The PISA STUDY

A comparative study of plasma pharmacokinetics of intravenous and nebulized sedatives and analgesic agents in mechanically ventilated patients: a single centre, prospective observational study.

FULL STUDY TITLE

Comparative plasma pharmacokinetics of intravenous and nebulized sedatives and analgesic agents in mechanically ventilated patients: a prospective observational study.

SHORT STUDY TITLE

The PISA Study

Protocol Version: 1.1

CONFIDENTIAL

1 STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

2 PROTOCOL SIGNATURE PAGE

Investigator's statement

I agree to conduct this clinical investigation in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only with a mutually agreed upon protocol amendment as approved by the sponsor and ethics review board. I agree to await ethics review board approval of the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrolment in the study, to collect and record data as required by the protocol and case report forms, and to maintain study documents for the period of time required.

Confidential

This document contains confidential information belonging to the investigators except as may be otherwise agreed to in writing, by accepting or reviewing these materials, this information should be held in confidence and not disclosed to others (except where required by applicable law), nor used for unauthorized purposes.

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3 ADMINISTRATIVE INFORMATION

3.1 Chief Investigator

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4 PROTOCOL SYNOPSIS

Title	Comparative plasma pharmacokinetics of intravenous and nebulized sedatives and analgesic agents in mechanically ventilated patients: a prospective observational study.
Objectives	**Primary:** To compare the plasma pharmacokinetics of single dose intravenous and nebulized sedative (midazolam, dexmedetomidine, ketamine) and analgesic (fentanyl, morphine, clonidine) agents in mechanically ventilated patients. **Secondary:** To evaluate the safety of nebulized sedative (midazolam, dexmedetomidine, ketamine) and analgesic (fentanyl, morphine, clonidine) agents in mechanically ventilated patients.
Study Design	Single site, cross-over, observational study 1. Intravenous group – intravenous administration of sedatives (midazolam, dexmedetomidine, ketamine), analgesic (fentanyl, morphine, clonidine) agents 2. Nebulized group – nebulized administration of sedatives (midazolam, dexmedetomidine, ketamine), analgesic (fentanyl, morphine, clonidine) agents.
Planned Sample Size	At least 10 patients per drug administration total n=60 for 6 drugs under investigation. 10 patients in the intravenous group - IV and the nebulized group – NEB.
Selection Criteria	**Inclusion:** • Adult (≥ 18 years) intensive care unit patient

	• Patient is receiving mechanical ventilation, $FiO_2 \leq 40\%$, PEEP≤10 cm H_20. • Patient has arterial line or central venous line for blood sampling • Patient requiring sedation and or analgesia as per the treating team. • Informed consent to participate in the study **Exclusion:** • Suspected or known hypersensitivity to the drug being studied. • Severe chronic lung disease e.g. severe chronic airways disease, lung cancer • High ventilatory requirement. For e.g. $FiO_2 \geq 40\%$ and PEEP≥10 cm H_20 • Receiving extra-corporeal membrane oxygenation • Receiving renal replacement therapy • Liver failure or Child-Pugh C liver cirrhosis • Pregnant patients or lactating mothers
Study Procedures	Screening and assessment for suitability for the study. At any given time, patient can be enrolled for up to two study drugs. A single dose of the study drug will be administered by the intravenous route. Following the sampling period the same drug will be nebulized. The order of administration may be reversed. For e.g. nebulization first followed by intravenous route.
Statistical Procedures, Sample Size Calculation: Analysis Plan.	The sample size for the pilot study is at least 10 participants per study drug per route of administration. This sample size is adequate to inform the plasma pharmacokinetics of the study drugs. Sample assay for the study drugs will be performed in the bioanalysis laboratory.

	Pharmacokinetic analyses will be performed and statistical comparisons made between the two routes of administration.
Duration of the study	Total duration of the study is approximately 36 months.

5 SUMMARY

Inhaled therapeutics is a promising field of medicine (vast lung surface area, entire cardiac output perfusion, thin alveolar barrier); an alternative and complimentary to conventional routes (intravenous, enteral, subcutaneous, intramuscular). Recent developments (novel delivery devices, formulations, research techniques) have successfully renewed interest in this field (inhaled insulin, tranexamic acid, tobramycin[1,2]).

Adequate analgesia-sedation are essential in clinical settings (pre-hospital trauma, emergency medicine, postoperative, critical care and palliative care). Inadequate analgesia-sedation leads to adverse consequences affecting patient outcomes. Despite conventional administration, there are sub-optimal effects and side-effects[3]. Thus, alternative administration routes to improve analgesia and sedation need investigation.

Nebulization of sedatives and analgesics has been used clinically and extensively reported[4, 5]. Nebulized (neb) morphine for analgesia has been used in emergency settings[4] and nebulized fentanyl was as effective as intravenous opioids with fewer side-effects[5]. A pre-clinical study[6] (Figure 1) showed better pharmacokinetic (PK) profile with nebulized morphine compared to intravenous route, with lower peak concentrations (less side-effects) and increased area under the curve (longer duration of action). However, clinical PKs of these agents is poorly understood, affecting dosing and patient outcomes. Factors affecting nebulized drug delivery (particle size, nebulizer type, drug formulation, patient-related factors) have been described previously thus signifying role of mechanistic research of aerosol therapy [7].

Effective nebulized sedative and analgesic therapy needs optimal drug plasma concentrations. Whilst PKs of intravenous (IV) drug administration is predictable, the PKs of nebulized therapy is affected by patient factors (alveolo-capillary membrane barrier)[8]. We will perform comparative (IV vs neb) studies in mechanically ventilated patients to establish the safe and effective nebulization dose for these drugs.

6 INTRODUCTION

Adequate analgesia and sedation are essential in a number of clinical settings such as pre-hospital trauma, emergency medicine, postoperative, critical care and palliative care. Inadequate analgesia and sedation can lead to severe adverse consequences which can affect patient outcomes. Despite its use via various routes, there remains concerns regarding sub-optimal effect and concerns regarding side effects[3]. Thus, there is currently a need to investigate alternate modes of administration to improve analgesia and sedation.

Administration of nebulized drugs via the inhaled route provides a viable non-invasive alternative for systemic therapy as the lungs provide a vast extensively perfused surface area. Inhaled insulin has already been investigated and is considered a paradigm shift in insulin delivery[1]. A clinical trial is underway investigating the safety and efficacy of inhaled loxapine for agitation management[2]. A pre-clinical study in dogs [6] (Figure 1) found that, compared to intravenous administration, the nebulized route has the potential to achieve an improved PK profile with lower peak concentrations (less side-effects) and increased or comparable area under the curve (potentially longer duration of action).

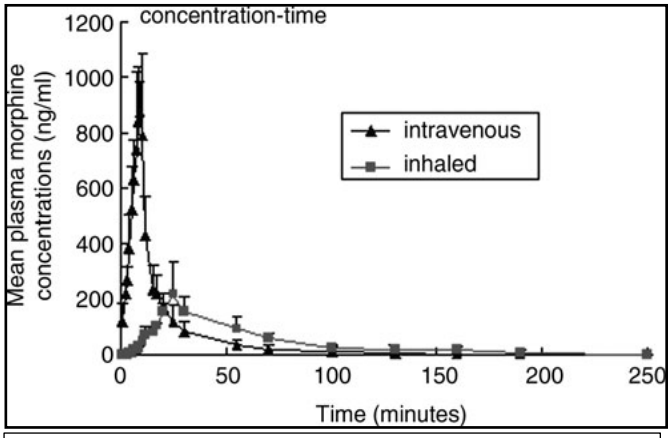

Figure 1 Plasma morphine concentrations by intravenous and inhaled administration in six dogs in a randomized crossover study(7).

Nebulization of sedatives and analgesics has been used and extensively reported in literature[4, 5]. While nebulized morphine was effectively used to manage pain in emergency settings[4], a systematic review showed that nebulized fentanyl was as effective as intravenous opioids with fewer side effects[5]. Other studies have reported suboptimal effect with nebulized morphine and have called for comparative studies between intravenous and nebulized routes[9]. However, the PKs of these agents is poorly understood, thus affecting dosing and hence patient outcomes.

Sedative and analgesic therapy administered by the pulmonary route (nebulization) needs optimal drug plasma levels for effect. Whilst PKs of intravenous drug

administration is predictable, the PK profile of nebulized therapy is affected by other factors at the alveolo-capillary membrane barrier[8]. The PKs of many drugs could be affected by a number of patient-related factors such as the presence of critical illness. Comparative clinical (IV vs neb) *in vivo* studies in mechanically ventilated patients for analgesic and sedative agents will need to be performed to establish the safe and effective nebulization dose for these drugs.

Effective nebulized dosing data thus derived can be applied in the emergency medicine, palliative care and post-operative patient groups for analgesic and sedative drugs as indicated. Thus, the critical issue of providing safe and adequate analgesia and sedation in a wide variety of patient group can be addressed by investigating a novel route of drug delivery.

7 RESEARCH HYPOTHESES

7.1 Plasma PKs of sedatives and analgesics are significantly different with nebulized route compared with intravenous route in mechanically ventilated patients.

7.2 Plasma PKs of nebulized sedatives and analgesics are better compared to that of intravenous route in mechanically ventilated patients.

7.3 Nebulized sedative and analgesics are not associated with any significant adverse effects in mechanically ventilated patients.

8 STUDY OBJECTIVES

The overall objective is to characterise the plasma PK of nebulized sedative and analgesic agents compared to that of intravenous route in mechanically ventilated patients to define optimal dosing regimens to inform future clinical trials.

8.1 Primary Objectives

The primary aim of the study is to compare the plasma PKs of intravenous and nebulized route of administration of sedative and analgesic agents in mechanically ventilated patients.

8.2 Secondary Objectives

Secondary study objectives are to evaluate the immediate adverse effects on airway and lungs.

9 STUDY DESIGN

9.1 Study Design

This study is a single site, cross-over study, comparing the plasma PKs of sedative and analgesic agents with two routes of drug administration in critical care mechanically ventilated patients. In this study 60 patients who meet the inclusion criteria and none of the exclusion criteria will be recruited. In addition to the standard analgesia and sedation prescribed by the treating clinician, each patient will be assigned up to two drugs of investigation at any given time. The drug selection will depend on the following factors:

- Exclusion of drugs with known hypersensitivity in the patient.
- Exclusion of drugs that patient is already receiving as therapy via any route or frequency.

Each drug will be serially administered via one route (IV/NEB) and after a minimum washout period of 12 hours following the sampling time, the 2nd route of administration. When enrolment is for two drugs, these will be administered via different routes. For example, if recruited for fentanyl and midazolam, then if fentanyl is administered intravenously, midazolam will be given via nebulized route initially with the administration routes changed to nebulization and intravenous respectively in the subsequent stage.

9.2 Setting

This study will be conducted in Royal Brisbane and Women's Hospital, Intensive care unit (ICU).

9.3 Patient recruitment

A mechanically ventilated patient requiring sedation and or analgesia who meets all the inclusion criteria and none of the exclusion criteria will be considered for study participation.

9.3.1 Inclusion criteria

1. Adult (≥ 18 years) ICU patient
2. Patient is receiving mechanical ventilation, $FiO_2 \leq$ 40%, PEEP≤10 cm H_20.
3. Patient has arterial line or central venous line for blood sampling
4. Patient requiring sedation and or analgesia as per the treating team.
5. Informed consent to participate in the study

9.3.2 Exclusion criteria

1. Suspected or known hypersensitivity to the drug being studied.
2. Severe chronic lung disease e.g. severe chronic airways disease, lung cancer
3. High ventilatory requirement. For e.g. $FiO_2 \geq$40% and PEEP≥10 cm H_20
4. Receiving extra-corporeal membrane oxygenation
5. Receiving renal replacement therapy
6. Liver failure or Child-Pugh C liver cirrhosis
7. Pregnant patients or lactating mothers

9.4 Study Drugs

This study is a comparative study between intravenous and nebulized sedatives and analgesic drugs in order to compare their systemic bioavailabilities. With this data dosing guidelines for future clinical trials will be able to be derived.

Based on data from existing studies, the study drugs and their doses according to the route of administration include:

Drugs	**Nebulization doses**	**Intravenous doses**
Sedative agents		
Midazolam	5 mg	5 mg
Clonidine	75 µg	75 µg
Dexmedetomidine	50 µg	50 µg
Analgesic agents		
Fentanyl	50 µg	50 µg
Morphine	5 mg	5 mg

Ketamine	25 mg	25 mg

The doses are similar so as to enable accurate comparisons of plasma PK.

9.5 Study Procedures

9.5.1 Intravenous drug administration

Participants will be administered the study drug intravenously via an existing peripheral or central intravenous catheter. Study drug will be diluted using normal saline to make up a volume 10 mL and administered with a slow (over a 1 to 2 minutes) push followed by a 10 mL normal saline flush as per ICU policy and practise. The time of commencement of injection will be recorded as T=0.

9.5.2 Nebulized drug administration

A disposable vibrating mesh nebulizer that is currently being used in ICU will be utilised for the nebulization of the study drug. As per current practice, the nebulizer will be placed in the inspiratory limb of the circuit before the Y-piece. If there is a nebulizer in the circuit, only the nebulizer chamber will be replaced and the T-piece will not be changed. The study drugs will be diluted with normal saline to make up a final volume of 5 ml. This solution will be instilled in the nebulizer reservoir. The nebulization will be commenced, and the time at commencement of nebulization recorded as T=0.

9.5.3 Blood Collection

Blood samples (3 mL) will be collected over six hours (T+5, +10, +15, +30, +60, +90, +120, +180, +240 and +360 minutes) from an existing arterial line or central venous catheter into heparinised tubes.

9.5.4 Urine Collection

Beginning with the sampling period (T=0), the total urine volume over 8-hour period will be collected on the sampling days to calculate urine creatinine clearance measurement. This will be analysed by the Queensland Pathology laboratory. A 1 mL aliquot of the total volume urine sample will be kept to determine renal excretion of the study drug.

9.5.5 Sample handling and storage

Blood

- Immediately place in an ice-water bath and centrifuged within 6 hours of collection at 3000 rpm for 10 minutes.

- Transfer 1 – 2 mL of plasma to a polypropylene cryovial for storage at –80°C for later drug analysis.

Urine

- Transfer 1 mL of total volume urine collected for creatinine clearance into an aliquot and store at –80°C for further analysis.

9.5.6 Bioanalysis

The plasma samples will be analyzed for the drug concentrations using a validated high-performance liquid chromatography (HPLC) method on a Nexera2 UHPLC system coupled to a 8050 triple quadruple mass spectrometer (Shimadzu Corporation,

Kyoto, Japan). Bioanalysis will be conducted in accordance with U.S.A FDA guidance for industry on bioanalysis.[10] at the Central Bioanalysis Laboratory at the University of Queensland. Any part of the remaining sample after analysis will be destroyed.

9.5.7 Data collection on enrolment will include:

Data collection will be performed by trained personnel in the ICU and the data will be entered into an electronic case report form (eCRF). The following parameters/variables will be collected from the patient medical record:

- Participant demographics (age, sex, height, weight)
- APACHE II ICU admission diagnosis
- Acute Physiology and Chronic Health Evaluation (APACHE) II score (intensive care severity of illness on admission score)[11] and sequential organ failure assessment (SOFA) [12] on the day of admission.
- Study drug details- name, route of administration, dose, time of administration.
- Concomitant sedative and or analgesic infusion names.
- Laboratory results as per standard practice in ICU care during sampling (e.g. serum biochemistry on the sampling day)
- Study blood and urine sampling details
- Any complications during the study period in relation to nebulization and blood collection (e.g. bronchospasm, hypoxia)

9.6 Number of Participants

It is planned to enrol a minimum of 60 patients meeting the inclusion criteria; with a minimum of 10 patients per study drug that have been able to complete both routes (IV and NEB) of administration. Where only one study route (IV or NEB) could be completed due to unforeseen events, data will be used in the final analyses as appropriate. Each patient will undergo drug administration and sampling period for the study drug when administered by intravenous and nebulized route serially in any order. For e.g. IV followed by NEB or NEB followed by IV.

9.7 Study Sites

The study will be conducted in one site; the ICU of the Royal Brisbane and Women's Hospital (RBWH), Metro North Hospital Health Service, Queensland, Australia.

9.8 Expected Duration of the Study

Total duration of the study is approximately 36 months.

10 STATISTICAL AND PHARMACOMETRIC ANALYSIS PLAN

10.1 Power calculation and sample size

Whilst it is not possible to perform a sample size calculation for an observational PK modelling study because there is no intervention applied, a minimum of 10 participants will be recruited for each study drug - based on data from similar studies.[11] This sample size will provide a power of 80% (assuming an α of 0.05 and r^2 of 30%) and is expected to obtain robust population PK parameter predictions in this patient population, which demonstrates high PK variability.[11]

In their study, Tam et al., demonstrated that with a sample size of 10, the bias and precision of PK predictions were <25% (predictions were considered acceptable if bias/precision for the mean and variability of PK parameters were <25%)[11]

10.2 Pharmacometric analysis plan

Primary PK parameters will be calculated using a non-compartmental PK analysis as previously described (6). An attempt will be made to correlate any differences in these primary PK parameters between patients, with clinical and demographic characteristics of the patient. Equivalent nebulization dose compared to the intravenous dose will be computed so as to inform future clinical trials.

11 ETHICS AND DISSEMINATION

11.1 Ethical principles

The study will be conducted in accordance with ethical principles consistent with the Declaration of Helsinki,[12] and all relevant national and local guidelines on the ethical conduct of research.[13]

11.2 Independent Ethics Committee

Ethics application will be submitted according to the requirements of the relevant Human Research Ethics Committee (HREC), all of which are formed and are conducted in accordance with the guidelines laid down by the local governing agency.

The content and format of the patient and substitute decision maker information statements and consent forms will be approved by the relevant HREC and produced in line with their own guidelines and requirements. During the study, any amendment or modification to the study protocol and study materials will be notified to the HREC by the Principal Investigator and should be approved by the HREC before implementation, unless the change is necessary to eliminate an immediate hazard to the participants, in which case the HREC will be informed as soon as possible thereafter.

The Principal Investigator will be responsible for informing the HREC of any event likely to affect the safety of patients or the continued conduct of the study.
The Principal Investigator will produce progress reports, adverse event reports, and any other required documentation to the HREC in accordance with their guidelines.

It is the responsibility of the Principal Investigator to keep an up to date record of all correspondence and applicable documentation with the HREC. A clean copy of the consent forms and information statements that are to be used, together with the original of all signed consent forms and any other consent related correspondence, must be kept in a separate file for this study.

11.3 Informed consent procedures

The Principal Investigator, or the nominated delegate, is responsible for obtaining written informed consent in accordance with relevant HREC approval and any regulatory requirements. The informed consent procedure will involve a verbal explanation of the study and the provision of a written information sheet. There will be adequate time given to consider participation in the study and opportunity to ask questions. A copy of the information sheet and the signed and dated consent form will be supplied to the person providing written consent, as well as any other documentation discussed through the consent process. A copy of the information sheet and signed and dated consent form will be placed in the patient's medical record at site and the original will remain in the trial site file.

As participants must be sedated and ventilated to be eligible to be enrolled into the study, participants will not be able to give informed consent to participate in this study. Therefore, consent will be obtained from a legally recognised substitute decision maker. If the participant gains capacity to consent, they will be provided with an information sheet and be given the opportunity to withdraw their data if they choose to.

A hierarchy for obtaining consent has been developed based on the Australian National Health and Medical Research Council (NHMRC) National Statement on the Ethical Conduct of Human Research and the ANZICS Clinical Trials Group Ethics Handbook for Researchers.

11.4 Participant Withdrawal

11.4.1 Reasons for withdrawal

The possible circumstances for early termination of this study include the participant or substitute decision maker's wish to withdraw and death. If there is a significant adverse event, the substitute decision maker can withdraw from any further participation in the study.

Withdrawal from the study will be managed by the principal investigator who will record the reason for withdrawal, if the person responsible for the participants wishes to provide this, documented in study participant file and CRF. Further, the principal investigator and research nurses will correspond with HREC and compile a final study report.

11.4.2 Handling of withdrawals

An individual participant may be prematurely discontinued from study participation the following reasons:

- Adverse event
- Substitute decision maker voluntarily withdraws
- Participant is withdrawn by the investigator
- Death

The reason for termination will be documented in study participant file and CRF. Already-accrued data, relating to participants who cease participating in this study, will be maintained as part of the study data except for patients who are withdrawn voluntarily. For voluntary withdrawals, all clinical data will be destroyed and only medical record number, date of birth and enrolment and withdrawal dates retained.

12 SAFETY AND ETHICAL CONCERNS

Apart from additional blood needed for PK analysis and the drug administration procedure, this study will not interfere with patient routine clinical care or affect clinician decision making for participants involved. The additional blood sampling that needs to be collected over pre-specified intervals will be performed in an aseptic manner by experienced research nurses.

The safety/risk profile for nebulization procedures are:

Risks and complications (1-5%) include

- Bronchospasm
- Hypoxia

- Patient-ventilator dyssynchrony

12.1 Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a participant administered the study intervention which does not necessarily have to have a causal relationship with the study treatment.

It is recognised that the patient population in the ICU will experience a number of aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard treatments in the ICU. These will not necessarily constitute adverse events unless they are considered to be related to study treatment/procedures (i.e., nebulization and blood collection) or in the Principal Investigator's clinical judgement are not recognised events consistent with the patient's underlying disease and expected clinical course. Therefore, reporting of adverse events in this study will be restricted to events that occur during the study period (i.e., during and up to 24 hours after sampling occasions), which are considered to be related to study-specific nebulization procedures and blood collection for PK analysis.

Any adverse events thought to be related to study-specific nebulization procedures and blood collection for PK analysis will be reported to the site Principal Investigator as soon as there is knowledge of the event. The site Principal Investigator will be responsible for determining the causal relationship as either possible, probable or definitely related. All adverse events thought to be attributable to the study specific procedures should be reported via electronic case report form.

12.2 Serious Adverse Events (SAE)

Serious adverse events (SAEs) are defined as any untoward medical occurrence that meets one or more of the following criteria:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event which may require intervention to prevent one of the previously listed outcomes.

The classification of SAE is not related to the assessment of the severity of the adverse event. An event that is mild in severity may be classified as a serious adverse event based on the above criteria. Given that critically ill patients are likely to experience any of the above listed criteria in the course of their ICU admission, only serious adverse events that are reasonably suspected by the site principal investigator to be study study-specific nebulization procedures and blood collection for PK analysis will be reported. Reporting of SAE in this study will be restricted to events that occur during the study period (i.e., during and up to 24 hours after sampling occasions).

SAEs will be recorded on separate case report forms. The SAE reports will then be forwarded to the HREC in accordance with local requirements.

13 DATA COLLECTION AND MANAGEMENT

The principle means of data collection and data processing will be electronic via a password protected website (electronic Case Report Form – eCRF). All computerised forms will be electronically signed by the authorised study staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date.

13.1 Data Confidentiality

Privacy and confidentiality of information about each participant shall be maintained in study documentation, reports, and in any publications. Each participant participating in this study will be assigned a unique identifier (e.g., alpha-numeric sequence based on order of enrolment) and will be stored securely at site. All CRFs or other study-related data will be tracked, evaluated, and stored using only this unique identifier.

The Investigator will maintain and keep confidential a study participant list identifying all enrolled study participants. This list will contain the assigned study participant's unique identifier and name.

Participant names will not be used in any reports or publications resulting from this study.

13.2 Data Storage

Any information obtained in connection with the study will remain confidential and will only be disclosed with the patient or person responsible for the patient's permission, except as required by law. All study information will be kept in a locked room at the RBWH. The information will only be available to the principal investigators and the research team. After the study is finished, the information will be stored for 15 years as per Australian regulations. After that it will be destroyed as per the institution's Standard Operating Procedure.

14 OUTCOME AND SIGNIFICANCE

Inadequate clinical effect and significant side effects associated with the conventional administration of sedative and analgesic agents indicate a need for investigating novel routes of drug delivery. Published clinical studies indicate variable clinical effect with nebulized route. An important reason will be inadequate dosing as drug PKs are affected by the route of administration. Currently there is no PK data with nebulized or intravenous sedative and analgesic agents. This study will generate a comparative data between intravenous and nebulized route of administration for sedatives and analgesic agents. Using this data, it will be possible to compute the equivalent nebulized dose required to achieve comparative blood concentrations. The study will also collect comparative safety data. This data will inform designing of future clinical

trials in various patient groups including pre-hospital, emergency medicine, post-operative pain and palliative care.

15 FUNDING

This study has been funded by a Royal Brisbane and Women's Hospital Foundation research grant and the MNHHS-UQ Collaborative Research Grant.

16 ADMINISTRATIVE ASPECT

This study will be registered with a publicly accessible trials registry, the Australian New Zealand Clinical Trials Registry (ANZCTR). The registration number is to be confirmed.

16.1 Independent HREC approval

This study will be reviewed and approved by The Royal Brisbane and Women's Hospital and Queensland University of Human Research Ethics Committees (HRECs).

16.2 Amendments to the protocol

Any amendments will be submitted to the HREC for review prior to implementation as per HREC guidelines.

16.3 Participant reimbursement

There is no participant reimbursement for this study.

17 USE OF DATA AND PUBLICATIONS POLICY.

The study results will be disseminated in de-identified and aggregate form only (i.e. no individual patients will be referred to or be able to be identified). We will use the following multi-level dissemination strategy;

- Presentation of the study results at an international conference,
- Publication of study results in a blind peer- reviewed high quality scientific journal

  - The publication policy for this study will follow NHMRC guidelines for contribution of authors. Subsequent order of authorship will be negotiated via email with the team of investigators at the commencement of the study with records kept in the study files of individual agreements. Research nurses will be publication authors.
- Hosting of study results to the community and/ or the participants via a publicly available hospital research web page. i.e. https://www.health.qld.gov.au/metronorth/research/journal-articles/default.asp,
- Policy makers, particularly hospital, health service and state-wide committees, will be informed of the results via direct communication and where possible, presentations.

18 REFERENCES

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