PROTOCOL TITLE

PROMPT: PROcedural sedation vs Methoxyflurane a Prospective cohorT Study.

SPONSOR
Department of Interventional Radiology, Liverpool Hospital

CONFIDENTIAL

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).

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1. SUMMARY

1.1 Synopsis

Study Title	PROMPT: PROcedural sedation vs Methoxyflurane a Prospective cohorT Study.
Aims/Objectives	Aim: To improve the quality of care in interventional radiology by minimising pain and anxiety in everyday procedures whilst optimising resources for Liverpool Hospital and SWS LHD. Primary: to assess the efficacy and safety of methoxyflurane in IR, if methoxyflurane leads to decreased levels of pain and anxiety in common IR procedures, if methoxyflurane is more effective in certain procedures, if the efficacy of methoxyflurane is related to procedure length. Secondary: to assess the importance of patient-controlled analgesia for patients, clinician/proceduralist satisfaction with methoxyflurane in IR procedures.
Study design	Prospective randomised double arm study comparing methoxyflurane vs intravenous fentanyl and midazolam.
Planned sample size	Approximately 200 patients.
Inclusion criteria	Patients requiring periprocedural analgesia or sedation above local anaesthesia alone + hemodynamically stable + expected procedure time <2h + able to consent + over 18 years of age.
Exclusion criteria	renal impairment (eGFR<50) + liver dysfunction + pregnancy + opt out or refusal + requiring general anaesthesia or formal support by anaesthetist (e.g. needing intubation) + prior allergy or adverse reaction to methoxyflurane, midazolam or fentanyl.
Study procedures	Patients will be electronically randomised to methoxyflurane or intravenous fentanyl/midazolam (administered by trained staff). Patients will be assessed through standardised questionnaires pre and post procedure in addition to monitoring levels of analgesia and anxiolysis at discrete time points during the procedure (10 minute intervals). A proceduralist questionnaire will also be conducted. Procedure time, adverse events or complications will also be recorded for correlation and analysis.
Analysis considerations	Continuous variables will be summarised using mean (SD) or median (IQR) and comparison between study groups

	will be made with student T test or Mann-Whitney U test. Categorical variables will be recorded as counts and percentages and comparisons between study groups will be made using chi-square or Fisher's exact test. Calculated P-values will be two tailed with $P<0.05$ indicating statistical significance. Non-inferiority analysis will also be implemented.
Study duration	Data collection 6 months. Expected study duration 12 to 18 months.

1.2 Study investigators

Coordinating Principal Investigator:
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Institution: Interventional Radiology, Liverpool Hospital

Principal Investigator:
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Supervising Investigator:
Name: Dr Jules Catt
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Associates Investigator
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1.3 Funding

No financial disclosures, please see section 13. Funding for details.

1.4 Statistician

None required. Statistical analysis will be conducted by the investigators.

2. BACKGROUND AND RATIONALE

Patient-controlled analgesia (PCA) has greatly improved the patient experience postoperatively and greatly enhanced recovery [1]. PCA can provide effective analgesia in a timely fashion [1]. Methoxyflurane has largely been used as an opioid-sparing, safe and feasible alternative to traditional procedural sedation in a variety of clinical settings. It has been used in the acute management of pain including trauma and prehospital setting [2-3]. It was also shown utility in the procedural setting with a role in colonoscopies, bone marrow biopsies, burn dressing changes, prostate biopsies, minor surgical and vascular procedures where traditional procedural sedation is the standard of practice [4-11].

Resource allocation is critical in a high turnover department. Traditional procedural sedation is resource intensive both intra-procedurally and throughout the recovery phase. Ongoing intra-procedural boluses of midazolam and fentanyl in traditional procedural sedation is an additional element that the proceduralist must continue to closely manage in addition to technical aspects of the procedure. Traditionally the proceduralists and sedation nurses manage intraprocedural analgesia, the use of methoxyflurane allows the patient to be involved in the management of their intra-procedural analgesia will empower patients and improve pain control.

The pharmacokinetics present as a suitable adjunct. Patient-controlled analgesia (PCA) in the form of methoxyflurane offers a safe and viable solution to providing short-term pain relief. It is an opioid-sparing alternative that is easier to administer than nitrous oxide, being delivered via a self-contained single use portable inhaler. To receive a bolus of traditional procedural sedation the patient must request it, the produralist must approve it then the sedation nurse can administer. These critical steps to administering midazolam and fentanyl result in an inherent delay. Timely access to analgesia has become the focus of pain management in the hospital setting, and is essential for procedural success [4]. Therein lies an inherent advantage of patient controlled and administered analgesia. This study aims to evaluate this advantage in clinical practice and whether an acceptable level of analgesia is achieved.

The ideal characteristics of effective procedural sedation and analgesia medications; include rapid onset, short duration, rapid metabolism, short recovery and minimal side effects. [11] The pharmacokinetics of methoxyflurane allows for a rapid onset and offset time with minimal toxicity facilitating its role in a variety of healthcare settings [3,5,6]. Other benefits include opioid sparing analgesia in lieu of increased opioid dependency and other agents conventionally used for procedural sedation which carry risks of respiratory depression and necessitate a recovery period of post-procedure [4,7-9].

Methoxyflurane appears to be a safe patient centered alternative to traditional sedation for various procedures that historically required midazolam and fentanyl or fentanyl and ketamine. [10] The higher degree of patient control, rapid onset and a faster recovery and least post-procedural monitoring.[10] In a high turnover department like Liverpool interventional radiology this Methoxyflurane facilitates an effective utilization of staff significantly faster throughput of patients whilst using a patient centered analgesia model that is opioid sparing.

[10] Methoxyflurane has been used in Australia for the last 40 years and was in regular use in 140 individual hospitals across Australia in 2020. In Australia, methoxyflurane is TGA registered for:

1. Emergency relief of pain by self-administration in conscious hemodynamically stable patients with trauma and associated pain, under supervision of personnel trained in its use
2. The relief of pain in monitored conscious patients who require analgesia for surgical procedures.

Hypotension, hypoxia, and dysrhythmias are not uncommon side effects in traditional procedural sedation [10-12]. In a study that looked at procedural sedation for colonoscopies 90% of participants were agreeable to receiving methoxyflurane for a similar procedure in the future [11,12]. Adverse clinical sequelae were over 25 times more frequent in traditional sedation vs methoxyflurane.[11].

Methoxyflurane has been routinely used in Liverpool Hospital interventional radiology department as an analgesic adjunct for a variety of procedures with very positive feedback collected from pilot data collected over the past 6 months. The three main areas where methoxyflurane has demonstrated non-inferiority include the patient experience of analgesia during the procedure, it did not impact the procedural success, and the ability of the sedation nurse to monitor the patient more closely with respect to other parameters like observations and positioning.

Analgesia in interventional radiology is often variable, this stems from the heterogeneity of procedures and their analgesia requirements. Interventional radiology departments have historically used opioids and non-opioid analgesics in an effort to minimise anxiety and pain. Optimisation of resource allocation and staff utilization is a critical factor particularly in high traffic departments. The volume, scale and complexity of interventional radiology procedures has progressed rapidly, similarly we are experiencing a rapid change in analgesia and sedation requirements. Patient centred analgesia plans result in more favourable outcomes with improved patient satisfaction, less opioid dependence and shorter lengths of stay in the hospital setting.

Patient controlled analgesia in the form of inhaled methoxyflurane has been part of our clinical practice and collecting prospective data will help evaluate this analgesia model in the IR setting. Our experience throughout the past 2 years and our pilot study on the role of inhaled methoxyflurane in interventional radiology merits further investigation. Furthermore, methoxyflurane confers lower risk than IV sedation in most cases, and even allows for analgesia in non-fasted patients which would not be possible. An internal audit of the role of methoxyflurane has suggested an augmented standard of clinical practice and patient centered care in our department, indicating non-inferiority to IV sedation, and this study will help further validate these preliminary findings.

Traditional procedural sedation and inhaled methoxyflurane have been used interchangeably in our clinical practice for the previous 2 years. The latter has been a valuable alternative in a variety of clinical situations. These factors include procedure type, a variety of clinical and non-clinical factors.The interplay of clinical these factors including; clinician preference, staffing,

availability and access to medications, patient preference, allergies and fasting status. This study has been developed to evaluate the role of inhaled methoxyflurane in IR. Effective analgesia plans are developed to enhance patient experience, procedure time, safety and resource utilisation.

Randomisation of cohorts in this study controlled for these various clinical and non-clinical factors informs future practice in the form of clinical research. The heterogeneity of procedures in our department and their analgesia requirement necessitates innovation. The inherent variability of analgesia plans to cater for different clinical situations and resources is another factor that necessitates formal validation. This study aims to validate our experience with methoxyflurane through a robust randomised study design in order to help guide future practise. Given that traditional intravenous sedation and inhaled methoxyflurane are already used interchangeably as analgesic adjuncts for medium acuity procedures in our current practise, this does not represent a deviation from current clinical practise.

The use of methoxyflurane in this setting has not been formally evaluated versus traditional anaesthetic procedures. Other studies have illustrated its utility as a valuable adjunct in a variety of clinical contexts with similar analgesia requirements [2-6]. Pilot data collected in Liverpool hospital interventional department has also been informative. The proposed research will directly test the efficacy of methoxyflurane compared to traditional intravenous anesthesia.

3. STUDY AIMS/OBJECTIVES

Aim: To improve the quality of care in interventional radiology by minimising pain and anxiety in everyday procedures whilst optimising resources for Liverpool Hospital and SWS LHD.

Primary objectives:

- to determine the efficacy and safety of methoxyflurane use in interventional radiology procedures requiring periprocedural analgesia above local anaesthesia alone compared to the current standard of intravenous midazolam and fentanyl
- to determine if the use of methoxyflurane results in decreased levels of pain and anxiety in common interventional procedures compared to the current standard of intravenous midazolam and fentanyl
- to determine if the efficacy of methoxyflurane is related to procedure length when compared to the current standard or intravenous midazolam and fentanyl

Secondary objectives:

- to assess clinician/proceduralist satisfaction with the use of methoxyflurane in interventional radiology procedures requiring peri procedural analgesia above local anesthesia alone, compared to the current standard of intravenous midazolam and fentanyl

Hypotheses: We hypothesise, based on anecdotal experience, preliminary data and evidence in the literature, that methoxyflurane (Penthrox) is safe and effective for general interventional radiology procedures and is non-inferior as an adjunct to local anaesthesia compared to intravenous midazolam and fentanyl for stable patients requiring periprocedural analgesia.

The primary outcomes to be measured are levels of pain and anxiety and patient satisfaction between the two groups. We hope to prove non-inferiorly between methoxyflurane and

traditional sedation (i.e. similar levels of pain, anxiety and satisfaction), especially as this is a safer medication with less burden on staffing and resources.

4. PARTICIPATING SITES

Liverpool Hospital.

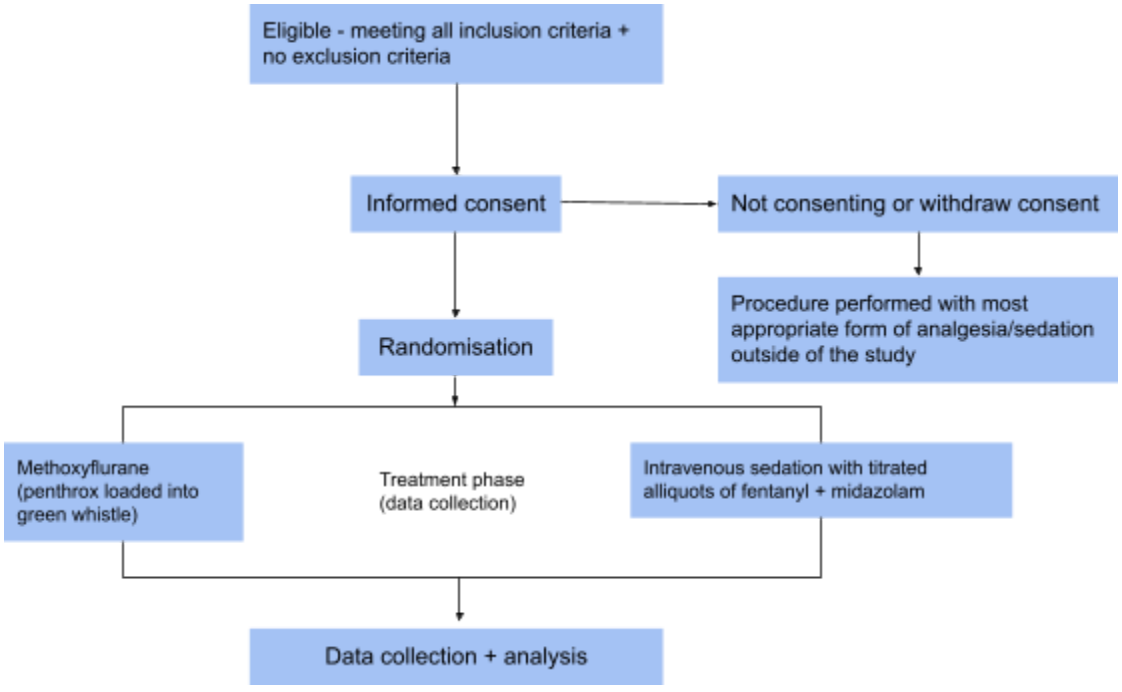
5. STUDY DESIGN

Prospective randomised double arm study comparing the efficacy of methoxyflurane (penthrox) and intravenous fentanyl/midazolam for common interventional radiology procedures. In conjunction with local anesthesia, patients will be given either:

1. Inhaled methoxyflurane via the “green whistle” OR
2. Intravenous midazolam and fentanyl given in titrated aliquots by trained medical staff

This would predominantly include inpatient procedures such as arterial and venous percutaneous angiography and intervention, inferior vena cava filter insertion and removal, ultrasound and CT guided intervention (deep tissue biopsy, drainages, ablations).
All patients clinically requiring periprocedural analgesia above local anaesthesia alone in the Liverpool Hospital Interventional Radiology Department who meet all inclusion criteria and none of the exclusion criteria will be provided informed consent and enrolled into the study.

Participation in the study will not affect any other aspects of their clinical management. Participants will be randomly assigned either methoxyflurane or intravenous midazolam and fentanyl using a randomisation strategy. All patients will undergo a complete anaesthetic checklist and sedation checklist regardless of allocation as required in standard of care. Additionally, all patients will be fasted for the procedure as required with all sedation or intravenous analgesia. Participants will be continuously monitored by a sedation nurse in accordance with standard periprocedural monitoring guidelines and established standard of care.



5.1 Study Type

Prospective open label randomised double-arm study.

5.2 Expected Study Duration

Data collection for the study will be carried out over 6 months. During this time, it is expected that approximately 200 patients will be enrolled in the study.

5.3 Data Source and Population

Pilot data has qualitatively appraised the experience of approximately 50 participants in an internal departmental audit for quality assurance. The expected duration of the study is 6 months with expected recruitment of approximately 200 participants subject to the inclusion and exclusion criteria. This study will recruit from a single site and department; namely the Liverpool Hospital Interventional Radiology Department.

Consent enrolment and participation in patient experience questionnaires (PEQ) for this study will be offered in a culturally appropriate format. PEQs will be offered to cater for a culturally and linguistically diverse participant cohort. The use of standardised graphics accepted in the literature for pain scores and patient satisfaction surveys will be utilised for a culturally and linguistically diverse participant cohort. The PEQ form will include a visual-analogue scale for collection of research data, negating the need for the interpreters service in data collection.

The patients will be assessed through standardised questionnaires post procedure in addition to monitoring levels of analgesia and anxiolysis at discrete time points during the procedure (10 minute intervals). Pain will be assessed using a visual analogue scale. Pre procedure data will be collected at the time of procedural consent and the post procedure questionnaire will be performed one hour post procedure. A proceduralist questionnaire will also be conducted. The questionnaires/data collection sheets have been attached as *appendix 1*. The procedure time, any adverse events or complications will also be recorded for correlation, analysis and reporting. If the patient withdraws consent or requires ‘rescue analgesia’ , we will exclude these patients from the main component of the analysis as this would confound direct comparison between methoxyflurane vs intravenous sedation but we will include all of these patients in the discussion in order to identify any issues or areas for improvement. This has been rare in clinical practise but would form an important part of the analysis when considering its use longer term. This will be clearly communicated at the time of consent and outlined in the participants information sheet.

5.4 Recruitment and Screening

All patients clinically requiring periprocedural analgesia above local anaesthesia alone in the Liverpool Hospital Interventional Radiology Department who meet all inclusion criteria and none of the exclusion criteria will be consented for enrolment in the study where clinically safe and feasible. Participation in the study will not affect any other aspects of their treatment or care. Participants will be randomly assigned either methoxyflurane or intravenous midazolam and fentanyl. All patients will undergo a complete anaesthetic checklist and sedation checklist regardless of allocation. This study cannot be blinded however participants will be randomly allocated with equal participants in each study group. Patients can opt out of the study at any time.

5.5 Inclusion Criteria

Patients requiring periprocedural analgesia or sedation above local anaesthesia alone for procedures in the Liverpool Hospital Interventional Radiology Department will be offered participation in the study. Participants must be over 18 years of age and have capacity to provide consent. Written informed voluntary consent will be obtained. Patients must be hemodynamically stable. Expected procedure time must be under 2 hours.

- able to consent for procedure and participation in research
- patients requiring periprocedural analgesia or sedation above local anaesthesia alone
- hemodynamically stable
- expected procedure time <2h
- over 18 years of age

5.6 Exclusion Criteria

The research project will be discussed with the patients at the time of consent. It will be clearly explained that they may opt out of the study or deny/withdraw consent at any stage. Patients unable to provide informed, voluntary, competent consent will be excluded. Similarly, if a sufficient understanding or communication cannot be established, including NESB/CALD, the patient will need to be excluded from the study and included in the discussion/exclusions analysis.

Any patient with allergy or prior adverse reaction to methoxyflurane, midazolam or fentanyl will be excluded from the study. Patients requiring general anaesthesia or formal support by anaesthetist (e.g. needing intubation) will also be excluded.

Patients with impaired renal function (eGFR<50) or liver dysfunction will be excluded due to the random possibility of receiving methoxyflurane as per standard of care for the safe administration of methoxyflurane based on the Australia Medical Handbook, Liverpool Hospital protocol and the Australian Therapeutic Goods Administration.

- renal impairment (eGFR<50)
- liver dysfunction
- pregnancy
- opt out or refusal
- requiring general anaesthesia or formal support by anaesthetist (e.g. needing intubation)
- prior allergy or adverse reaction to methoxyflurane, midazolam or fentanyl

5.7 Consent Process

Capacity to provide research and procedural consent will be clinically assessed on admission to the interventional radiology department by the most senior medical officer involved in the patient's care. The study will be discussed with the patient, including both forms of periprocedural analgesia (inhaled methoxyflurane/"green whistle" and intravenous midazolam/fentanyl), and information will be provided to the patient. The patient will be informed about the role of the research, the use of different forms of periprocedural analgesia/sedation (including risks, benefits and alternatives), what they can expect if they agree to participate (including any potential risks, rights and responsibilities). The patient will be provided enough time to make an informed choice and all questions asked will be answered facilitating the consent discussion. They will be reassured that they are able to withdraw/revoke consent at any point without penalty. If the patient is agreeable to participate in the study at this point, informed

written consent will be obtained and documented in the patients' medical records and line with ICH-GCP guidelines.

It will be ensured that consent is informed, voluntary and competent in accordance with *National Statement Chapters 2.2.9, 4.3.* If the patient requires the use of an interpreter, a partial witness will be present to ensure the informed consent discussion has taken place. The impartial witness will then be instructed to sign the informed consent document. The Investigate conducting the consent discussion will document this discussion in the patients' medical records inclusive of the use of an interpreter to facilitate the discussion.

The pain and anxiety scores will be explained at the time of consent, including the visual analogue scale (VAS) for both metrics, with an interpreter present if required. If a sufficient understanding and communication can be facilitated with staff and/or interpreter, then a patient will be eligible to be enrolled in the study. If this cannot be established, although uncommon, the patient will need to be excluded from the study and included in the discussion/exclusions. The visual analogue scales are routinely used in practise for patients including NESB/CALD to measure pain and anxiety.

5.8 Study Procedures

Both forms of periprocedural analgesia/sedation (methoxyflurane and midazolam/fentanyl) are used regularly in clinical practice in Liverpool Hospital. An internal departmental audit on methoxyflurane for quality assurance has shown positive feedback from patients in terms of anxiolysis and analgesia and we aim to formally validate its use for interventional radiology procedures through this research.

Methoxyflurane has been in routine use throughout the interventional radiology department for over 2 years. All the medications in this study are part of an imprest stock located in the interventional radiology department medication stock. The supply and restocking procedures are established as per SWSLHD medication supply guidelines. This study does not require access to the pharmacy, This study aims to collect data on the efficacy of inhaled methoxyflurane or intravenous aliquots of fentanyl and midazolam. This study will not affect the established pharmacy department procedures currently in place for prescribing, dispensing, storing, restocking or discarding of these medications. These medications are already in routine use at Liverpool hospital.

Potential patients will be enrolled into the study just after informed consent has been completed and the patient has met all inclusion criteria and none of the exclusion criteria. The patient will be assigned a randomised study code for de-identification and anonymisation which will be subsequently recorded on all study documents. Patients will be given a green whistle preloaded with methoxyflurane or intravenous aliquots of fentanyl and midazolam administered by trained sedation nurses, based on the predetermined study group that they are randomised to.

Only the nursing staff (including the delegated study trial nurse) have access to methoxyflurane, which is stored in accordance with S4 medication protocol. The Penthrox® inhaler is a registered medical device (ARTG number 136219) that complies with GMP and can be lawfully supplied in Australia. Patients will receive education on how to use the inhaler device by trained nursing staff.

The patients will be assessed through standardised questionnaires post procedure in addition to monitoring levels of analgesia, sedation and anxiolysis at discrete time points during the

procedure (10 minute intervals). Pain will be assessed using a visual analogue scale. Pre procedure data will be collected at the time of procedural consent and the post procedure questionnaire will be performed one hour post procedure. A proceduralist questionnaire will also be conducted. Time metrics will be recorded, including the duration of the procedure, when the patient receives sedation, when the patient completes the questionnaires and when the patient leaves the IR department/recovery. The questionnaires/data collection/time metric sheets have been attached as *appendix 1*. The procedure time, any adverse events or complications will also be recorded for correlation and analysis. If the patient withdraws consent or requires 'rescue analgesia', they will be excluded from the main group of analysis (i.e. methoxyflurane vs sedation) and treated appropriately, and analysed in the overall discussion to identify any issues or areas for improvement.

Statistical analysis will be performed by the investigators using Microsoft Excel and SPSS. There is no plan to use a biostatistician at this stage. Continuous variables will be summarised using mean (standard deviation) or median (interquartile range) where appropriate and comparison between the study groups will be made using the student T test or the Mann-Whitney U test. Categorical variables will be recorded as counts and percentages and comparisons between the study groups will be made using chi-square or Fisher's exact test. Calculated P-values will be two tailed with $P<0.05$ indicating statistical significance. Non-inferiority analysis will also be implemented with significance level (alpha) 5%, power 90%, percentage success expected in each group >90% and non inferiority limit (d) 20%.

Treatment whistle (left) and training whistle (right).

5.9 Randomisation

Randomisation will be predetermined and generated by a randomisation engine (randomizer.org) in order to allocate participants into two groups, either patient-lead sedation (inhaled methoxyflurane via “the green whistle”) or doctor/nurse lead sedation (IV fentanyl and midazolam). The results will be stored securely in sealed envelopes in the interventional radiology department, consecutively numbered and only accessible to the clinical nurse educator/study nurse. Once a patient is assessed and enrolled at the time of consent, the envelope will be opened revealing the allocated study group only to the study nurse.

5.10 Data Linkage

Not applicable.

6. TISSUE COLLECTION/BIOBANKING

Not applicable.

7. ETHICAL CONSIDERATIONS

7.1 Study Procedure Benefits

Landmark studies have found methoxyflurane (Penthrox) to be a safe and well-tolerated addition to current procedural sedation agents, in conjunction with local anaesthesia [2-7]. There is also emerging evidence to support the use of patient-controlled analgesia/sedation for procedures, including in interventional radiology, rather than the standard proceduralist-controlled analgesia. It has been proposed that this can avoid issues related to under or overdosing and empowering patients with control over their own levels of pain or anxiety may be therapeutic in itself. Safe analgesic agents such as methoxyflurane ("the green whistle") are widely used in the community (e.g. surf life saving, first aid, emergency), highlighting their safety without the need for monitoring [2-7].

Furthermore, many patients know or have heard of the "green whistle", providing an additional layer of comfort or reassurance to patients. In addition, methoxyflurane does not require additional staffing for monitoring of sedation that is required for IV sedation (such as midazolam or fentanyl), thereby reducing the barriers to patient comfort whilst easing the burden/drain on resources required for these high volume procedures. This should translate to optimisation of resources in the interventional radiology department, Liverpool Hospital and SWS LHD while improving overall patient comfort and care.

The role of methoxyflurane (penthrox) in procedural analgesia has a significant body of research supporting it; as a safe PCA device [2-7]. The progress of analgesia models centres on patient control, timely administration and opioid sparing alternatives [1,7,8]. Methoxyflurane meets all of these criteria; it is a safe effective non-opioid analgesia that provides strong analgesia within minutes and can be safely used by the patient if and when they need it. This instant administration of analgesia and the ability of the patient to titrate their analgesia by increasing frequency or dose provides layers of control to the patient. This control could lead to a better patient experience and support evidence that suggests there are increased levels of patient satisfaction associated with patient-directed analgesia. Methoxyflurane is generally used in the pre-hospital, dental and clinical setting and applying this analgesic to the highly controlled and monitored environment of an interventional radiology suite should allow better levels of pain control than local anesthesia alone. Its role as a non-sedating agent in comorbid patients may also prove a safer practice. This inhaled agent has a rapid onset and offset allowing a faster recovery for patients thus translating to avoiding prolonged periods of observation required with IV analgesics and reduced unnecessary occupancy of hospital beds even in the outpatient/recovery setting.

So far, our experience with methoxyflurane has been supportive of these benefits, which has been reflected in proceduralist, nursing and patient feedback. Of the patients that participated and responded to a recent intradepartmental audit for quality assurance, 73% reported a positive experience with methoxyflurane and 79% would recommend it for others, and there have been no significant adverse events or complications since commencing its use in interventional radiology.

7.2 Study Procedure Risks

Patients undergoing sedation require anaesthetic risk assessment, fasting for a period of at least 6 hours and constant monitoring by a sedation nurse. Methoxyflurane is well established in the acute setting [2,3] and does not require the same levels of fasting or monitoring. It has also been advantageous in elective and emergency procedures [4,5,6] providing immediate patient controlled intraprocedural analgesia without the risks of traditional procedural sedation such as intravenous midazolam and fentanyl. Due to the sedative effect and higher risk of respiratory depression and hypotension in intravenous sedation, methoxyflurane carries several advantages. The pilot data on the role of methoxyflurane has found it to be an opioid sparing adjunct to local anaesthesia with rapid onset and offset times and faster recovery times. These findings are consistent with a large body of evidence that illustrates the role of methoxyflurane in intraprocedural analgesia [1-6]. Risks in this study include over-analgesia or under-analgesia or adverse reactions to penthrox.

Over-analgesia (7.2.1)

The risk of over-analgesia is mitigated by several factors. Primarily, the methoxyflurane in the penthrox device has a 3 mL dose, which is not sedative nor nephrotoxic at these levels via the inhalation device. The patient will be continuously monitored by the proceduralist and nursing staff, in addition to assessment of pain, anxiety and sedation at 10-minute intervals. If over-analgesia, sedation or other adverse side effects are encountered, the study will be aborted to ensure the safety of the patient. Previously, patients have been escalated to intravenous procedural sedation, including which involves opioids and benzodiazepines, which carry much higher risks of over analgesia, over-sedation and even respiratory depression [8].

Under-analgesia (7.2.2)

There is also a possibility of under-analgesia in participants receiving methoxyflurane or intravenous (IV) sedation. Both arms of this study will receive local anaesthetic and have intravenous access for rescue analgesia if required. The IV sedation group will receive standard of care in addition to regular monitoring of pain and analgesia levels. The Penthrox® group will receive the green whistle with 3mls of methoxyflurane in addition to regular monitoring of pain and analgesia levels.

Upon enrollment, participants will receive education on safe use of the green whistle. They will also be instructed on how to occlude the dilution hole with their finger and deliver an increased dose of methoxyflurane or placebo to achieve optimal analgesia. Education on use of the green whistle will be given upon enrolment to the study, and sedation nurses will require participants to demonstrate the use of the device prior to the commencement of the procedure to verify correct technique. Participants may also be instructed on use of the green whistle throughout the duration of the procedure as required. Patients' pain and anxiety levels will be monitored regularly throughout the duration of the procedure (please see Master data collection form v3 (PENTHROX VS SEDATION)). Enrollment in the methoxyflurane or IV sedation arm of this study will necessitate frequent pain and anxiety monitoring. This robust procedural monitoring alone will alert the procedualist and sedation nurse of potential under-analgesia and facilitate more timely access to analgesia, be it via the green whistle in the trial or rescue analgesia outside the trial. This regular pain and anxiety monitoring will ensure prompt access to procedural analgesia. This procedural monitoring serves as a safety mechanism in the trial procedures to minimise under-analgesia in addition to facilitating prompt access to rescue analgesia as clinically indicated.

If a patient reports under-analgesia or uncontrolled levels of pain not relieved by the Penthrox® inhaler rescue analgesia will be administered as per the pre-existing standard of care. The procedure may be aborted if deemed clinically appropriate; the patient will be treated appropriately with further analgesics and withdrawn from the study.

If additional analgesia is requested or required, or if the patient becomes distressed in any way, the patient will be immediately excluded from the main group of the study and treated appropriately. The procedure will be aborted if necessary or additional medication given where needed. We will exclude these patients from the main component of the analysis as this would confound direct comparison of methoxyflurane vs IV sedation but we will include all of these patients in the discussion in order to identify any issues or areas for improvement. This has been rare in clinical practise but would form an important part of the analysis when considering its use longer term.

Adverse reactions (7.2.3)

Methoxyflurane

Methoxyflurane is well tolerated and side-effects are rare. Side-effects of methoxyflurane are relatively non-specific, mild and self-limiting in nature, with headache, nausea and vomiting being the most prevalent [9]. Methoxyflurane rarely causes severe or clinically significant sequelae; with negligible changes to the cardiovascular and respiratory function [9]. The risk of these adverse reactions will be mitigated by procedural regular observations so if hypotension occurs the study will be ceased and methoxyflurane will be removed from the patient [9,10]. Participants in this study will be monitored closely with observations of heart rate, oxygen saturations and blood pressure checked every 10 to 15 minutes and in accordance with standard of care in Liverpool hospital interventional radiology department. This level of monitoring exceeds that in the settings of approved methoxyflurane use, such as the pre-hospital setting, out-of-hospital setting dental practise and burns clinics [4,5]. Any other adverse reactions encountered from the administration of methoxyflurane or placebo will be managed as per the hospital protocol to ensure participants safely. It should be noted that no significant adverse events have been reported with methoxyflurane use in our clinical practice.

Midazolam and Fentanyl

Traditional procedural sedation with midazolam and fentanyl is well established. The primary side-effects/adverse reactions with clinically significant sequelae include over-sedation, respiratory depression and hypotension. As with all procedures, regular observations will be recorded and reversal agents can be administered if clinically indicated, as stipulated in the Liverpool hospital policy for procedural sedation. Participants in this study will be monitored closely with observations of heart rate, oxygen saturations and blood pressure checked every 10 to 15 minutes in accordance with standard of care in Liverpool hospital.

Nephrotoxicity (7.2.4)

Methoxyflurane found in the penthrox inhaler is a gaseous ether that was reported to cause nephrotoxicity at anaesthetic doses, which are over ten times the dose used in the penthrox device, but is routinely and safely administered in the unmonitored pre-hospital setting and intra-procedurally [2-6,10]. To minimise the already low risk of transient renal impairment, patients will be screened for renal impairment prior to any procedure. Any patients with renal impairment will be excluded from the study as per current practise.

All efforts will be made to ensure participant privacy and confidentiality is respected, (please see section 7.3).

Selection Bias (7.2.5)
This study will look at interventional radiology procedures where procedural sedation is indicated, safe and feasible. These procedures will be randomly allocated to either methoxyflurane or intravenous midazolam/fentanyl. The randomisation process thus mitigates selection/allocation bias. The study design will allocate the same number of participants to each procedure subgroup through the predetermined randomisation process. Selection bias will be minimised by the randomisation process, organised by the dedicated clinical nurse educator, but not associated with the participant or proceduralist.

Radiation safely (7.2.6)
All radiation safety guidelines will be adhered to as standard of practice in Liverpool hospital interventional radiology. Enrolment in this study does not alter radiation exposure to staff or participants.

7.3 Confidentiality and Privacy

All data will be stored on two password-protected computers in the Liverpool interventional radiology department, locked in the doctor's office. All patient data will be de-identified and anonymised in order to protect patient privacy. Anonymised data will be coded using a randomly assigned study number and stored separately to the data collection sheet. The separate file will link the key MRN data information and the file will be password protected. Specific patient details or identifiers such as name or ethnicity will not be required for the purposes of this study and will not be used or accessed. Confidentiality will be maintained by limiting access to only a few investigators involved in the project. Hard copy information will be destroyed once stored electronically and all data will be disposed of at the end of the standard retention period (15 years for clinical trial as stipulated by NSW requirements). All information in publication will not be identified by individual cases.

Collected data will be stored securely for the protection of patients' confidentiality. All data will be de-identified minimising the risk of confidentiality breach. All aggregated data will be stored on a SWSLHD network drive only accessible to research investigators listed.

7.4 Data Storage and Record Retention

All data will be stored on two password-protected computers in the Liverpool interventional radiology department, locked in the doctor's office. Only authorised personnel will have access to the office which requires key and swipe card access and log in credentials would be required to access the computer. The computer is non-portable, no laptop devices will be used. All hard copy forms will be securely stored in the locked filing cabinet in the interventional radiology office and destroyed once stored electronically. The data will only be accessible to investigators involved in the study. Electronic data will be backed-up to protect against data loss. Patients details will be anonymised from the data collection sheet. Data security is based on the SWS LHD network security as it will be on a SWS LHD network drive in accordance with the institution's data management protocol. The data will be stored for a minimum of 5 years and disposed of at the end of the standard retention period (15 years for clinical trial as stipulated by NSW requirements).

8. SAFETY REPORTING

ADVERSE EVENT REPORTING
The use of methoxyflurane vs midazolam/fentanyl will be reported in accordance to standard of practice in Liverpool hospital. Methoxyflurane, midazolam and fentanyl will be used safely in accordance with TGA and hospital guidelines in a controlled environment and monitoring for adverse events will be reported in accordance to departmental and hospital policy. The NHMRC standards for safety reporting have been read and will be adhered to for the duration of the study. Additionally processes for the management of patient safety will be governed by ICH GCP guidelines and local policy and procedures

9. DATA SAFETY AND MONITORING BOARD

Methoxyflurane (Penthrox) is registered with the TGA registered for self-administration in conscious haemodynamically stable patients, under supervision of personnel trained in its use. and in monitored conscious patients requiring analgesia for various procedures. All patients in the study will be closely monitored by the proceduralist and nursing staff assisting. All staff involved in the study will have inservice training on the correct and safe administration of penthrox. all patients in group (1) and (2) will receive education on the safe use of penthrox before their procedure. Given this is a widely used analgesic being used for on-label indications in a monitored and controlled environment that meets and exceeds the requirements set by the manufacturer and the TGA this study carries identical risk to other pre-existing uses of this product. Given this is on-label use of a formulary medication all the procedures for the detection, management, evaluation and reporting adverse events/drug reactions are already in place at Liverpool hospital. This study does not look at the safety of the penthrox in procedural analgesia that has already been established [2-6]. This study aims to assess the role of penthrox in interventional radiology and improving the patient experience with regards to procedural pain, anxiety and recovery.

Please see section 10 for early termination protocol.
Please see section 8 for adverse event reporting.
Please see section 7.3 for the privacy protection protocol.

10. EARLY TERMINATION

Methoxyflurane (Penthrox) is already used in clinical practise, and has been regularly used in the interventional radiology department for the last 2 years. There have been no issues or concerns with safety. In addition, it is used in other departments in Liverpool hospital, interstate and in other countries without significant adverse events. Similarly, the use of midazolam and fentanyl is well established in clinical practise. Nonetheless, data (including adverse) will be collected and regularly reviewed for quality assurance, and the study would be terminated in the unlikely event that there were any concerns for patient safety.

11. BLINDING AND UNBLINDING

Randomisation will be predertmined and generated by a randomisation engine (randomizer.org) in order to allocate participants into two groups, either methoxyflurane or IV midazolam/fentanyl.

12. CONFLICT OF INTEREST

There are no conflicts of interest. No sponsorship has been requested nor required. The investigators do not stand to benefit financially or otherwise from the outcomes of the study.

13. FUNDING

No funding has been requested nor is required for this project. All investigators are contributing their support willingly and voluntarily in their own time.

Inhaled Methoxyflurane in the form of Penthrox is already used on a daily basis for IR procedures and is locally sourced and covered via Medicare in line with standard of care. The supply and restocking procedures of all medications in this trial are established as per SWSLHD medication supply guidelines.This study will not affect the established pharmacy department procedures currently in place for the funding of these medications. This medication is imprest stock and Liverpool interventional radiology staff have in-service training on preparation, patinet education and all matters regarding the safe use of “green whistle”.

Methoxyflurane is already used on a daily basis for these procedures and overall is of lesser cost than intravenous sedation.

14. RESEARCH OUTCOMES

There is no intention to return results or feedback to research participants on completion of the study unless required for safety reporting. Research outcomes will however inform future clinical practice. Potential uses of this de-identified data at the end of the project include publication to share insights gained from this study. Given Liverpool interventional radiology departments promising pilot study on the role of methoxyflurane in interventional procedures the outcomes of this study can inform future practice. The data collected covers a variety of patient experience endpoints and can hence provide various qualitative insights on the role of methoxyflurane in interventional radiology procedures.

We will aim to publish the research in a peer reviewed journal such as CVIR or JVIR. We can also use the results to guide best practice in our department, potentially using methoxyflurane more or less or in certain circumstances, as clinically appropriate. The data will be archived on two password-protected computers in the interventional radiology department and deleted at the end of the standard retention period. There are no plans to perform secondary analysis on the data at this stage. There are no plans to share the data in the future. There are no contractual obligations or other agreements with any sponsors/funders/other parties that would influence publication or sharing of the data.

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