1. Title page

Title: A prospective, non-inferiority randomized double-blinded trial comparing fentanyl and midazolam vs diazepam and pethidine for pain relief during oocyte retrieval

Version: 2
Date: 24 Mar 2015

Chief investigator:
Name: Dr. Lai Shui Fan
Title: Resident Specialist
Address: Department of Obstetrics and Gynaecology, Kwong Wah Hospital
Tel. No.: 35176914
E-mail: lsf087@ha.org.hk

Co-Investigators:
Dr. LAM Mei Ting
Resident Specialist, Department of Obstetrics and Gynaecology, Kwong Wah Hospital

Dr. LI Hang Wun Raymond
Associate Professor, Department of Obstetrics and Gynaecology, the University of Hong Kong
Honorary Consultant, Department of Obstetrics and Gynaecology, Kwong Wah Hospital

Professor NG Hung Yu Ernest
Professor, Department of Obstetrics and Gynaecology, the University of Hong Kong
Honorary Consultant, Department of Obstetrics and Gynaecology, Kwong Wah Hospital

2. Background:

In-vitro fertilization / embryo transfer (IVF / ET) is a well-established method to treat various causes of infertility. It involves multiple follicular development, retrieval of oocytes and embryo transfer after fertilization. Egg retrieval at the majority of IVF units is performed through the transvaginal route under ultrasound guidance (TUGOR) [1]. During TUGOR, the needle has to pass through the mucosa in the vaginal vault in order to puncture the follicles in the ovary. The procedures are generally short, lasting about 20-30 minutes but are still painful without anaesthesia or analgesia.

Intravenous sedation with or without local anaesthesia is the most widely used method. Conscious sedation is a safe and cost-effective method of providing analgesia and anesthesia for TUGOR. [2] It is easy to administer in cooperative and motivated patients. It has a relatively low risk for adverse effects on oocyte and embryo quality and pregnancy rates. [3] Paracervical block (PCB) in conjunction with conscious sedation during TUGOR was shown to significantly reduce the pain during TUGOR when compared to PCB alone [4].

A Cochrane review on various methods of sedation and analgesia for pain relief during TUGOR has shown no single method or delivery system appeared superior for pregnancy rates and pain relief. [5] Most of the methods seemed to work well and the effect was usually enhanced by addition of another method such as pain relief with paracervical block. [6]

Our reproductive centre has recently aligned with the Assisted Reproduction Centre of the University of Hong Kong (HKU). We are using 0.1mg fentanyl and 5mg midazolam intravenously for pain relief in TUGOR at KWH whereas 5mg diazepam and 25mg pethidine intravenously are being used in HKU. We would like to compare fentanyl and midazolam vs diazepam and pethidine in terms of pain levels and post-operative side effects of TUGOR in this prospective non-inferiority randomized double-blinded trial. We postulate there are no differences in the pain levels between two groups but the postoperative side effects may be different.

References:

1. Hammarberg K, Enk L, Nilsson L, Wikland M. Oocyte retrieval under the guidance of a vaginal transducer: evaluation of patient acceptance. Hum Reprod 1987; 2: 487-490
2. Trout SW, Vallerand AH, Kemmann E. Conscious sedation for in vitro fertilization. Fertil Steril 1998;69:799-808.
3. Vlahos NF, Giannakikou I, Vlachos A, Vitoratos N. Analgesia and anesthesia for assisted reproductive technologies. Int J Gyne Obs 2009;105:201-205
4. Ng EHY, Tang OS, Kwai DCC, Ho PC. A prospective, randomized, double-blind and placebo-controlled study to assess the efficacy of paracervical block in the pain relief during egg collection in IVF. Hum Reprod 1999;14:2783-2787
5. Kwan I, Bhattacharya S, Knox F, McNeil A. Conscious sedation and analgesia for oocyte retrieval during IVF procedures: a Cochrane review. Hum Reprod 2006;21:1672-1679
6. Kwan I, Bhattacharya S, Knox F, McNeil A. Pain relief for women undergoing oocyte retrieval for assisted reproduction. Cochrane Database Syst Rev 2013;1:CD004829

3. Trial objectives and purpose:

The objective of the trial is to compare fentanyl and midazolam vs diazepam and pethidine in terms of the pain levels and post-operative side effects of TUGOR

4. Research design:

This is a prospective non-inferiority randomized, double-blinded trial. Patients will be randomized into two groups receiving either

A. Intravenous 0.1mg fentanyl and 5mg midazolam
B. Intravenous 5mg diazepam and 25mg pethidine

5. Selection and withdrawal of subjects:

5.1 Subject selection criteria:

The study will be jointly conducted in the N10, Dr Chow Chun-Kay Assisted Reproduction Centre, Department of Obstetrics and Gynaecology, Kwong Wah Hospital and K5N, the Assisted Reproduction Centre, Department of Obstetrics and Gynaecology, the University of Hong Kong.

Patients fulfil the following criteria will be recruited into the study:
(a) presence of both ovaries;
(b) body mass index ≤ 30
(c) written informed consent and
(d) Chinese

5.2 Subject exclusion criteria:
(a) IVF cycle converted from ovulation induction or intrauterine insemination cycles;
(b) patient requests general anaesthesia for TUGOR;
(c) history of drug sensitivity to lignocaine/fentanyl/midazolam/diazepam/pethidine;
(d) less than 3 dominant follicles present;
(e) dominant follicles present in one ovary only and
(f) TUGOR performed on one side only.

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.

6. Treatment of subjects:

Women undergoing IVF will be assessed for eligibility. They will follow the ovarian stimulation regimen according to the Standard Operation Procedures (SOP) of our unit. Human menopausal gonadotrophin (HMG, Pergonal, Serono, Switzerland) injection is started on the next day after ultrasound when there is no abnormality in ultrasound and serum estradiol levels are below <220 pmol/L at a dosage according to the antral follicle count. Ovarian response will be monitored by both serum estradiol level and transvaginal scanning. Human chorionic gonadotrophin (HCG, Profasi, Serono, Switzerland) 10,000 IU will be given to trigger the final maturation when the leading follicle reaches 18mm in diameter and there are at least 3 follicles >15mm in diameter.

Transvaginal ultrasound-guided oocyte retrieval will be performed 36 hours after the ovulatory dose of hCG injection. Patients will be admitted early in the morning and an intravenous cannula will be inserted in a convenient location in the forearm. Prophylactic antibiotic (1gram cefazolin or 1.5mg/kg gentamicin and 500mg flagyl if penicillin allergy) will be given intravenously 30 minutes before the retrieval. TUGOR will be performed in the minor operation theatre. The patient will be positioned in a dorsal lithotomy position on an electrically operated chair with calf-supporting stirrups.

Eligible women will be recruited for the study on the day of TUGOR. Informed written consent will be obtained.

Randomization

Before the procedure, each patient will be randomized into two groups with a predetermined computer-generated randomization code prepared by a research nurse to receive

A. Intravenous 0.1mg fentanyl and 5mg midazolam
B. Intravenous 5mg diazepam and 25mg pethidine

Blinding
Fentanyl, midazolam, diazepam and pethidine are all colourless. They will be each admixed with normal saline to make it 2.5ml in total in a 2.5ml syringe. The nurse assisting TUGOR will open the sealed envelopes arranged according to the computer-generated list and helps preparing and giving the medications. The patient and the physician will not know the group allocation.

The procedure
In addition to the study medications, a paracervical block will be given by injecting 10ml 1% lignocaine at 4 and 8 o'clock positions through a 21 gauge needle into the vaginal vault 2.5cm beneath the mucosa. The retrieval will be performed 5 minutes after the administration of paracervical block. Vaginal puncture sites during TUGOR would be kept at two i.e. one for each ovary. Each follicle will be flushed once and the follicular fluid from aspiration and flushing will be examined by an embryologist for an oocyte as usual. They will usually be discharged from the day ward 4 hours after the procedure.

Assessment of pain levels
Patients will be asked to rate their pain levels during (intraoperative) and within 4 hours after the procedure (postoperative) by means of 100mm linear visual analogue scale (VAS, 0 = non to 100 = intolerable).

The surgeon will also rate the levels of sedation of patients (S = sleeping, easily aroused; 1 = awake and alert; 2 = occasionally drowsy, easy to arouse; 3 = frequently drowsy, arousable, drifts off to sleep during conversation; 4 = somnolent, minimal or no response to stimuli). The patient will be asked by another nurse not involved in the TUGOR procedure to give the anticipated pain levels before TUGOR and report the vaginal and abdominal pain levels associated with TUGOR within 4 hours after the procedure. Side-effects such as nausea, vomiting, drowsiness and dizziness will be noted and graded by patients.

A maximum of two normally cleaved embryos will be replaced into the uterine cavity 48-72 hours after the retrieval. Excess embryos will be frozen for subsequent transfer if the women are not pregnant in that cycle. Luteal phase will be supported by endometrin vaginal pessary 100mg twice daily for 14 days starting 2 days after TUGOR.

Data collection
Apart from assessment of pain levels and side effects, we will also record patient characteristics including age, BMI, number of follicles/oocytes aspirated, the retrieval rate, the fertilization rate, duration of procedure, complications, clinical pregnancy rate, ongoing pregnancy rate and patient's satisfaction.

Follow-up

Urine pregnancy test will be checked 18 days after ovulation trigger (day of HCG) and pelvic scan will be scheduled later to confirm intrauterine pregnancy and assess number of gestational sacs.

7. Assessment of Efficacy:

The primary outcomes are the pain level during and after the procedure as assessed by the visual analogue scale. Secondary outcome measures include sedation level, side effects of medications, patient's satisfaction, clinical pregnancy rate and ongoing pregnancy rate.

8. Safety assessment:

Both the combinations of fentanyl and midazolam vs diazepam and pethidine were well-established drugs of choice for conscious sedation and proven to be safe. Patients will be monitored closely with continuous oxygen saturation throughout the procedure of TUGOR to look for respiratory depression. Blood pressure and pulse monitoring will be carried out before TUGOR and then hourly up to 4 hours after TUGOR. Emergency trolley with equipment for airway support is readily available in both centres. Anaesthetic support for difficult airway is available in both centres.

Lignocaine is a commonly used anaesthetic agent. Its use as paracervical block was evaluated in many studies and proven to be safe and effective.

9. Statistics

Sample size estimation

The mean pain score and standard deviation of pain level during TUGOR after diazepam and pethidine with paracervical block is 25 and 25 respectively based on our previous trial [1]. The sample size needed for this trial will be determined by the pre-defined non-inferiority margin and a non-inferiority margin of 10 was considered appropriate. Therefore, 78 patients in each arm are required to achieve a power of 80% at a type I error of 0.05 in order to account for drop outs, 85 patients will be recruited into each group and therefore 170 patients will be recruited for the whole study.

Data analysis

Demographic features of two groups will be compared. The primary outcome is the pain level during TUGOR and 4 hours after TUGOR. Secondary outcome measures include side effects of medications, patient's satisfaction, clinical pregnancy rate and ongoing pregnancy rate.

Chi-square test and Fisher's exact test will be used for categorical variables. P values of <0.05 will be considered clinically significant. Subjects may be excluded from the data analysis if essential data is missing.

References:

1. Ng EHY, Tang OS, Kwai DCC, Ho PC. A prospective, randomized, double-blind and placebo-controlled study to assess the efficacy of paracervical block in the pain relief during egg collection in IVF. Hum Reprod 1999;14:2783-2787

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 investigators who are specialists in obstetrics and gynaecology.

12. Ethics:

Ethics approval for the current study will be obtained from the Kowloon West Cluster Research Ethics Committee and Hong Kong West Research Ethics Committee. 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

We are now applying for the TWGH Research Fund 2014/2015

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.