hours after the needle-related procedure using the FPS-R phrased in terms of recall[66] (T-4). After the needle-related procedure, the research nurse will give a paper copy of the FPS-R to each parent or legal guardian with the corresponding instructions. They will be informed that they will be contacted in the next 24 hours (±6 hours) by telephone, text message or email,

depending on their preference. The research nurse will then ask the child to point at face that corresponds with how much pain they remember feeling during the needle-related procedure at the ED. The child/parent will report by telephone, text message or email the chosen face (first, second, third, fourth, fifth, sixth) and the research nurse will record the answer.

Covariates

Data will be collected from participants and their parents for potential covariates. Pre-procedural pain (CAS) and pre-procedural level of distress (PBCL, CFS) will be assessed 5 minutes before the needle-related procedure (T-1). Clinical data will also be recorded during the needle-related procedure (T-2), including: type of procedure (venipuncture, IV catheter insertion), healthcare professional performing the procedure (nurse, nursing assistant, phlebotomist), presence of parent/legal guardian during the procedure (one parent, two parents, none), position of the child during the procedure (sitting position, on a parent's lap, dorsal decubitus, dorsal decubitus against his will), restraints used during the procedure (yes/no) and use of other non-pharmacological interventions during the procedure.

Data management

All data collected with the CRFs will be manually entered into an electronic database statistical software and the original CRFs will be kept on file at the participating site. Data entry and coding will be performed by the same person. A verification will be done by a second person to compare with the original CRFs. Each participant's file will be assigned an identification number to preserve participant confidentiality. Files will be stored in numerical order in a locked file cabinet in the principal investigator's office at the research center. Files will be maintained in storage for a period of minimum 25 years after completion of the study, according to Health Canada regulations for Health Canada Regulated Clinical Trials.

Randomization and allocation

An independent biostatistician of the Applied Clinical Research Unit (Unité de Recherche Clinique Appliquée - URCA) will generate the sequence of randomization as per a computer-generated random listing of interventions applying a permuted block design with random blocks stratified by age (4-7 years; 8-12 years; 13-17 years). The SAS software version 9.3 (SAS

Institute Inc, Cary, NC) will be used to generate the randomization list using a pre-specified seed to ensure reproducibility and proof of random allocation. To ensure concealment, the block size will not be disclosed. Enrolled participants will be randomly assigned, in a 1:1 allocation ratio, to receive either the experimental intervention (Buzzy® device intervention) or the control intervention (liposomal lidocaine 4% cream).

The allocation concealment will be ensured by the use of sequentially numbered, opaque and sealed envelopes previously prepared by the URCA. The randomization sequence will be stored at the URCA for the whole duration of the study in order to keep the investigators and blinded from the study conditions. After the enrolled participant completed all baseline measurements, the appropriate numbered envelope will be opened by the research nurse. Each envelope will contain the randomization number and the allocated intervention.

Due to the major differences between the two interventions in appearance and timing of application, it will not be possible to blind participants, parents, healthcare providers and outcome assessors (research nurses) to the participant's allocation.

Data analyses

Sample Size

The primary aim of this trial is to demonstrate the non-inferiority of the Buzzy device compared to a topical anesthetic (liposomal lidocaine 4% cream) for procedural pain management during needle-related procedures in the ED. To determine the non-inferiority margin, an electronic survey was sent to 34 pediatric emergency physicians working in ED settings from Quebec and Ontario. The following scenario and question were presented: "You are seeing a four-year old female requiring an IV catheter for drug delivery. You are considering two interventions for pain management during the needle-related procedure: a topical anesthetic application (liposomal lidocaine 4% cream) or the Buzzy® device. You need to assume that both of these interventions have the potential for reducing needle-related pain." "What is the greatest difference in mean pain reduction, on a numerical scale from 0 to 10, between the topical anesthetic (liposomal lidocaine 4% cream) and the Buzzy® device you are willing to accept to routinely adopt the use of the Buzzy® device over the topical anesthetic (liposomal lidocaine 4% cream) for needle-related procedures?". Respondents had to choose a difference ranging from 0.1 to 1.5 with 0.1

increments. The mean answer was 0.70, consequently, this value was chosen as the non-inferiority margin. Considering that the minimal clinically significant difference (MCSD) on the CAS in children with acute pain is 1.0 on a scale from 0 to 10[71], the choice of a 0.70 non-inferiority margin is considered conservative and insures that a minimally important difference would not be missed. Therefore, a sample size of 346 participants would be necessary to provide the trial with 90% power to show the non-inferiority of the Buzzy® device compared to a topical anesthetic at a one-sided alpha level of 0.025 with the use of a non-inferiority margin of 0.70 for the per-procedural pain intensity. We anticipate no loss to follow-up considering the short time frame between the intervention and the assessment of the primary outcome. The sample size was calculated using the G*Power software version 3.0.10.

Statistical methods

The primary analysis was designed to test whether the Buzzy® device is non-inferior to a topical anesthetic (4% liposomal lidocaine) for procedural pain management during needle-related procedures, as evaluated by calculating the confidence interval (CI) for the mean differences in pain score between groups. Non-inferiority would be declared if the upper limit of the two-sided 95% CI (1-2α x100%CI), or equivalently, the upper limit of the one-sided 97.5% CI, for the between-group difference (experimental group – control group) is less than the predetermined non-inferiority margin of Δ 0.70. In this case, the null hypothesis of inferiority will be rejected in favor of the alternative hypothesis of non-inferiority and the non-inferiority of the Buzzy® device over the topical anesthetic (liposomal lidocaine 4% cream) will be established. A two-sided 95%CI will be applied because it will provide additional information if the superiority of the experimental intervention is demonstrated[51]. In the case where the non-inferiority is met, superiority testing will be performed using a two-sided alpha of 0.05 and in looking if the upper limit of the confidence interval is less than zero. Non-inferiority analysis will be evaluated according to the intention-to-treat principle (primary analysis) as well as to the per-protocol principle (secondary analysis) to examine for consistency and avoid bias[51].

The secondary analysis was designed to test the superiority of the Buzzy® device over the liposomal lidocaine 4% cream for secondary outcomes. The Student's t-test will be performed to compare the between-group mean differences in pre-procedural and procedural distress scores.

The memory of pain 24 hours after the needle-related procedure will also be evaluated by the Student's t-test to compare the mean differences in pain scores between the experimental and control groups. The proportion of participants achieving the success of the procedure at first attempt will be calculated in each group and compared using the Chi-square test. Descriptive statistics will be used to report data collected on satisfaction, as well as socio-demographic and clinical data. Means and standard deviation will be reported for continuous variables and proportions will be calculated for categorical and nominal variables. Potentially relevant pre-procedural and procedural variables will be included in covariate model (ANCOVA) in an attempt to determine predictors of pain scores reduction. All secondary analysis will be carried out according to the intention-to-treat principle. For superiority testing, a p value <0.05 will be considered as indicating statistical significance.

Preplanned subgroups non-inferiority analyses will be carried out for the primary outcomes based on age group (4-7 years vs. 8-12 years vs. 13-17 years). As we will not have the statistical power in each subgroup to conclude to non-inferiority, the results will be considered as exploratory and will primarily serve for hypothesis generation for future studies. Subgroups superiority analyses will be also performed by age group for secondary outcomes. Multiple imputation methods and sensitivity analysis will be used when possible and appropriate to handle the missing data.

No formal interim analysis is planned for this non-inferiority trial for different reasons. First, there is no necessity to conduct interim analysis for futility reasons in non-inferiority trials considering that even if non-inferiority is established before the completion of the trial, the data collection should be pursued in hope of demonstrating superiority[51]. Second, considering that we do not expect potentially serious adverse events, interim analysis for safety reasons and stoppings rules are not required[50 72]. There is also no need to implement a data monitoring committee (DMC) as the known risks are minimal for both interventions[50 73 74].

Patient and Public Involvement

Patients and public were not involved in the design, recruitment and conduct of this study.

DISCUSSION

This study protocol provides the rational and methods associated with a randomized controlled non-inferiority trial comparing the Buzzy® device to a topical anesthetic with the aim of improving procedural pain and distress management in children undergoing needle-related procedures. To our knowledge, this is the first study assessing the efficacy of the Buzzy® device in Canada in any clinical setting. A systematic review currently in preparation by our team has identified several limitations in the studies previously conducted on the Buzzy® device (PROSPERO ID: CRD42017076531). The present study is carefully designed to overcome these limitations and provide rigorous evidence on its efficacy. The large sample size will allow to determine if the Buzzy® device is at least as efficacious as the liposomal lidocaine 4% cream in decreasing procedural pain. Therefore, this study has the potential to improve clinical care and outcomes of children undergoing needle-related procedures in the ED. More specifically, findings from this trial could potentially prevent pain and distress experienced by children, as well as improve nurses pain management practices. In addition, this study could determine the efficacy of the Buzzy® device intervention across age ranges and developmental differences. If the non-inferiority of the Buzzy® is demonstrated, steps will be taken to eventually obtain a Medical Device Licence from Health Canada to make this device available in the EDs across Canada.

This study presents some limitations which are important to recognize. First, considering the nature and the major differences between both interventions, blinding of participants and personnel is not possible. Consequently, they are aware of the intervention allocation once the randomized envelop is opened. This lack of blinding could influence their behaviour and responses to outcomes, particularly subjective ones like pain and distress creating therefore a potential performance bias[75]. However, the use of an active comparator (anesthetic) could potentially reduce or overcome this bias. Indeed, a recent study[76] has demonstrated that randomized controlled trials using an active comparator reported similar expectation ratings from participants between groups. Second, it is not possible to blind the secondary outcome assessors (research nurses) as it requires observing the behavior of the participant during the procedure. However, the primary outcome assessment is by self-report, which is considered as a primary source of evidence for pediatric pain intensity[77]. This could increase the magnitude of the detection bias as pain is a subjective measure[78]. However, some have argued that self-report assessment could be considered as equivalent to blinding of outcome assessors considering that self-report is not associated with an overestimated intervention effects, as is the case in

psychotherapy meta-analyses[79 80]. Third, we decided to exclude children under the age of four years old as the large majority of blood samples of this population are performed via micromethod (blood collected in capillary tubes from finger sticks) and the use of the Buzzy device is not applicable for these cases. The inability of these children to self-report pain was also a reason for exclusion.

Finally, although there is an increase in use and development of pharmacological and non-pharmacological interventions in research, pain management is still suboptimal. It suggests that evidence is not being translated and implemented in clinical practice or that it is underused by healthcare providers[38 81]. Therefore, it is important to provide healthcare professionals with interventions that are likely to be translated into clinical practice for routine use. The Buzzy® device is an easy-to-use and fast intervention that seems to be a promising option in the ED setting.

ETHICS AND DISSEMINATION

Ethics and safety consideration

This study has been reviewed and approved by the Research Ethics Board (REB) of the study setting (CHU Sainte-Justine Research Centre, University of Montreal; #2017-1405). This approval covers the protocol, informed consent forms and the data collection forms. To date, no important protocol modification has been made after the initial ethics approval. As recommended by the International Committee of Medical Journal Editors (ICMJE)[82], this clinical trial was registered in a public trials registry prior to the beginning of the recruitment (ClinicalTrials.gov: NCT02616419). An Investigational Testing Authorization from the Medical Device Bureau of Health Canada was also granted (#272708). Finally, this study will be conducted in accordance with the principles of the Declaration of Helsinki[83] and all REB policies and guidelines. Written informed consent will be obtained from parents or legal guardians and assent will be obtained from children over 7 years old. Consent involve a follow-up 24 hours after the needle-related procedure. Only the principal investigators (AB, CK and SLM) will be given access to the complete final data sets. Other investigators will have access to the complete final data set if a formal request is formulated and approved by the principal investigators.

Dissemination

The research protocol has been already presented to local clinicians and stakeholders, as well as at national and international conferences. Scientific results will be disseminated at regional, national and international conferences targeting nurses, emergency physicians and pediatric researchers. A manuscript will be submitted to a high impact peer-reviewed journal.

Trial status

Recruitment for this study is ongoing.

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Authors' contribution

AB conceptualized and designed the study and wrote the first draft of this research protocol. CK, EDT, BB, NP, JT and SLM provided feedback to refine the research methodology. SA, EDT and BB contributed to the implementation of the study. SA is involved in the data collection process. All authors read, critically revised and approved the final version of this research protocol.

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Competing interests statement

None declared.

Ethics approval

Research Ethics Board (REB) of the CHU Sainte-Justine (# 2017-1405)

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**2, 18**
	2b	All items from the World Health Organization Trial Registration Data Set	**n/a**
Protocol version	3	Date and version identifier	**n/a**
Funding	4	Sources and types of financial, material, and other support	**19**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1**
	5b	Name and contact information for the trial sponsor	**n/a**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**n/a**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**n/a**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4**
	6b	Explanation for choice of comparators	**4**
Objectives	7	Specific objectives or hypotheses	**6**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**6**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**7**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**n/a**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**n/a**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**n/a**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**10**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**9**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**14**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**9**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**13**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**14**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**13**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**14**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**n/a**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**10**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**n/a**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**13**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**15**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**16**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**16**

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**16**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**16**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**n/a**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**n/a**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**18**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**18**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**9, 18**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**n/a**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**13, 18**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**19**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**18**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**n/a**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**18**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**n/a**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**n/a**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**n/a**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**n/a**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.