Comparison of two different doses of lignocaine used in paracervical block during oocyte collection in an IVF programme

Ernest Hung Yu Ng1, Oi Shan Tang, David Kwan Chi Chui and Pak Chung Ho

Department of Obstetrics and Gynaecology, Queen Mary Hospital, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, People’s Republic of China

1To whom correspondence should be addressed at: Department of Obstetrics and Gynaecology, The University of Hong Kong, 6/F, Professorial Block, Queen Mary Hospital, Pokfulam Road, Hong Kong. E-mail: nghye@hkucc.hku.hk

We have recently demonstrated the efficacy of paracervical block (PCB) used in conjunction with conscious sedation during egg collection. The dosage of lignocaine used in various studies ranges from 50 mg to 200 mg. There are, however, no studies evaluating the efficacy of different doses of local anaesthetic agents used in PCB. In this prospective, double-blind and placebo-controlled study, 150 women undergoing egg collection in their first IVF cycle were randomized to receive 200 mg and 150 mg lignocaine during TUGOR. The median pain levels during egg collection were not significantly different between the two groups. The use of 200 mg lignocaine in PCB is not justified, even in the absence of toxic effects.

Key words: egg collection/lignocaine/pain relief/paracervical block

Introduction

Transvaginal ultrasound-guided oocyte retrieval (TUGOR) may be the most painful procedure during IVF and embryo transfer treatment. Conscious sedation is the most widely used method for pain relief in this situation. A survey of programmes of the Society of Assisted Reproductive Technology in the USA found that 95% of respondents used conscious sedation (Ditkoff et al., 1997). The perception of pain and discomfort during TUGOR is an important issue because repeated attempts may be required before a livebirth is achieved. Little information, however, exists in the literature with regard to pain relief during TUGOR.

Paracervical block (PCB) has been used in some IVF units, either alone or in combination with conscious sedation (Hammarberg et al., 1987; Ben-Shlomo et al., 1992; Godoy et al., 1993; Gohar et al., 1993; Corson et al., 1994; Gonen et al., 1995). We have recently demonstrated the efficacy of PCB in conjunction with conscious sedation during TUGOR (Ng et al., 1999). Lignocaine is often used in PCB but the dosage of lignocaine used in various studies ranges from 50 mg (Wikland et al., 1990) to 200 mg (Soussis et al., 1995). In our previous study (Ng et al., 1999), 150 mg lignocaine was employed in PCB. There are, however, no studies evaluating the efficacy of different doses of local anaesthetic agents used in PCB. The aim of this prospective, randomized, double-blind and placebo-controlled study was to compare the efficacy of PCB in pain relief using two different doses of lignocaine solution during TUGOR in IVF/embryo transfer cycles.

Materials and methods

Infertile patients attending the Assisted Reproduction Unit at Department of Obstetrics and Gynaecology, Queen Mary Hospital for IVF/embryo transfer treatment were recruited for study. Every patient gave written informed consent prior to participating in the study, which was approved by the Ethics Committee, Faculty of Medicine, the University of Hong Kong. Criteria for inclusion included: (i) the first IVF cycle proceeding to TUGOR and (ii) the presence of follicles in both ovaries. Exclusion criteria were: (i) IVF cycles converted from ovulation induction or intrauterine insemination cycles because of excessive ovarian responses; (ii) general anaesthesia requested by patients; (iii) <3 dominant follicles present; (iv) the presence of dominant follicles in one ovary only and (v) any history of drug sensitivity to lignocaine.

All patients had gone through a three-step counselling procedure prior to TUGOR: before enrolment into IVF treatment, 2–3 months prior to their treatment cycle and on the day of human chorionic gonadotrophin (HCG) injection. They all followed the long protocol of ovarian stimulation regimen. Gamete handling, conventional insemination and intracytoplasmic sperm injection (ICSI) were as previously described (Ng et al., 2000). A maximum of three normally cleaved embryos was replaced into the uterine cavity.

PCB and TUGOR

The details of PCB and TUGOR were previously given (Ng et al., 1999). All patients were pre-medicated with 50 mg pethidine (Antigen Pharmaceuticals Ltd., Roscrea, Ireland) and 25 mg promethazine (Phenergan®, M&B, Dagenham, Essex, UK) i.m. 30 min prior to the retrieval in common with our long-standing practice to relieve anxiety before the procedure. Five mg diazepam (Valium, Roche, Basel, Switzerland) and 25 mg pethidine were then given i.v. 5–10 min before the procedure. The same dosage of drugs would be repeated during TUGOR on patients’ request if they felt the procedure was too painful.
Patients were randomized into two groups: PCB with 10 ml of 2% lignocaine (Weimer Pharma, Rastatt, Germany) i.e. 200 mg, and with 10 ml of 1.5% lignocaine i.e. 150 mg. Both the patient and the doctor carrying out the procedure were blind to the dosage of lignocaine solutions, which were prepared and supplied by the hospital pharmacy. The nurse assisting TUGOR opened the sealed envelopes arranged according to the computer-generated randomization list. The randomization list was unblinded only after the study was completed.

Assessment of pain level

Nurses who were not involved in the Assisted Reproduction Unit asked patients about the pain levels, which were assessed by means of a 100 mm linear visual analogue scale (0 = none to 100 = intolerable). Prior to TUGOR, patients were asked to give pain levels related to venepuncture, transvaginal scanning, the insertion of an i.v. cannula and the expected pain level during TUGOR. The maximum levels of vaginal and abdominal pain during TUGOR were rated by patients within 4 h after TUGOR. On the day of embryo transfer, the patient graded the vaginal and abdominal pain over the 2 days preceding the embryo transfer and the pain associated with embryo transfer after the procedure.

Statistical analysis

TUGOR was timed from the first vaginal puncture to the removal of the needle after aspiration of all follicles >10 mm diameter on both sides. Retrieval rate was defined as the proportion of punctured follicles that contained an oocyte. Fertilization rate was defined as the proportion of oocytes resulting in two pronuclei formation. Implantation rate was considered to be the proportion of embryos transferring resulted in an intrauterine gestational sac.

In our previous study (Ng et al., 1999), the abdominal pain level during TUGOR after the use of conscious sedation and PCB with 150 mg lignocaine was 21.2 ± 23.1 (mean ± SD). Assuming that a reduction of pain level by 50% after using 200 mg lignocaine is acceptable, the sample size required would be 75 in each arm of therapy to give a test of significance of P = 0.05 and a power of 0.8 (Sigmastat, Jandel Scientific, USA). The primary outcome measures were levels of vaginal pain and abdominal pain scored by patients. Demographic data, the ovarian responses and the duration of TUGOR were also compared. As the data were not normally distributed, results were given as median (2.5th–97.5th centiles). Statistical tests were carried out by Mann–Whitney U test and \( \chi^2 \) test, where appropriate. P value (two-tailed) of < 0.05 was taken as significant.

Results

A total of 150 women was recruited between June 1999 and February 2000. Demographic data of these women are given in Table I. There were no differences between the two groups with regard to the age of women, body mass index, the type and causes of infertility, and the type of treatment received. The duration of TUGOR, the ovarian responses, the number of embryos replaced, pregnancy and implantation rates were comparable between the groups (Table II). Multiple pregnancy rates seemed to be higher in patients receiving 200 mg lignocaine than those receiving 150 mg lignocaine although the difference was not statistically significant.

Table III depicts the pain levels of various procedures scored by patients. The pain levels related to venepuncture, transvaginal scanning, i.v. cannula insertion and the anticipated pain levels during TUGOR were similar in the two groups.
The median pain levels during vaginal punctures were 14.0 (2.5th–97.5th centiles: 0–75.4) and 14.0 (2.5th–97.5th centiles: 0–86.5) in patients receiving 200 mg and 150 mg lignocaine respectively whereas the corresponding median abdominal pain levels were 14.0 (2.5th–97.5th centiles: 0–85.6) and 14.0 (2.5th–97.5th centiles: 0–99.1). These pain levels during TUGOR were not significantly different between the two groups. One patient in each group requested a repeated dose of i.v. sedation/analgesia during the retrieval.

Discussion

An optimal anaesthetic method should provide rapid onset of anaesthesia with adequate anaesthetic level during the procedure, followed by a rapid recovery. Conscious sedation remains the most widely used method for pain relief during TUGOR (Trout et al., 1998). However, the use of conscious sedation only does not provide adequate pain relief to patients during the procedure. The mean abdominal pain during TUGOR scored on a 100 mm visual analogue scale was 43.7 ± 32.0 (mean ± SD) in patients receiving conscious sedation only (Ng et al., 1999). When PCB was used in conjunction with conscious sedation, the mean abdominal pain scores were reduced by 40 and 50% compared with placebo and no local injection respectively. These pain levels were not significantly reduced even when the administration of i.v. analgesia was controlled by patients themselves (Bhattacharya et al., 1997).

We therefore recommend that both conscious sedation and PCB should be used during TUGOR in order to reduce the pain of the procedure. It is logical to use the most effective dose of lignocaine without toxic effects. Despite the fact that lignocaine is the most widely used local anaesthetic agent, the maximum recommended dose for lignocaine remains unclear. It is recommended in the UK that the maximum dose for lignocaine is 200 mg without adrenaline (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1997). This recommendation is different in different countries, as the maximum recommended dose in the US is 300 mg of plain lignocaine. The maximum dose of 200 mg is probably based on inadequate animal data from 1957 which did not incorporate reliable knowledge of plasma concentrations or pharmacokinetics of the compound in humans (Scott, 1989). A much higher dose of lignocaine has been used without toxic symptoms (Pälve et al., 1995).

The site of injection is another important consideration for recommending the maximum dose of a local anaesthetic drug. A plasma concentration of lignocaine 5 µg per ml is usually considered to be required for development of toxic symptoms. This toxic concentration could be achieved by the administration of 300 mg in the intercostal area, 500 mg extradurally, 600 mg in the region of brachial plexus and 1000 mg s.c. (Tucker and Mather, 1988). There seems to be no consensus in the literature with regard to the most effective dosage of lignocaine used in PCB. Various dosages have been empirically used in the studies, including 50 mg (Wikland et al., 1990), 100 mg (Hammarberg et al., 1987), 150 mg (Ng et al., 1999) and 200 mg (Ben-Shlomo et al., 1992; Soussis et al., 1995). The hypothesis of this study was that the pain levels during TUGOR were further reduced by increasing the dosage of lignocaine used in PCB from 150 mg to 200 mg.

The results of this study did not demonstrate any difference in pain levels during vaginal puncture and the retrieval procedure in patients receiving 150 mg and 200 mg lignocaine used in PCB. The sample size of this study was calculated based on the assumption to detect a 50% reduction in pain level after using 200 mg lignocaine, compared with 150 mg lignocaine. A smaller difference in the pain level might be detected when a larger sample size is considered. It seems that this possibility is rather unlikely as the median abdominal pain levels observed were 14 in both groups. The abdominal pain shortly after TUGOR was not evaluated in this study and it is possible that different doses of lignocaine used may have different efficacy in this respect.

The pouch of Douglas or uterosacral ligaments was most painful to stimulation, which was followed by uterus, oviducts or ovaries (Koninckx and Renaer, 1997). We postulated that lignocaine used in PCB anaesthetized both the vaginal mucosa and the peritoneal membrane over the pouch of Douglas or the uterosacral ligaments (Ng et al., 1999). Another explanation for the results of this study is that the pain arising from the peritoneal membrane over the pouch of Douglas or the uterosacral ligaments may be easily controlled by a low dosage of lignocaine. It is still unknown whether the use of 50 mg or 100 mg lignocaine is as effective as 150 mg lignocaine. Further studies should be performed to find out the lowest effective dose.

Lignocaine has been found in the follicular fluid. When 50 mg lignocaine was used, the mean concentration was 0.36 µg/ml follicular fluid (range 0–155 µg/ml) and the fertilization of the human oocyte or early cleavage of the human embryo were not negatively affected (Wikland et al., 1990). We have confirmed the absence of adverse effects on fertilization, implantation and pregnancy rates when 150 mg was used (Ng et al., 1999). The concentration of lignocaine was not measured in this study but it appears that the fertilization, pregnancy and implantation rates were not impaired either when 200 mg or 150 mg lignocaine was used (Table II). Multiple pregnancy rates were similar in both groups as well.

In conclusion, this study did not find any difference in the pain levels during the egg collection when 150 mg and 200 mg lignocaine were used in the paracervical block. The fertilization, implantation and pregnancy rates appeared to be similar when either 150 mg or 200 mg lignocaine was employed. The use of 200 mg lignocaine in PCB is not justified, even in the absence of toxic effects.

References


Received on April 25, 2000; accepted on June 29, 2000