STUDY PROTOCOL

1. **General Information**

Protocol: Randomized controlled trial of transcutaneous electrical nerve stimulation for pain relief during transvaginal oocyte retrieval using conscious sedation

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2. **Background**

Oocyte retrieval under the transvaginal ultrasound guidance is an essential part of in-vitro fertilization. It involves passing an aspiration needle into the pelvic cavity through the vaginal mucosa and puncturing the ovarian cortex to reach the ovarian follicles. Despite being less invasive when compared with retrieval through laparoscopy in the old days, it is still a painful procedure. Different methods of pain relief have been used. The most commonly used modalities are conscious sedation with analgesia with or without paracervical block[1-3], patient-controlled conscious sedation and analgesia[4], spinal anaesthesia and general anaesthesia.

The best type of analgesia has not been established. A Cochrane review in 2013 by Kwan et al[5] on pain relief for women undergoing oocyte retrieval for assisted reproduction conclude that the current evidence from 21 randomized controlled trial did not support one particular method over another. The concurrent use of more than one method of sedation and pain relief resulted in better pain relief than a single modality alone.

The pain relief method used should be safe, effective and with minimal side-effects. Transcutaneous electical nerve stimulation is an non-pharmacological and non-invasive pain relief for nocieptive, neuropathic and musculoskeletal pain involving delivering pulsed electric current across skin[6]. It reduces labour pain and postpone the use of pharmacological angelsia in labouring women[7]. It has also been reported for reducing pain and increasing patients' satisfaction when used in office hysteroscopy without sedation[8]. It has not been studied as a pain relief method for oocyte retrieval in assisted reproduction.

This randomized double-blinded control trial aims to compare the pain levels experienced by the women using the standard conscious sedation and those who had TENS in addition to conscious sedation. The hypothesis is that there will be less pain in women with both conscious sedation and TENS.

Reference :

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3. E.H. Ng, D.K. Chui, O.S. Tang, P.C. Ho. Paracervical block with and without conscious sedation: a comparison of the pain levels during egg collection and the postoperative side effects. Fertil Steril, 75 (2001), pp. 711-717

4. Lier, M. C., Douwenga, W. M., Yilmaz, F., Schats, R., Hompes, P. G., Boer, C. and Mijatovic, V. (2015), Patient-Controlled Remifentanil Analgesia as Alternative for Pethidine with Midazolam During Oocyte Retrieval in IVF/ICSI Procedures: A Randomized Controlled Trial. Pain Pract, 15: 487–495. doi:10.1111/papr.12189

5. Kwan I, Bhattacharya S, Knox F, McNiel A. Pain relief for women undergoing oocyte retrieval for assisted reproduction. Chochrane Database Syst Rev 2013:1CD004829.

6. Johnson M. Watson T. Transcutaneous electrical nerve stimulation, *Electrotherapy: Evidence-based Practice.* , 2008 Edinburgh Churchill Livingstone (pg. 253 -96)

7. Santana LS et al. Transcutaneous electrical nerve stimulation (TENS) reduces pain and postpones the need for pharmacological analgesia during labour: a randomised trial. J Physiother. 2016 Jan;62(1):29-34. doi:10.1016/j.jphys.2015.11.002. Epub 2015 Dec 11.

8. Lison F, et al. Transcutaneous Nerve Stimulation for Pain Relief During Office Hysteroscopy: A Randomized Controlled Trial. JF Lisón et al. Obstet Gynecol 129 (2), 363-370. 2 2017.

3. **Trial objectives and purpose**

To evaluate if TENS is effective in reducing pain during transvaginal oocyte retrieval using conscious sedation

4. **Trial design**

This is a randomized, double-blinded placebo-controlled trial. Women who are eligible will be recruited and randomized into one of two groups.

a. Treatment group: conscious sedation with 25 mg IV pethidine and 5mg IV diazepam and active TENS
b. Placebo group: conscious sedation with 25 mg IV pethidine and 5mg IV diazepam and placebo TENS

5. **Selection and withdrawal of subjects**

5.1 Inclusion Criteria Women who undergo transvaginal oocyte retrieval who is aged 18 or above will be recruited.

5.2 Exclusion Criteria

Women will be excluded from the study if

- There is only one ovary
- Oocyte retrieval performed on one ovary only
- There are less than three follicles >=16mm in diameter
- Allergic to pethidine or midazolam
- Previous experience with TENS
- Skin damage or allergy at site of TENS pads application
- History of pacemaker insertion

5.3 Subject withdrawal criteria

Participation in the study is totally voluntary. The subjects can withdraw from the study at any time and they will receive standard medical care. Their participation may be discontinued in case of severe side effects during the procedure.

5.4 Criteria for exclusion from secondary analysis

None

6. **Treatment of subjects**

Women who are indicated to undergo IVF in our center will be assessed for eligibility for the study. Written consent will be obtained from those who agreed to join the study.

Randomization

Eligible women recruited will be randomized according to a computer-generated randomization list prepared by a designated research staff into one of the two groups on the day of oocyte retrieval:

1. Patient with both conscious sedation and active TENS
2. Patient with conscious sedation and placebo TENS

Blinding

Both the women and the physician performing the procedure will be blinded from the group allocation.

Checking of effectiveness of blinding will be done by asking the patient and the physician after the procedure as to which group they think the women is in.

The procedure

Women will receive ovarian stimulation according to the departmental Standard Operating Procedures. Ovarian stimulation will be monitored by ultrasound. Human chorionic gonodotrophin or an agonist (decapepty) will be given when the dominant follicle is at least 18mm and there are three more follicles of at least 16mm. Oocyte retrieval will then be arranged 36 hours later.

Prior to oocyte retrieval, two sets of self-adhesive electrodes will be placed on the women back on each side of the spine at T10 to S4 level. Instructions on how to titrate the TENS amplitude to the desired level that gives a strong non-painful electrical paraesthesia will be given to the women by the research nurse who is unaware of the group allocation. TENS therapy will start 5 minutes before the procedure and stop 5 minutes after the removal of oocyte aspiration needle. The TENS machine used in the study will be the Endomed 482 that delivers biphasic pulsed currents using pulse duration of 400 μs and pulse frequencies between 80-100 pulses s^{-}. The women in the treatment group will be given a TENS machine with electrodes emitting impulses while those in the placebo group will be given a TENS machine with electrodes that is not emitting any impulses.

The woman lies on the operative bed in a lithotomy position. 25mg Pethidine and 5mg Diazepam will be given intravenously. The blood pressure and pulse of the woman are checked after the drug administration and the oxygen saturation is monitored continuously throughout the procedure. 10ml 1% lignocaine is injected to the paracervical region by the operating surgeon with a 21-gauge needle after cleansing the vagina and cervix with chlorhexidine. Under transvaginal ultrasound guidance, a 16-gauge ovum aspiration needle is introduced. Aspiration of follicles is performed with a suction pressure of 100 mmHg.

Assessment of pain level

The women will be asked to rate the pain according to a 100mm linear visual analogue scale. They will be asked to rate the pain level related to insertion of an intravenous cannula and the anticipated pain level of the retrieval.

Then women will be asked to rate
1. The maximum vaginal pain during the procedure
2. The maximum abdominal pain during the procedure
3. Pain immediately after the procedure before they leave the operating room
4. Pain at 1 hour after the procedure

Patient's satisfaction towards pain relief will be assessed before discharge. They will be rated as 5, 'excellent'; 4, 'satisfactory'; 3, 'fair'; 2,'not very satisfactory' and 1, 'totally unsatisfactory'.

Collection of data

Apart from the pain score, patient's satisfaction level, occurrence of side effects, patient's characteristics including age, body mass index, blood pressure, heart rate, past history of dysmenorrhea, chronic pelvic pain, mood disorders will be recorded. The duration of procedure, number of follicle aspirated and experience of surgeons will be documented.

Follow-up

No routine follow-up visits will be arranged solely for the study unless considered necessary by the investigators.

7. Assessment of outcome

The primary outcome will be the pain level during oocyte retrieval experienced by patient.

Secondary outcomes include side effects and satisfaction of patient.

8. Assessment of safety

The use of Pethidine and midazolam has been widely used and proven to be safe. They are the standard medications used in our unit for conscious sedation. Oxygen saturation, heart rate of the patient will be monitored throughout the procedure. Blood pressure will be measured before and after the procedure.

TENS is a non-invasive and non-pharmacological pain relief method. The side effects are minimal including possible allergy to the skin pads, soreness in case of overuse and having an unpleasant sensation if the energy is set too high. The intensity of the TENS machine will be controlled by the patients thus minimizing the possibility of unpleasant sensation.

9. Statistics

Sample size calculation

According to our previous study, the pain level of the retrieval using conscious sedation alone was 23.0 ± 21.0 (mean ± SD) on a 100-point visual analogue scale. Effect size is estimated based on recommendations for a minimum clinically relevant change of 10 mm on a 0–100 mm VAS for pain. Assuming the pain level is reduced from 23.0 to 13.0 on a 100-point visual analogue scale following TENS, the sample size required would be 70 in each

treatment arm to give a test of significance of 0.05 and a power of 0.8 (Sigmastat, Jandel Scientific, U.S.A.). A total of 160 subjects or 80 subjects in each treatment group are needed if we anticipated a dropout rate of 10%

Statistical analysis

Demographic features between the two groups will be compared. Comparison of categorical variables between groups will be done using X2 – test. For continuous variables, the Student's t-test and Mann-Whitney U-test will be used for parametric and non-parametric data, respectively. All statistical analyses will be performed using the Statistical Program for Social Sciences, SPSS and MedCalc software.

10. Direct access to source data / documents

The investigators permit trial-related monitoring, audits, IRB/IEC review and regulatory inspections, providing direct access to source data/documents.

11. Quality control and quality assurance

Patients will be managed by the clinicians who have appropriate experience in performing transvaginal oocyte retrieval.

12. Ethics

Ethics approval for the current study will be obtained from the joint Institutional Review Board of the University of Hong Kong and Queen Mary Hospital. Written consent will be obtained from recruited subjects. Their participation is totally voluntary. They can withdraw from the study at any time.

13. Data Handling and record keeping

All data will be stored in locked computer files that are accessible only to the investigators and research staffs involved in the study. The principal investigator will be responsible for data management including data coding, monitoring and verification.

14. Financing and insurance

The study will be financed by the Department of Obstetrics and Gynaecology, the University of Hong Kong.

15. Publication policy

The findings of this study will be submitted for consideration for publication in peer-reviewed scientific journal.

16. Supplements

The study will be conducted in compliance with the Declaration of Helsinki and Good Clinical Practice (ICH-GCP).

17. We certify that the information given is complete and accurate to the best of our knowledge.