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Protocol for a double blind, randomised placebo-controlled trial using ondansetron to reduce vomiting in children receiving intranasal fentanyl and inhaled nitrous oxide for procedural sedation in the emergency department (the FON trial)

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ABSTRACT

Introduction Intranasal fentanyl and nitrous oxide (N_2O) can be combined to create a non-parenteral procedural sedation regimen for children in the paediatric emergency department. This combination of intranasal fentanyl and N_2O provides effective pain relief for more painful procedures, but is associated with a higher incidence of vomiting than N_2O alone. Our aim is to assess whether ondansetron used preventatively reduces the incidence of vomiting associated with intranasal fentanyl and N_2O for procedural sedation compared with placebo.

Methods and analysis This study is a double blind, randomised placebo-controlled superiority trial. This is a single-centre trial of 442 children aged 3–18 years presenting to a tertiary care Paediatric Emergency Department at the Royal Children's Hospital (RCH), Melbourne, Australia, requiring procedural sedation with intranasal fentanyl and N_2O. After written consent, eligible participants are randomised to receive ondansetron or placebo along with intranasal fentanyl, 30–60 min prior to N_2O administration. The primary outcome is vomiting during or up to 1 hour after procedural sedation. Secondary outcomes include: number of vomits and retching during procedural sedation, vomiting 1–24 hours after procedural sedation, procedural sedation duration and associated adverse events, procedure abandonment, parental satisfaction and the value parents place on the prevention of vomiting. This trial will allow refinement of a non-parenteral sedation regimen for children requiring painful procedures.

Ethics and dissemination This study has ethics approval at the RCH, Melbourne, protocol number 36174. The results from this trial will be submitted to conferences and published in a peer-reviewed journal.

Trial registration number Australian New Zealand Clinical Trials Registry (ACTRN12616001213437).

INTRODUCTION

Inhaled nitrous oxide (N_2O) is used increasingly as a sedative and analgesic in the paediatric emergency department (PED).[1 2] N_2O has many advantages that make it an attractive sedative agent: it has fast onset of action, is administered by a non-parenteral route, requires a short recovery period, is associated with minor adverse effects and has a documented safety profile in large paediatric case series.[3–8] However, N_2O alone does not provide adequate analgesia for some common procedures in children, such as fracture reduction.[9]

Intranasal fentanyl (INF) can be administered with minimal discomfort and delivers rapid and potent analgesia in children. A recent meta-analysis found INF to have analgesic efficacy equal to intravenous morphine and identified no serious adverse event following administration as a single agent.[10] INF can be combined with N_2O to create a non-parenteral regimen for children requiring procedural sedation and analgesia (PSA). However, the only two prospective studies (n=131) using INF and high-concentration N_2O in combination reported a 20%–30% incidence of vomiting.[11 12] This is a much higher vomiting incidence than when N_2O is used alone, reported as 2.2%–5.7%.[4 6 13] The use of INF in combination with N_2O would be appealing if the incidence of vomiting was lower. However, no strategies to prevent vomiting when using INF and N_2O have been reported and it is not routine practice at our institution to administer an antiemetic before its use.

Although pulmonary aspiration has seldom been reported during procedural sedation in children, vomiting is a risk factor for its occurrence.[14–16] Vomiting during procedural sedation can also be disruptive to the procedure, distressing to the patient and the family and potentially lead to procedure abandonment. Ondansetron is a potent antiemetic agent with selective 5-HT_3 receptor antagonist activity. Ondansetron is commonly used off-label in the PED to prevent and treat nausea and vomiting related to gastroenteritis, ketamine sedation and concussion.[17–19] In the PED, ondansetron use for dehydration from gastroenteritis is associated with diminished costs and greater caregiver satisfaction compared with placebo and standard therapy for gastroenteritis.[20 21] In the current randomised controlled trial, we set out to assess whether preventative use of ondansetron can reduce the incidence of vomiting when INF is combined with N_2O for procedural sedation compared with placebo. If successful, the combination of INF and N_2O with ondansetron would provide a new management strategy that will add to the current standard of care for paediatric procedural sedation.

METHODS

Study design and setting

This is a phase III, double blind, placebo-controlled superiority trial of ondansetron for the prevention of vomiting associated with PSA using the combination of INF and N_2O. The target population is children aged 3–18 years requiring PSA for a painful procedure and presenting to a single tertiary care PED at the Royal Children's Hospital (RCH), Melbourne, Australia.

Eligibility criteria

Inclusion criteria comprise the following:

1. Age 3–18 years.
2. Weight ≥15 kg.
3. Planned PSA with the combination of INF and N_2O (potential indications include, but are not limited to, fracture reduction, laceration repair and abscess drainage).
4. Written informed consent provided by a parent or legal guardian. The participant may also provide consent if he/she is deemed competent.

Exclusion criteria comprise the following:

1. Contraindication to receiving INF: opioid allergy and acute/chronic nasal problems.
2. Contraindication to receiving N_2O: severe acute respiratory infection, current asthma exacerbation, possible expansion of a gas-filled body cavity and increased risk of N_2O-induced bone marrow suppression.
3. Contraindication to receiving ondansetron: known arrhythmia, use of QT-prolonging drugs or allergy to any component of the ondansetron or placebo syrups.
4. Cardiorespiratory instability.
5. Decreased level of consciousness.
6. Concomitant head injury with concern for concussion or intracranial injury.
7. Active illness associated with nausea and vomiting.
8. Planned use of additional sedatives.

Study intervention

Ondansetron

Ondansetron oral syrup (Zofran: Aspen Pharmacare Australia) is stored below 30°C in the original bottle at room temperature in the RCH clinical trials pharmacy. It is transferred into labelled oral syringes (5 and 10 mL) by a trial pharmacist and stored in a designated secured study box in the PED.

Placebo

The placebo syrup has the same appearance, taste and smell to match the ondansetron oral syrup. The placebo is manufactured by the RCH clinical trials pharmacy using water, strawberry flavour, sucrose and compound hydroxybenzoate solution. It is transferred into labelled matching oral syringes (5 and 10 mL) by a trial pharmacist and stored in the same designated secured study box in the PED.

Administration

In the PED, there are two secured study boxes, one designated for the 4 mg (5 mL) doses and the second box with 8 mg (10 mL) doses. The syringe kits are stored in order of administration and protected from light. Each syringe kit contains a sticker with a randomisation number to attach to the participant's case report form (CRF).

Following randomisation, participants receive a single dose of the study drug according to their weight; patients weighing 15–30 kg are administered a 4 mg dose and patients weighing >30 kg are given an 8 mg dose. In the event of vomiting or spitting out of the study drug, the dose is not repeated. In the rare event of persistent vomiting following PSA, treating clinicians have the discretion to provide a dose of ondansetron to the participant.[22]

Study procedures

The study procedures are summarised in figure 1.

PED doctors, nurse practitioners (NPs) and research assistants (RAs) are trained to provide and explain the parent/guardian information sheet (PGIS) to families. Potential participants are approached after assessment by a clinician when the need for procedural sedation with INF and N_2O has been established. The PGIS is provided and explained to the families of potential participants. When eligibility is confirmed, signed written informed consent is obtained for each participant prior to performing any study-specific procedures. Consent is voluntary and free from coercion. At the time of consent, the investigator, RA or substitute (medical staff or NP) accesses the study drug supply in the PED and administers the next available syringe from the weight-appropriate box to the participant, and documents the syringe number on the participant's CRF.

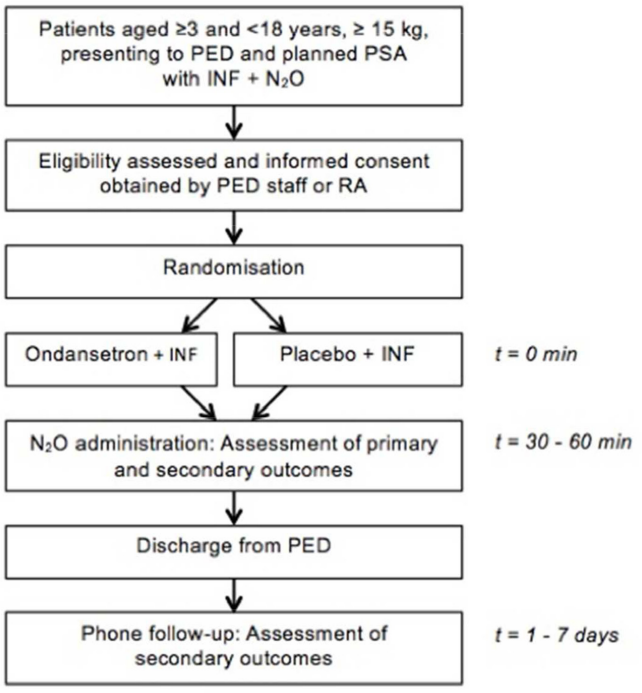

Figure 1 Study of flow chart. INF, intranasal fentanyl; N_2O, nitrous oxide; PED, paediatric emergency department; PSA, procedural sedation and analgesia; RA, research assistant; t, time.

The allocated study drug is given 30–60 min prior to N_2O. INF is administered shortly before or after the study drug. To account for variability of prestudy INF administration (such as prehospital administration or earlier use in the PED):

- Participants who have not received INF or who have received INF greater than 1 hour prior to study drug administration receive a dose of 1.5 mg/kg of INF (up to a maximum of 75 mg).
- Participants who have received INF between 30 and 60 min prior to study drug administration receive a minimum dose of 0.75 mg/kg of INF (up to a maximum of 75 mg).
- Participants who have received INF less than 30 min prior to study drug administration do not require an additional dose of INF. However, an additional dose may be given according to physician discretion (up to a maximum of 75 mg).

N_2O via continuous flow is administered within 30–60 min of the study drug, immediately prior to beginning the planned painful procedure initiated at 50%–70% concentration. At RCH, N_2O is delivered by Quantiflex Monitored Dial Mixer (Matrx, Orchard Park, New York, USA) via face mask. There is no prescribed fasting time before N_2O administration as there is no consensus on how long this should be.[23–25]

After completion of the procedure, participants are discharged from the PED at the physician's discretion. A study investigator or RA calls the parents after discharge to assess postprocedural vomiting, satisfaction and value placed on preventing vomiting. This follow-up phone call takes place within a week of hospital discharge, aiming for less than 72 hours after discharge to optimise recall. When calls are unanswered, attempts are made to reach participants at least three times, at 24 hours intervals, within a week of discharge.

Outcomes

The primary outcome is PSA-associated vomiting (yes/no) from the commencement of PSA with INF and N_2O until discharge from the PED or within 1 hour of the procedure (whichever comes first).

Secondary outcomes are: (1) vomiting (yes/no) preprocedure, intraprocedure, postprocedure and postdischarge (up to 24 hours); (2) number of vomits during PSA defined as vomiting episodes occurring at more than 2 min intervals; (3) retching during PSA; (4) PSA duration; (5) procedure abandonment; (6) PSA-associated adverse events defined as per consensus-based recommendations;[26] (7) satisfaction with the procedure performed and (8) parental value and importance placed on the prevention of vomiting.

Sample size

The sample size calculation was based on the primary outcome, the proportion of participants experiencing vomiting associated with PSA with INF and N_2O during or immediately after the procedure. Prior to the start of this trial, there were two reports on vomiting associated with the administration of INF and N_2O in children with incidences of 20% (95% CI 9% to 35%; n=41)[11] and 28% (95% CI 13% to 47%; n=29).[12] Assuming, conservatively, that 20% of children in the placebo group will vomit during or shortly after PSA, we propose that reducing the incidence of vomiting to 10% would be a clinically significant improvement and one that would potentially change practice. A sample size of 398 patients would be required in order for us to detect a reduction from 20% to 10% or lower with 80% power, based on a two-sided test with a type 1 error of 0.05 (calculated with nQuery Advisor 7.0; Statistical Solutions, Cork, Ireland). We, therefore, aim to recruit 442 participants to allow for a 10% loss to follow-up.

Recruitment

PED doctors, NPs and RAs are educated regarding the study protocol during regular in-service training and are able to undertake the consent process and the initial assessment for eligibility. A reminder message is attached to presentations commonly requiring PSA in the electronic medical record (EMR) system to prompt eligibility assessment. Recruitment began in October 2016 and the proposed study duration is 3 years.

Randomisation and blinding

Participants are randomised in a 1:1 ratio to ondansetron or placebo. Randomisation is stratified by weight (15–30 kg and >30 kg). An independent statistician generates the randomisation schedule using block randomisation with variable block sizes. A study pharmacist uses the

randomisation schedule to prepare and label the blinded ondansetron and placebo syringes, which are identical in nature. The syringes are labelled with the unique study number from the computer-generated randomisation schedule provided by the statistician and placed in two boxes, one for 4 mg and one for 8 mg syringes.

Following eligibility checks and consent, the PED staff assessing the participant takes the next available syringe in the appropriate box for the weight category and administers it to the participant.

Data collection methods

Data collected at enrolment and during the hospital visit are recorded on specific study CRFs by a study investigator or substitute. The CRF is the source document for the following data items: indication for procedure, fasting time, time(s) of INF administration, time of study drug administration, timing of procedural sedation, vomiting, retching, procedure abandonment, adverse events and sedation quality. Demographic data are acquired from the participant's EMR data. Data from the phone follow-up are entered directly on to the CRFs by the researcher conducting the phone call. All of the study data are entered into a study-specific database in REDCap[27] by an investigator or RA.

Data management and access to data

Consent forms and CRFs are kept in paper form, locked in research cabinets accessible only by the study team. All study data are entered in a password-protected REDCap database, accessible to study investigators only. Participants are deidentified within REDCap and only entered according to study ID number.

Data from this study will be stored until the youngest study participant is 25 years old or 15 years after trial completion, whichever is longer, in accordance with the local ethics requirements.

Statistical methods

Statistical analysis will be undertaken and reported following standard guidelines for randomised controlled trials.[28] Data will be analysed on an intention-to-treat basis.

The primary outcome of the incidence of PSA-associated vomiting will be presented as the number and proportion in each treatment group, with a comparison between the groups presented as a difference in proportions and as an OR from a logistic regression model adjusted for weight (15–30 kg or >30 kg), with a 95% CI and P value. In addition, we will present the results as number needed to treat and its 95% CI.

All secondary outcomes will be summarised by treatment group. Binary outcomes will be presented as proportions, with comparisons between the groups presented as a difference in proportions and as ORs from logistic regression adjusted for weight (15–30 kg or >30 kg), with 95% CIs and P values. The number of vomits during PSA will be presented as a median and an IQR in each group. The groups will be compared using a log-rank test. The duration of PSA will be presented as a mean and SD in each group, with the comparison between groups made using linear regression adjusted for weight (15–30 kg or >30 kg), presented as a mean difference and its 95% CI and P value. Finally, the value placed by parents on the prevention of vomiting and overall parental satisfaction will be presented descriptively across the two treatment arms.

For both the primary and secondary outcomes, we will repeat the analysis adjusted for age, sex and fasting time, as potentially important confounders.

Assuming that there is a reasonable amount (>5%) of missing data, the primary analysis of all outcomes will be conducted using multiple imputation. Imputation will be conducted using a single model for all outcome, including the following covariates: age, sex, fasting time, type of procedure and times of drug administration as well as any others which appear to be predictive of missingness or the missing values. Results will also be presented from a complete case analysis for comparison. In the event that there is little missing data, the results from the complete case analysis will form the primary analysis.

Data monitoring and auditing

An independent Data and Safety and Monitoring Board (DSMB) was established to oversee the safety and progress of the trial. The DSMB consists of three independent clinicians and biostatisticians, who collectively have experience in the management of paediatric patients, biostatistics and the conduct and monitoring of randomised controlled trials. The DSMB met prior to the trial commencing, 9 months after commencement and are meeting every 12 months for the trial duration.

A single interim analysis of the primary outcome will be undertaken and reported to the DSMB after 50% of participants have completed the study. The Haybittle-Peto[29] stopping rule will be used as a guideline for the DSMB, where the DSMB may recommend the trial be stopped for early superiority if the P value for difference between groups is <0.0001.

Safety monitoring

There is no specific risk associated with this study. The majority of paediatric trials on efficacy and safety of ondansetron are from the oncology and anaesthetic literature. A recent Cochrane review of 34 trials (n=2023) concludes that 5-HT_3 receptor antagonists are better than older agents at preventing and treating vomiting in children receiving emetogenic chemotherapy.[30] In this review, no major adverse events associated with the use of 5-HT_3 receptor antagonists were reported. Furthermore, a systematic review of the published literature and review of international adverse events reporting databases found no case of arrhythmia associated with single oral dose of ondansetron despite extensive use for over 25 years.[31]

In the current study, adverse events are recorded from the time the patient signs the informed consent form

until the phone follow-up within 7 days of entering the study. Any serious adverse event will be reported to the DSMB and the Human Research Ethics Committee of the RCH within 24–72 hours of occurrence, in accordance with the safety reporting policy.

Outlook and significance

If successful, this randomised placebo-controlled trial will allow refinement of a non-parenteral sedation regimen for performing painful procedures in children. If preventative use of ondansetron reduces the vomiting incidence when using INF and N_2O in combination, it may be adopted as a standard premedication for this regimen to increase patient comfort, decrease parental distress and minimise procedure disruption.

Limitations

The results from this trial may not be generalisable to settings using lower concentrations of N_2O and performing less painful procedures than used in the current study protocol. Furthermore, this trial was not designed to identify the patients who might benefit the most from receiving ondansetron such as those with preprocedural nausea or individuals known to vomit easily.

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Competing interests None declared.

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