RESEARCH PROPOSAL
OBSTETRICS AND GYNAECOLOGY
DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
UNIVERSITI MALAYA

A Randomized Controlled Trial Comparing Parecoxib-Midazolam With Fentanyl-Midazolam as Conscious Sedation During Transvaginal Ultrasound Guided Oocyte Retrieval

BY:
DR. NURUL AIN ROSLAN
MGG190019

SUPERVISOR:

PROF. DR TAN PENG CHIONG
ASS.PROF NUGUELIS RAZALI
DEPARTMENT OF OBSTETRICS & GYNAECOLOGY
UNIVERSITY MALAYA MEDICAL CENTRE

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1. INTRODUCTION

A Randomized Controlled Trial Comparing Parecoxib-Midazolam with Fentanyl-Midazolam as Conscious Sedation During Transvaginal Ultrasound Guided Oocyte Retrieval

In vitro fertilization (IVF) accounts for 1.6% and 4.5% of all live births in the United States and Europe, respectively.[2] IVF is a four-stage procedure involving: ovarian stimulation protocols to induce the development of multiple follicles, oocyte retrieval, fertilization, and finally embryo transfer [3]. Ultrasound-guided transvaginal follicle aspiration has become the gold standard technique for oocyte retrieval, and it may be the most painful stage of IVF.

Pain relief options for the retrieval procedure are conscious sedation, local anesthetics, epidural spinal, general anesthesia, patient-controlled analgesia and acupuncture. Conscious sedation refers to the use of one or a combination of drugs to produce a state of relaxation and pain relief during a medical procedure. The simultaneous use of more than one method of sedation and analgesia result in better pain relief than one modality alone [3]. Conscious sedation results in less pain than placebo in oocyte retrieval [4]. The addition of paracervical block further reduces the pain level during retrieval under conscious sedation [4]. A Cochrane meta-analysis did not support one method or technique over another in providing effective conscious sedation and analgesia for pain relief during and after oocyte recovery [3].

Midazolam is the benzodiazepine of choice in endoscopic procedures owing to its faster onset of action and shorter duration of action than diazepam. Fentanyl is preferred to pethidine because the former is associated with more rapid onset and clearance, with less nausea [5]. When giving fentanyl-midazolam as conscious sedation, fentanyl must be given first as the synergy increases the potency of midazolam by 8 times[6]. ESHRE (European Society of Human Reproduction and Embryology) in their recommendations for good practice in ultrasound ovum pick up, suggests fentanyl-midazolam for normal conscious sedation without an anaesthetist and notes that the addition of para-cervical local anaesthetic infiltration appears superior to sedation alone [6]. However, combining midazolam with opioids increases the risk of hypoxemia and apnea[7], hence avoiding this combination in conscious sedation for procedures is of value.

Parecoxib sodium a parenterally administered prodrug of valdecoxib (a selective COX-2 inhibitor) is an adjunct or alternative to parenteral opioid analgesics in the treatment and prevention of moderate to severe postoperative pain[8]. Its onset of action is rapid, from 7 minutes.

In a recent study conducted in Reproductive Unit UMMC on conscious sedation in oocyte retrieval which was halted after 61 women had been recruited, 26/31 women in the placebo-midazolam arm required rescue parecoxib during the procedure compared to 0/30 in the fentanyl-midazolam arm. However, after rescue intravenous bolus parecoxib, the primary outcome pain score at 15 minutes after awakening was not significantly different median [interquartile range] placebo 0 [0– 2.25] vs fentanyl 1 [0-3] p = 0.79. Pain scores pre procedure, at awakening, 15, 30, 45, 60 minutes after awakening, prior to discharge and 3 days after procedure were also not different on repeated measures analysis of variance. Patient satisfaction and surgeon scores were also similar. Both trial arms received paracervical lignocaine infiltration. The findings show that placebo-midazolam is clearly unsatisfactory as sedation for oocyte retrieval as 87% required intra-procedure parecoxib rescue but after parecoxib rescue, outcomes were very similar. Hence it

is highly plausible that parecoxib-midazolam is not inferior to fentanyl-midazolam in providing sedation and pain relief for oocyte retrieval.

We plan a double-blind randomized control trial to test the hypothesis.

2. OBJECTIVES OF STUDY/ RATIONAL OF STUDY

The aim of the present study is to compare combination of parecoxib-midazolam to fentanyl-midazolam in conjunction with lignocaine paracervical infiltration in providing successful sedation and analgesia in the transvaginal oocyte retrieval in IVF treatment.

3. RESEARCH HYPOTHESIS

Parecoxib-midazolam is non inferior to fentanyl-midazolam in transvaginal oocyte retrieval in IVF treatment.

4. OUTCOMES

4.1 Primary outcome:

Successful sedation using Procedural Sedation Assessment Survey (PROSAS tool)[9]

"In accordance with patients' priorities, procedural sedation was judged as successful when there was no adverse event, no issues with sedation leading to an incomplete procedure, when patient-reported procedural discomfort was scored 2 or less, and the patient was comfortable with the level of sedation obtained with a sedation preference score of between -2 and 2"

4.2 Secondary outcomes:

- Pain measured using the numerical rating scale (NRS 0-10) at awakening, 15, 30, 45, 60 minutes and just before discharge
- Nausea
- Vomiting
- Surgeon satisfaction during transvaginal oocyte retrieval with the sedation-pain relieve effect
- Hypotension/Hypertension (SBP <90 or >160mmHg)
- Tachycardia / bradycardia (Heart rate <50 or >120/min)
- Oxygen desaturation (Any episode of desaturation <90%)
- Number of oocytes retrieved

5. METHODOLOGY

This study is a prospective double blind randomized controlled trial which will be conducted in Reproductive Unit, UMMC.

The reference population are patients undergoing oocyte retrieval as an IVF procedure.
Ovarian stimulation and oocyte retrieval are performed according to standard protocol and routine clinical care practice of the unit.

Both arms of study group will be injected with local anaesthesia 50mg lidocaine (10 ml of 1% lignocaine) in the paracervical area lateral and slightly above to the reflection of the vaginal mucosa to the cervix. [3] Prior to injection, aspiration will be done to avoid injection of local anaesthesia intravenously.

Interventions[10]

1) The study group (**Group PM)** will receive IV bolus of parecoxib 40mg followed by IV midazolam 5 mg bolus 15 minutes before the procedure and
2) The controls group (**Group FM)** will receive IV bolus of fentanyl 50 mcg followed by IV midazolam 5mg bolus 15 min prior to the procedure.

The medications will be prepared in syringes, pre-labelled for sequential administration and placed in numbered envelope by the investigator after randomisation in a private area. The investigator will dispose of identifiable wastes securely to sustain blinding. Randomisation is by opening of a sealed numbered opaque envelope with assignment of the lowest numbered envelope remaining to the latest recruit in strict sequential order.

The medications will be administered in sequence by the medical officer in charge, who is blinded. The provider (also blinded) doing the OPU (ovum pick up) will rate the adequacy of the conscious sedation and request rescue analgesia as needed. Instruction card will be provided to ensure the sequence of medications given. Patient will be tested when awakened from the sedation by a blinded assessor.

Awake is defined as when the patient is orientated to
1) Person: Name
2) Place: UMMC
3) Time: Month & Year
4) Procedure: Egg collection.

Successful Sedation will be assessed with Procedural Sedation Assessment Survey (PROSAS)[9] with blinded inputs from

1) Participants before discharge
2) Procedure assistant/nurse
3) Provider doing OPU
4) Recovery assistant/nurse

During pain score assessment at awakening, 15, 30, 45, 60 minutes and just before discharge; blood pressure, pulse rate and SPO2% will be recorded.

Nausea, vomiting dizziness will be also assessed with answer yes or no prior to discharge.

BREAKTHROUGH PAIN RESCUE PROTOCOLS

1) If a patient is perceived in distress due to pain during the procedure (in PM group) or upon completing the procedure and once patient awaken, a rescue dose of IV fentanyl of 50mcg in 5mls Normal saline may be given. [3] For FM group, rescue dose of IV parecoxib 40mg in 5mls normal saline will be given.

2) Upon discharge, patient will be discharged with oral paracetamol 1 g QDS/PRN if pain score ≤ 4 or celecoxib 200 mg BD/PRN if pain score ≥ 5.

3)Assess pain after 48-72 hours post procedure at embryo transfer or by telephone if not attending for physical follow up consultation within that time window

Amount of additional rescue dose will be recorded.

5.1 STUDY DESIGN

- A randomised double blind controlled trial

5.2 POPULATION OF STUDY

- Women undergoing OPU as part of IVF treatment

5.3 INCLUSION CRITERIA

- Women undergoing OPU between age 18 to 45 years old
- Suitable for conscious sedation

5.4 EXCLUSION CRITERIA

- Previous history of hypersensitivity or contraindication to midazolam/fentanyl/parecoxib
- Women not suitable for conscious sedation OPU e.g., presence of any medical comorbidity such as hypertension on treatment, inflammatory bowel disease, ischemic heart disease and heart failure on anticoagulants, history of bronchospasm, history of cerebrovascular disease and upper GI perforation, severe hepatic impairment
- Extreme anxiety
- Anticipated complicated OPU: extensive endometriosis, pelvic adhesions, difficult to access ovaries
- Prior issues with conscious sedation

5.5 RECRUITMENT

Women presenting for planned for OPU during IVF treatment.

A Patient Information Sheet will be provided to all potential participants. The recruiter will invite query and provide any other information sought, emphasize the voluntary nature of participation, reinforce the point that care will not be affected if trial participation is declined and that the participant may withdraw from the study at any time without having to provide a reason and their subsequent care will not be affected in anyway. Written consent will be obtained from all who agreed to participate.

Relevant demographic, medical data will be collected as per the Case Report Form.

5.6 RANDOMISATION

5.6.1 Participants will be randomized into 2 groups

a. IV Parecoxib combined with IV Midazolam (PM)
b. IV Fentanyl combined with IV Midazolam (FM)

5.6.2 Randomisation will be generated by random sequence generator, provided by random.org or https://www.sealedenvelope.com/simple-randomiser/v1/lists to avoid bias, and placed within a numbered, sealed and opaque envelope with the lowest numbered envelope remaining assigned to the latest recruit in strict sequential order

5.7 CASE REPORT FORM [CRF]
(Version 1 - 18/2/2022)

Study no: [ ]

Patient's Sticker
Contact no.:

Date of recruitment :

Date of birth :

Age :

Height : Weight : BMI :

Duration of infertility:

Race : Malay/ Indian/ Chinese/ Others - _____

Occupation : Employed / Own business / Housewife / Student / Unemployed

Smoking : Yes / No Alcohol : Yes / No

History of oocyte retrieval : Yes / No

Total oocytes retrieved : MII oocytes : Fertilized MII :

Please **Rate the Pain** by scoring the pain rating provided into the below table.

0 / 1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10

Time	Pain score	Blood Pressure	Heart Rate	Pain score	Nausea	Vomiting	Dizziness
Prior to op							
Awakening							
Awaken at 15 minutes							
Awaken at 30 minutes							
Awaken at 45 minutes							
Awaken at 60 minutes							

***Satisfaction score assessed using a NRS (0 to 10) will be assessed at from awaken.

For Surgeon :
Please **Rate your Satisfaction** DURING oocyte retrieval until awaken time

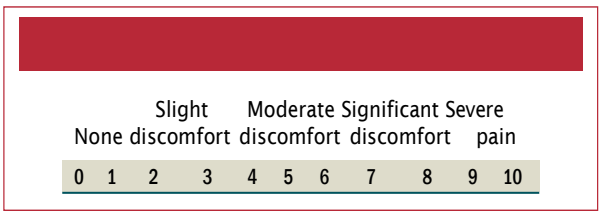
Circle your satisfaction rating below

0 / 1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10

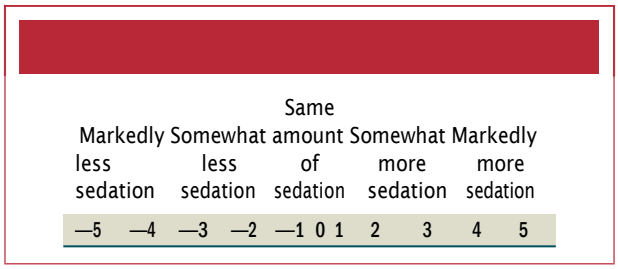
PROSAS

Patient to complete the following survey by herself with a family member or a nurse

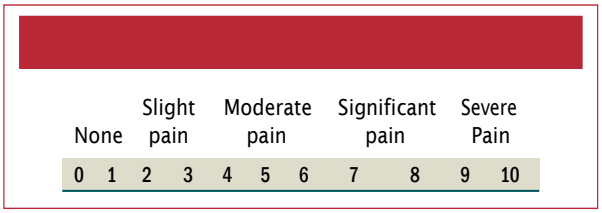
How much discomfort did you experience during the procedure?



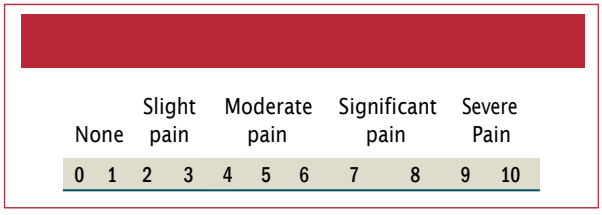
If having this procedure again in the future, how much sedation would you prefer to have?



On a scale of 0-10, how much pain were you feeling before the procedure?



On a scale of 0-10, how much pain are you feeling now?



Do you have any nausea now?

⬭ Yes
⬭ No

Other comments about your experience?

Procedure Nurse/Doctor (Name):

Any episodes of O_2 desaturation ≤90% or leading to intervention?

⬭ Yes
⬭ No

Any problematic changes in heart rate or blood pressure during intervention? (eg, systolic blood pressure ≤90, >160; heart rate ≤50, >120)

⬭ Yes
⬭ No

Any hemodynamic or respiratory conditions that inter- rupted the procedure?

⬭ Yes
⬭ No

Physician (Name):

Please rate the patient's cooperation during the procedure:

⬭ Procedure aborted due to lack of cooperation
⬭ Procedure delayed/interrupted due to lack of cooperation
⬭ Adequately cooperative

Was the exam interrupted in any way due to patient discomfort?

⬭ Yes
⬭ No

Recovery Nurse/Doctor (Name):

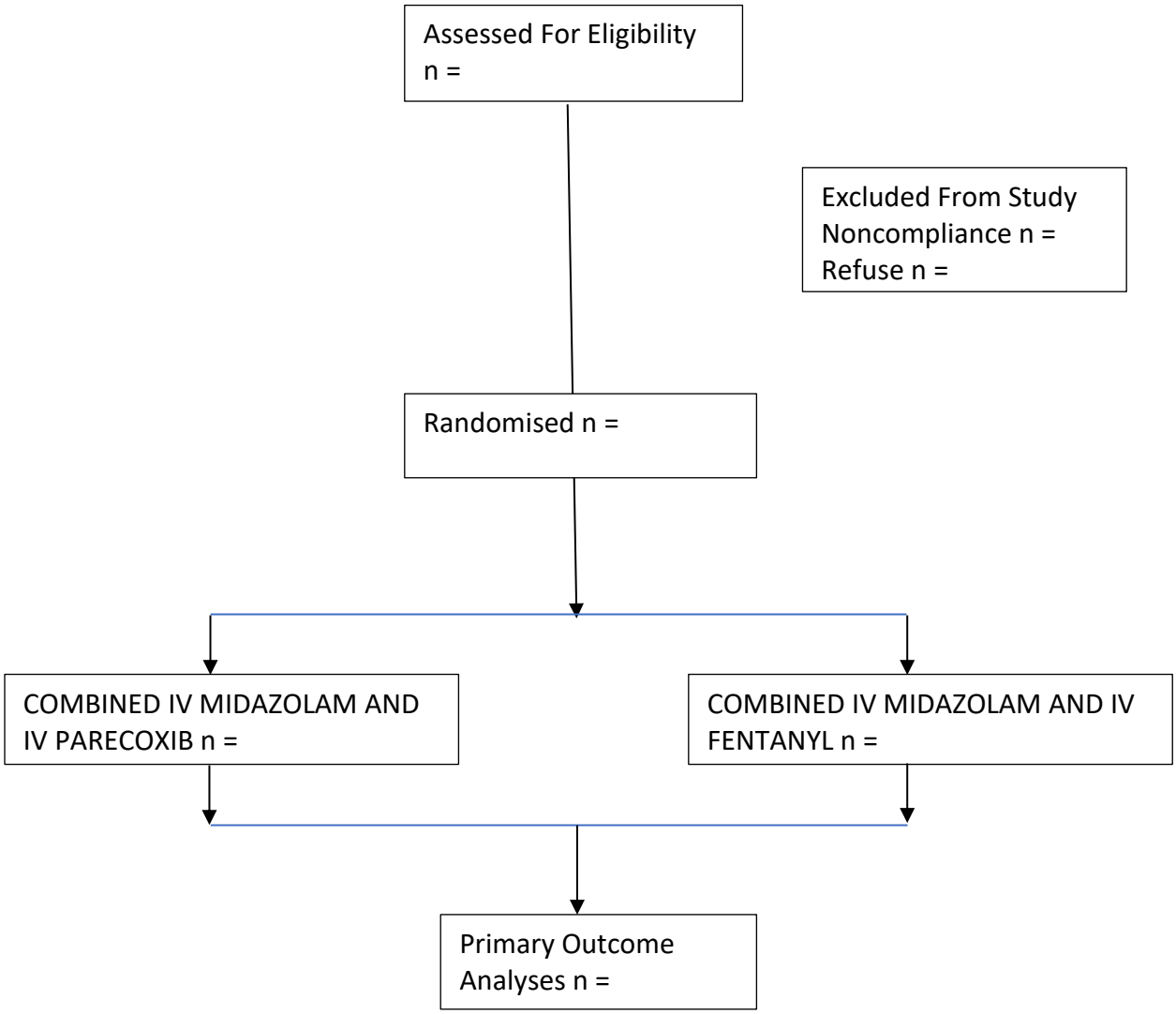
Did the patient report any pain during recovery?

⬭ Yes
⬭ No

Did the patient report any nausea during recovery?

⬭ Yes
⬭ No

6. STUDY FLOW CHART



7. ETHICAL CONSIDERATION

- All participants will provide informed written consent
- All participants information will be kept confidential
- Participant will have the right to withdraw at any point of the study without having to provide any explanation and their care will not affected
- This study is submitted to the Medical Research and Ethics committee, the local institutional review board for approval

8. SAMPLE SIZE CALCULATION

Sealed Envelope is used to calculate sample size,
https://www.sealedenvelope.com/power/binary-noninferior/

Based on Leffler [9], in the original PROSAS paper their successful sedation rate for endoscopy using PROSAS is 85.9%. If we incorporate a non-inferiority margin of 15%, alpha 5% and power 80% total sample size is 134, each arm 67.

9. STATISTICAL ANALYSIS

Data will be entered into SPSS 15 statistical software.

Primary analysis was qualitative with proceduralist and RN report used as measures of external validity. For evaluation of predictors of sedation quality, the Student T test, and the Fisher exact test were used for continuous and categorical variables, respectively. Spearman's Rho was used for correlation of linear data.
This includes the continuous variables of the secondary outcome such as BP, PR and SPO2 monitoring. Nausea and vomiting which are categorical data will be analyzed using Chi square test. P value < 0.05 will be taken as significant and P will be 2 sided

10. STUDY DURATION

This study will be conducted from June 2022 (or as soon as approved by Ethical Committee Board).

11. GANNT CHART

Duration	Nov- Dis 2021	Jan– Feb 2022	Mac - April 2022	June 22 – April 2023	May 2023	June 2023
Literature review	✓					
Proposal preparation & Presentation	✓	✓				
Ethics review			✓			
Data collection				✓		
Data analysis and writing					✓	
Thesis submission						✓

12. REFERENCES

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