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**RESEARCH PROPOSAL**

**OBSTETRICS AND GYNAECOLOGY**

**DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY**

**UNIVERSITI MALAYA**

**A prospective randomized trial comparing Midazolam Alone Compared With Midazolam Combined With Fentanyl During Transvaginal Ultrasound Guided Oocyte Retrieval**

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# TITLE

**A prospective randomized trial comparing Midazolam Alone Compared With Midazolam Combined With Fentanyl During Transvaginal Ultrasound Guided Oocyte Retrieval**

In vitro fertilization (IVF) is a well-established treatment for some cases of infertility which is increasingly being practiced worldwide. IVF is a four-stage procedure involving, ovarian stimulation protocols to induce the development of multiple follicles, oocyte retrieval, fertilization, and finally embryo transfer. Ultrasound-guided transvaginal follicle aspiration has become the gold standard technique for oocyte retrieval, and it may be the most painful stage among IVF procedures. The pain experienced during oocyte aspiration is caused by the passage of the needle through the vaginal wall and by mechanical stimulation of the ovary.

The procedures are generally short duration and low level of pain involved. The optimal anesthetic technique during oocyte retrieval should provide safe, effective , few side effects, a short recovery time, and be nontoxic to the oocytes which are being retrieved.

Various types of pain relief for the retrieval procedure have been studied, including conscious sedation, local anesthetics, epidural spinal and 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 resulted in better pain relief than one modality alone (1). It was previously shown that conscious sedation results in less pain than placebo in oocyte retrieval (3). The addition of paracervical block further reduces the pain level during retrieval under conscious sedation (3). A Cochrane metaanalysis did not support one method or technique over another in providing effective conscious sedation and analgesia for pain relief during and after oocyte recovery (1).

Two drug combination for conscious sedation is being used in our centre,pethidine and midazolam. No study, however, has compared the efficacy of the two different drug regimens. 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 (2).

Conscious sedation, on the other hand, may be associated with higher postoperative side effects such as nausea, vomiting, dizziness, and drowsiness. The most commonly used medications for monitored anesthesia care (MAC) are midazolam, propofol, and fentanyl. Unfortunately, all these drugs can cause respiratory depression.

Midazolam is the shortest-acting benzodiazepine available. Despite its rapid onset, it can cause prolonged sedation following repeated administration due to a relatively long half-life. Combining midazolam with opioids increases the risk of hypoxemia and apnea. Furthermore, adding propofol may cause cardio-respiratory depression.

In a study by (5) the visual analog scale scores was significantly decreased with dexmedetomidine than midazolam at 5 and 10 min during the procedure (*P* = 0.03 and 0.01, respectively), however at 20 min during post anesthesia time , the mean pain score was lower in the midazolam group ( 33.6 vs 37.8 (*P* = 0.04) ) and concluded that Dexmedetomidine is an effective analgesic alternative to midazolam during oocyte retrieval for IVF. The pain score documented in this study ranges from a score of 3 to 5. It offered not only a shorter post anesthesia stay without significant side effects, but also better overall patient satisfaction scores. The use of dexmedetomidine, however, may be limited by increased incidence of hypotension and bradycardia and limited ability to achieve deep sedation.

However it is not feasible for dexmedetomidine to be used in our study as this procedure is done as out patient. The use of dexmedetomidine also necessitate the presence of anesthetist on site. In addition to that dexmedetomidine is given in infusion pump rather than bolus doses.

Apart from analgesia method, pain during oocyte retrieval is also affected by needle diameter during oocyte retrieval (4). Pain score was shown to be significantly lower in the reduced needle diameter group compared to the standard group and the pain score in the study group was ranging from score 2 to 3.

However the mechanical comparison is not being studied in our study as the needle used in the reproductive unit in UMMC is 17 mm for all patient.

We believe that sedation alone is sufficient for this procedure as the procedure is done in short interval and involves low level procedure related discomfort and residual discomfort which dissipates very quickly.

In addition to that as this procedure is performed as outpatient, physician will be more assured upon the wellbeing of patient upon discharge post procedure and to ensure patient’s safety is at the optimum.

In addition to this, the study by (3) the fentanyl and midazolam group had significantly better satisfaction level on pain relief and satisfaction on the whole retrieval procedure than the pethidine and diazepam group.

As per recommendation (8), normal conscious sedation (not with an anesthetist or seditionist with anesthetic skills) may require:

• Midazolam 1 mg/ml to give no more than 7 mg in divided doses with Fentanyl (2 ml, 100 mg diluted with 8 ml of normal saline to make a dilution of 10 mcg/ml). When giving this combination Fentanyl must be given first as the synergy increases the potency of Midazolam by 8 times.

• If needed supplementary doses of 20 mcg Fentanyl can be given during the procedure up to a maximum of 100 mcg (not exceeding 1 mcg/kg).

However in this study, we are giving 50mcg as bolus dose.

A para-cervical block can be applied in addition to sedation, as pain relief during the OPU. It appears to be superior when compared with sedation alone (1). A local anesthetic agent is usually deposited in the vaginal mucosa.

A pilot study conducted in Reproductive Unit UMMC , From 28/3/2021 to 3/4/2021 , a total 7 patient data was collected and analyzed results showed that mean pain score at 15 minutes from the procedure is 3.42 with a standard deviation of 0.9. The mean pain score for 30 minutes from the procedure is 2.7 with a standard deviation of 0.7. The pain is more at 15 minutes post procedure compared to 30 minutes post procedure. In our study we decided to capture the pain score upon awake from the time of medication administered as the awaken time is different from person to person and the primary outcome will be pain score at 15 minutes from awaken.

# OBJECTIVES OF STUDY/ RATIONAL OF STUDY

The aim of the present study was to compare the effectiveness of midazolam alone compared to combination of midazolam and fentanyl in patients undergoing transvaginal oocyte retrieval in IVF treatment .

## RESEARCH HYPOTHESIS

Midazolam alone is non inferior compared to Combination of Midazolam and Fentanyl in patients undergoing transvaginal oocyte retrieval in IVF treatment.

## OUTCOMES

**Primary outcomes:**

* Pain Score at 15 minutes from awaken

**Secondary outcomes:**

* Nausea
* Vomiting
* Dizziness
* Patient Satisfaction

# METHODOLOGY

## 1. STUDY DESIGN

# A prospective randomized control trial

## 2. POPULATION OF STUDY

* Patients undergoing oocyte retrieval as part of IVF treatment

## 3. INCLUSION CRITERIA

* All patients undergoing oocyte retrieval between age 18 to 45 years old.

## 4. EXCLUSION CRITERIA

* Not consented
* Use of any other kind of analgesia before recruitment to the study
* Previous history of hypersensitivity to Midazolam/ Fentanyl.

## 5. METHODS

**Recruitment**

Women planned for oocyte retrieval during IVF treatment.

A Patient Information Sheet with essential information on the trial will be provided to all potential participants. The recruiter will also 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.

**Randomization**

1. Participants will be randomized into 2 groups
2. IV Midazolam alone
3. IV Midazolam combined with IV Fentanyl
4. Randomization will be generated by random sequence generator, provided by random.org to avoid bias, and labelled on an opaque envelope, which will be taken out from a designated box upon recruitment of the patient, which will determine which arm the patient belongs to.

**METHDOLOGY:**

This study design is a prospective double blinded randomized controlled trial which will be conducted in Reproductive Unit,UMMC in a duration of 6 months.

The reference population are those patients undergoing oocyte retrieval as an IVF procedure.

Ovarian stimulation and oocyte retrieval were performed according to the standard protocol and based on routine clinical care of the unit.

Both arms of study group will be injected with local anaesthesia ( 10 ml Lignocaine ) in the paracervical area lateral and slightly above to the reflection of the vaginal mucosa to the cervix. Prior to injection, aspiration will be done to avoid injection of local anaesthesia intravenously.

The study group ( **Group M )** will receive IV Midazolam 0.1/mg/kg 15 minutes before the procedure and the control group ( **Group F )** will receive IV bolus of Fentanyl 50mcg combined with IV Midazolam 0.1mg/kg 15 min prior to the procedure.

The medications will be pre-labelled and will be administered by the medical officer in charge of the reproductive unit.

The surgeon who is performing the procedure will be blinded and will rate the adequacy of the analgesia.

Patient will be tested if she is awaken from the sedation.

Awake can be defined as the patient is orientated to

1) Person : Name

2) Place : UMMC

3) Time : Month & Year

4) Procedure : Egg collection

A stop watch will be used to mark the timing for assessment of pain score.

Pain assessment by using VAS ( 0-10 ) will be done from the time patient is awaken.

* Prior to start of the procedure
* 0 minutes ( at awaken)
* 15 minutes
* 30 minutes
* 45 minutes
* 60 minutes
* Prior to discharging the patient
* First visit after Oocyte retrieval – For Embryo Transfer If Available

Time of awaken will be recorded.

Time to discharge will be recorded.

Time medications given.

Procedure start and end will be recorded.

During pain score assessment , blood pressure , pulse rate and SPO2% will be recorded.

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

BREAKTHROUGH PROTOCOLS

1. If patient perceived in distress due to pain during the procedure a rescue dose of IV Dynastat 40 mg will be given as stat dose.
2. Upon completing the procedure and once patient awaken , if the patient complaint of pain with a pain score > 5 as per VAS scale , a rescue dose of IV Dynastat 40 mg will be given as stat dose.
3. Upon discharge , patient will be discharged with T Paracetamol 1 g TDS/PRN if pain score < 4 and if pain score > 5 , patient will be discharged with C. Celebrex 200 mg BD for three days.
4. During return of patient for Embryo transfer on day three, pain score will be reassessed and and above (3) pain relief will be given.

Amount of additional rescue dose will be recorded.

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

Please circle the rate of satisfaction with your experience of the egg retrieval procedure using the score below.

Very Satisfied



Very dissatisfied



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

## 

## Case Report Form

Study Number

Patient’s Sticker

Randomisation to : M / F

Date of recruitment : \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_\_

Age : \_\_\_\_\_\_\_\_\_\_

Duration of infertility : \_\_\_\_\_\_\_\_\_\_

Education level : Up to Primary / Secondary / Diploma/ Degree

Occupation :

Employed / Own business / Housewife / Student / Unemployed

Race : Malay / Chinese / Indian / Other

Weight : \_\_\_\_\_\_\_\_\_\_\_\_ kg

Height : \_\_\_\_\_\_\_\_\_\_\_\_cm

Smoking: Yes / No

Alcohol: Yes / No

History of oocyte retrieval ? Yes / No

**Data collection On The Day Of Procedure:**

Please **Rate the Abdominal Pain** that at rest **PRIOR**  to the procedure

Circle your pain rating below

No pain



Worst pain imaginable



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

Please **Rate the Abdominal Pain** that you feel at **15 minutes** from awaken

Circle your pain rating below

No pain



Worst pain imaginable



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

Please **Rate the Abdominal Pain** that you feel at **30 minutes** from awaken

Circle your pain rating below

No pain



Worst pain imaginable



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

Please **Rate the Abdominal Pain** that you feel at **45 minutes** from awaken

Circle your pain rating below

No pain



Worst pain imaginable



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

Please **Rate the Abdominal Pain** that you feel at **60 minutes** from awaken

Circle your pain rating below

No pain



Worst pain imaginable



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

Other parameters recorded at every pain score assessment;

* Nausea Yes / No
* Vomiting. Yes / No
* Dizziness Yes / No

**6.Study Flow Chart**

Assesed For Eligibility

n =

Excluded From Study

Non compliance n =

Refuse n =

Randomised n =

Primary Outcome Analyses n =

IV MIDAZOLAM ALONE

n =

COMBINED IV MIDAZOLAM AND IV FENTANYL n =

7.ETHICAL CONSIDERATION

* An informed voluntary consent will be given to patient before involved in the study and written consent will be issued to the participants. The patient’s information will be kept confidential.
* Participant will have the right to withdraw at any point of the study if they decided to discontinue.
* 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.

The study by Ali et al, 20 minutes after the procedure, mean pain scores in the midazolam group was lower than the dexmedetomidine (33.6 {6.8} and 37.8 {9.94} ) ; P=0.04. This mean data using 100 mm VAS scale was converted to 10 mm VAS scale.

My study is the pain score from the time awaken compared to a fixed time post procedure because there are different awaken time for different patient.

With significant level (alpha) of 5% and power of 80%,standard deviation of outcome of 1 and non inferiority linit of 0.5, and 1:1 randomisation ratio, 50 patient needed in each arm with a total of 100 patients needed. This calculation is by using continuous ordinal data and the numbers are increased by 15% ( 115 ) . These number is rounded up to 120 with each arm is 60 patients.

## 9.STATISTICAL ANALYSIS

Data will be entered into SPSS 15 statistical software. Analysis will be by intention to treat. Primary outcome which is the pain score at 15 minutes will be analyzed by Student-t test. Secondary outcomes which consist of pain score at baseline, 30 minutes, 45 minutes , 60 minutes and at discharge will be analysed as repeated measure by computer analysis. 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 analysed 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 September 2021 (or as soon as approved by Ethical Committee Board).

**11.GANNT CHART**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Duration** | **Dec 2020** | **July 2021** | **August 2021 –Mac 2022** | **April 2022** | **May**  **2022** |
| **Literature review** | ✓ |  |  |  |  |
| **Proposal preparation**  **& presentation** | ✓ | ✓ |  |  |  |
| **Ethics review** |  | ✓ |  |  |  |
| **Data collection** |  |  | ✓ |  |  |
| **Data analysis and writing** |  |  |  | ✓ |  |
| **Thesis submission** |  |  |  |  | ✓ |

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