A Randomized Double-Blind Study to Compare the Effectiveness of Three Different Doses of Lignocaine used in Paracervical Block During Oocyte Retrieval

Ernest Hung Yu Ng,^{1,3} Benyu Miao,^{1,2} and Pak Chung Ho¹

Submitted May 5, 2002; accepted July 26, 2002

Purpose: To compare the effectiveness of three different doses of lignocaine used in paracervical block (PCB) during transvaginal ultrasound-guided oocyte retrieval (TUGOR)

Methods: In this double-blind study, 153 patients undergoing TUGOR in their first in vitro fertilization cycle were randomized to receive 50, 100, and 150 mg of lignocaine in PCB. Pain levels were measured by a 100-mm linear visual analogue scale (0 = none to 100 = intolerable).

Results: No differences were seen in the demographic data, the ovarian responses, the duration of TUGOR, and the number of follicles punctured. Vaginal and abdominal pain levels during TUGOR and 4 h after TUGOR were not significantly different among the three groups. The median vaginal and abdominal pain levels during the retrieval were 22.0–24.0 and 30.0–32.0 respectively.

Conclusions: The use of 50 mg of lignocaine is recommended in PCB because of the lack of improvement in pain relief on higher doses and potential dose-related risks.

KEY WORDS: Lignocaine; oocyte retrieval; pain relief; paracervical block.

INTRODUCTION

Conscious sedation is the most commonly used method for pain relief during transvaginal ultrasound-guided oocyte retrieval (TUGOR) (1,2). Paracervical block (PCB) has been given, either alone or in combination with conscious sedation (3–9), in some assisted reproduction units to reduce the pain levels. We confirmed in a randomized study the efficacy of

PCB in conjunction with conscious sedation during TUGOR (10).

Lignocaine is often used as a local anaesthetic agent in PCB and various doses ranging from 50 to 200 mg have been empirically used in the above studies. In another randomized trial (11), we could not find any difference in pain levels during TUGOR when 150 and 200 mg of lignocaine was used in PCB. Therefore, it was concluded that the use of 200 mg of lignocaine in PCB was not justified for pain relief during TUGOR. There seems to be no information in the literature with regard to the lowest effective dose of lignocaine used in PCB for pain relief during TUGOR.

The aim of this randomized double-blind study was to determine the lowest effective dose of lignocaine used in PCB during TUGOR by comparing three doses of lignocaine, namely 50, 100, and 150 mg.

¹ Department of Obstetrics and Gynecology, The University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China.

² Present address: A.R.T. Centre, First Affiliated Hospital, Sun Yat Sen University of Medical Sciences, No. 58, Zhong Shan Road 2, Guangzhou 510080, People's Republic of China.

³ To whom correspondence should be addressed at Department of Obstetrics and Gynecology, The University of Hong Kong, 6/F, Professorial Block, Queen Mary Hospital, Pokfulam Road, Hong Kong, People's Republic of China; e-mail: nghye@hkucc.hku.hk.

MATERIALS AND METHODS

Protocol

Infertile patients attending the Assisted Reproduction Unit at Department of Obstetrics and Gynaecology, Queen Mary Hospital, Hong Kong, for in vitro fertilization/embryo transfer (IVF/ET) treatment were recruited if they fulfilled the following criteria: (a) the first IVF/ET cycle proceeding to TUGOR and (b) the presence of follicles in both ovaries. Exclusion criteria were (a) IVF/ET cycles converted from ovulation induction or intrauterine insemination cycles because of excessive ovarian responses; (b) general anaesthesia requested by patients; (c) less than three dominant follicles present; (d) the presence of dominant follicles in only one ovary; and (e) any history of drug sensitivity to lignocaine. Every patient gave a written informed consent prior to participating in the study, which was approved by the Ethics Committee, Faculty of Medicine, the University of Hong Kong.

All patients had gone through a three-step counselling procedure prior to TUGOR: before enrolment into IVF/ET treatment, 3 months prior to their treatment cycle, and on the day of HCG injection. Ovarian stimulation regimens, gametes handling, conventional insemination, and intracytoplasmic sperm injection (ICSI) were as previously described (12). The details of PCB and TUGOR were given previously (10). All patients were premedicated with 50 mg of pethidine (Antigen Pharmaceuticals Ltd., Roscrea, Ireland) and 25 mg of promethazine (Phenergan[®], M&B, Essex, UK) intramuscularly 30 min prior to the retrieval. Five mg of diazepam (Valium, Roche, Basel, Switzerland) and 25 mg of pethidine was then given intravenously 5 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. A maximum of three normally cleaving embryos were replaced into the uterine cavity.

Assignment

Patients were randomized on the day of TUGOR according to a computer-generated randomization list in sealed envelopes to receive three different doses of lignocaine (Weimer Pharma, Rastatt, Germany) for PCB: (a) 10 ml of 0.5% lignocaine (50 mg), (b) 10 ml of 1.0% lignocaine (100 mg), and (c) 10 ml of 1.5% lignocaine (150 mg).

Assessment of Sedation Level and Pain Levels

The surgeon (EHYN/BM) recorded the level of sedation during the retrieval according to the scale used by Ramsay *et al.* (13). Level 1: Patient anxious and agitated or restless or both; Level 2: Patient co-operative, orientated, and tranquil; Level 3: Patient responsive to commands only; Level 4: Asleep and a brisk response to loud auditory stimulus; Level 5: Asleep and a sluggish response to loud auditory stimulus; Level 6: Asleep and no response to loud auditory stimulus.

Nurses who were not involved in the retrieval procedure 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 intravenous cannula, and the expected pain level during TUGOR. The maximum levels of vaginal and abdominal pain during TUGOR were rated by patients shortly after the retrieval procedure. Patients were asked to grade the vaginal and abdominal pain 4 h after TUGOR before discharge.

Masking

The patient, the surgeon, and the nurse performing pain assessment were blind to the dosage of lignocaine solutions, which were prepared and supplied by the hospital pharmacy. The codes for different doses were broken only after the completion of the study.

Statistical Analysis

TUGOR was timed from the first vaginal puncture to the removal of the needle after aspiration of all follicles >10 mm on both sides. Retrieval rate was defined as the proportion of punctured follicles that contained an oocyte. Implantation rate was defined as the proportion of embryos transferred resulting in an intrauterine gestational sac.

In our previous study (11), the abdominal pain level during TUGOR, measured by the same visual scale using 150 or 200 mg of lignocaine in PCB, was 14.0 ± 26.0 (mean $\pm$ standard deviation). Assuming that a pain level of >30 was not acceptable, the sample size required would be 51 in each arm of therapy to give a test of significance of 0.05 and a power of 0.8 (Sigmastat, Jandel Scientific, San Rafael, CA). Therefore, 153 patients were recruited in this study. The primary outcome measures were levels

Table I. Comparison of Demographic Data

Parameters	50 mg (<i>n</i> = 51)	100 mg (<i>n</i> = 51)	150 mg (<i>n</i> = 51)
Age ^a (years)	35.0 (28.3–40.0)	34.0 (25.6–42.5)	34.0 (23.6–42.1)
Body mass index ^a (Kg/m ²)	20.70 (17.2–30.7)	20.45 (15.7–25.6)	20.57 (17.3–29.4)
Primary infertility ^b	37 (72.5)	39 (76.5)	33 (64.7)
Causes ^b			
Tuboperitoneal	17 (33.3)	11 (21.6)	17 (33.3)
Male	20 (39.2)	24 (47.1)	21 (41.2)
Endometriosis	8 (15.7)	7 (13.7)	3 (5.9)
Unexplained	3 (5.9)	7 (13.7)	9 (17.6)
Mixed	3 (5.9)	2 (3.9)	1 (2.0)
Type of treatment ^b			
Conventional IVF	35 (68.6)	31 (60.8)	37 (72.5)
Intracytoplasmic sperm injection	17 (31.4)	20 (39.2)	14 (27.5)

^a Values are median (2.5th–97.5th centiles).

^b Values are *N* (%).

of vaginal pain and abdominal pain during TUGOR scored by patients. As the data were not normally distributed, results were given as medians (2.5th–97.5th centiles). Statistical tests were carried out by Kruskal–Wallis and chi-square test, where appropriate. *p* value (two-tailed) of <0.05 was taken as significant.

RESULTS

Participant Flow

One hundred and fifty-six consecutive eligible patients were approached and three declined to participate in the study. Therefore, a total of 153 patients were recruited between September 2000 and June 2001 and completed the study.

Analysis

Demographic data of patients are given in Table I. There were no differences among the three groups with regard to the age of women, body mass index, proportion of primary infertility, causes of infertility,

and the type of treatment received. The duration of TUGOR, the number of follicles punctured, the number of oocytes obtained, the number of embryos replaced, and pregnancy and implantation rates were comparable in the three groups (Table II). Only one patient in the 100-mg lignocaine group and two patients in the 150-mg lignocaine group requested a repeated dose of intravenous sedation during the retrieval.

Table III depicts the sedation level rated by the surgeon and the pain levels of various procedures scored by patients. Patients were noted to have similar sedation levels in the three groups. The pain levels related to venepuncture, transvaginal scanning, intravenous cannula insertion, and the anticipated pain levels during TUGOR were not different among the three groups. The median vaginal pain levels during TUGOR in patients receiving 50, 100, and 150 mg of lignocaine were 22.5 (2.5th–97.5th centiles: 0–64.4), 22.0 (2.5th–97.5th centiles: 0–100), and 24.0 (2.5th–97.5th centiles: 0–92.8) respectively whereas the corresponding median abdominal pain levels were 32.0 (2.5th–97.5th centiles: 0–89.2), 30.0 (2.5th–97.5th centiles: 0–94.0), and 30.0 (2.5th–97.5th centiles: 0–87.5).

Table II. Comparison of Ovarian Responses, Pregnancy, and Implantation Rates

Parameters	50 mg (<i>n</i> = 51)	100 mg (<i>n</i> = 51)	150 mg (<i>n</i> = 51)
TUGOR duration ^a (min)	10.5 (4.3–27.4)	12.0 (6.0–34.0)	11.0 (5.0–29.4)
No. of follicles punctured ^a	12.0 (3.3–34.4)	15.0 (5.0–37.9)	12.0 (3.3–52.1)
No. of oocytes obtained ^a	9.0 (2.0–42.1)	11.0 (2.6–29.8)	9.0 (2.3–40.0)
Retrieval rate ^a (%)	77.8 (32.5–109.4)	78.9 (26.6–128.5)	75.0 (20.0–118.1)
No. of embryos replaced ^a	2 (0–3)	2 (0–2.7)	2 (0–3)
Pregnancy rate/cycle (%)	17.6 (9/51)	23.5 (12/51)	11.8 (6/51)
Pregnancy rate/transfer (%)	18.4 (9/49)	26.7 (12/45)	13.6 (6/44)
Implantation rate (%)	7.9 (7/89)	15.4 (14/91)	8.3 (8/96)

^a Values are median (2.5th–97.5th centiles).

Table III. Comparison of Various Pain Levels and Sedation Scale

Pain levels	50 mg (<i>n</i> = 51)	100 mg (<i>n</i> = 51)	150 mg (<i>n</i> = 51)
Before TUGOR			
Venepuncture	27.0 (0–77.4)	24.0 (0–87.6)	34.0 (0–80.0)
Transvaginal scanning	9.5 (0–68.5)	20.0 (0–94.9)	13.0 (0–66.3)
Insertion of IV cannula	36.0 (0–99.7)	40.0 (1.5–100)	48.0 (0.9–100)
Anticipated oocyte retrieval	59.0 (3.3–100)	60.0 (21.6–100)	68.0 (16.9–100)
During TUGOR			
Sedation scale	3.0 (1–5)	3.0 (1–5)	3.0 (1–5)
Vaginal puncture	22.5 (0–64.4)	22.0 (0–100)	24.0 (0–92.8)
Abdominal pain	32.0 (0–89.2)	30.0 (0–94.0)	30.0 (0–87.5)
4 h after TUGOR			
Vaginal pain	0 (0–69.5)	0 (0–88.9)	8.0 (0–71.4)
Abdominal pain	22.0 (0–77.5)	0 (0–70.0)	20.0 (0–85.8)

Note. Values are median (2.5th–97.5th centiles).

Vaginal and abdominal pain levels during TUGOR and 4 h after TUGOR were not significantly different among the three groups.

DISCUSSION

We demonstrated the efficacy of PCB in conjunction with conscious sedation for pain relief during TUGOR as the mean abdominal pain scores after giving PCB with 150 mg of lignocaine were significantly reduced by 40 and 50% compared with placebo and no local injection respectively (10). It was postulated that lignocaine used in PCB anaesthetised the peritoneal membrane over the pouch of Douglas or the uterosacral ligaments, which was more painful to stimulation than were ovaries (14). Little information, however, exists in the literature with regard to the optimal dose of lignocaine used in PCB. Various doses of lignocaine have been empirically employed in different studies, including 50 (15), 100 (3), 150 (10) and 200 mg (4, 9).

In the United Kingdom, the maximum recommended dose for lignocaine is 200 mg without adrenaline (16). This recommendation is based on inadequate animal data in 1957, which did not incorporate reliable knowledge of plasma concentrations or pharmacokinetics of the compound in humans (17). In an attempt to find out the most effective dose of lignocaine without toxic effects, we compared in a randomized study the pain levels during TUGOR when 150 and 200 mg of lignocaine was employed in PCB (11). No improvement in pain relief was found in those receiving 200 mg of lignocaine. On the basis of these findings, we hypothesized that the pain arising from the peritoneal membrane over the pouch of Douglas or the uterosacral ligaments might be easily controlled by a lower dose of lignocaine. It remains unknown

whether the use of 50 or 100 mg of lignocaine is as effective as 150 mg of lignocaine.

To our best knowledge, this is the first study addressing the lowest effective dose of lignocaine in PCB for pain relief during TUGOR. Patients in this study had similar pain thresholds as reflected by similar pain levels related to blood taking, transvaginal scanning, insertion of intravenous cannula, and anticipated oocyte retrieval and they were also sedated to a similar extent. We could not demonstrate any difference in vaginal and abdominal pain levels during TUGOR among patients receiving 50, 100, and 150 mg of lignocaine in PCB. Similarly, Wiebe *et al.* (18) in a brief communication did not find any difference in pain levels experienced by women undergoing suction evacuation under local anaesthesia when the dose of lignocaine in PCB was reduced from the standard 200 to 100 mg.

In our previous studies (10, 11), we asked patients 4 h after TUGOR to rate the pain levels during the procedure. Different doses of lignocaine in PCB may have an effect on the pain levels in the postoperative period as its duration of action is about 70–140 min. These postoperative pain levels have not been evaluated in all studies mentioned above. In order to determine the vaginal and abdominal pain levels both during and after TUGOR, patients in this study were asked to rate the pain levels shortly after the procedure and at 4 h after TUGOR. No significant differences were found in the vaginal and abdominal pain levels at 4 h after TUGOR among the three groups. The change in the timing of pain assessment may explain higher median vaginal (22.0–24.0) and abdominal (30.0–32.0) pain levels reported in this study than the corresponding median pain levels (14.0 for vaginal and abdominal pain) reported in a previous study (11).

Although the administration of up to 200 mg of lignocaine appears to be quite safe, the determination of the lowest effective dose of lignocaine in PCB is still important. It is well accepted that patients should not be given higher doses of drugs, which do not provide added therapeutic benefit but may increase the potential complications. Reactions to local anaesthetic agents are the most common cause of deaths arising from first-trimester abortions in the United States and they were dose-related (19). The authors concluded that administration of an appropriate dose of local anaesthetic agents appeared to be the single most important factor in preventing these catastrophic reactions. The other concern is the adverse effects of lignocaine on mouse oocyte fertilization and embryo development (20). Lignocaine has been found in the follicular fluid although the fertilization of the human oocyte or early cleavage of the human embryo were not negatively affected (15, 21). Clinical pregnancy and implantation rates were not impaired as well in patients receiving lignocaine for PCB or placebo (10).

In conclusion, this randomized double-blinded study could not find any difference in the pain levels during the oocyte retrieval and 4 h after the procedure when 50, 100, and 150 mg of lignocaine was used in the PCB. The use of 50 mg of lignocaine is recommended in PCB because of the potential dose-related reactions to the drug and adverse effects on oocytes and embryos in animal studies.

REFERENCES

1. Ditkoff EC, Plumb J, Selick A, Sauer MV: Anesthesia practices in the United States common to in vitro fertilization (IVF) centers. *J Assist Reprod Genet* 1997;14:145–147
2. Trout SW, Vallerand AH, Kemmann E: Conscious sedation for in vitro fertilization. *Fertil Steril* 1998;69:799–808
3. 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
4. Ben-Shlomo I, Amodai I, Levran D, Dor J: Midazolam-fentanyl sedation in conjunction with local anesthesia during oocyte retrieval for in vitro fertilization. *J Assist Reprod Genet* 1992;9:83–85
5. Godoy H, Erard P, De Munck L, Camus M, Gepts E, Van Steirteghem AC, P Devroey: Comparison of two local anaesthetics in transvaginal ultrasound-guided oocyte retrieval. *Hum Reprod* 1993;7:1093–1097
6. Gohar J, Lunenfeld E, Potashnik G, Glezerman M: The use of sedation only during oocyte retrieval for in vitro fertilization: Patients' pain self-assessments versus doctors' evaluations. *J Assist Reprod Genet* 1993;10:476–478
7. Corson SL, Batzer FR, Gocial B, Kelly M, Gutmann JN, Go KJ, English ME: Is paracervical block anesthesia for oocyte retrieval effective? *Fertil Steril* 1994;62:133–136
8. Gonen O, Shulman A, Ghetler Y, Shapiro A, Judeiken R, Beyth Y, Benun I: The impact of different types of anesthesia on in vitro fertilization-embryo transfer treatment outcome. *J Assist Reprod Genet* 1995;12:678–682
9. Soussis I, Boyd O, Paraschos T, Duffy S, Bower S, Troughton P, Lowe J, Grounds R: Follicular fluid levels of midazolam, fentanyl, and alfentanil during transvaginal oocyte retrieval. *Fertil Steril* 1995;64:1003–1007
10. Ng EHY, Tang OS, Chui DKC, Ho PC: A prospective, randomised, double blind and placebo controlled study to assess the efficacy of paracervical block in the pain relief during egg collection. *Hum Reprod* 1999;14:2783–2787
11. Ng EHY, Tang OS, Chui DKC, Ho PC: A comparison of two different doses of lignocaine used in paracervical block during egg collection in an *in-vitro* fertilization programme. *Hum Reprod* 2000;15:2148–2151
12. Ng EHY, Yeung WSB, Lau EYL, So WWK, Ho PC: High serum oestradiol levels in fresh IVF cycles do not impair implantation and pregnancy rates in subsequent FET cycles. *Hum Reprod* 2000;15:250–255
13. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R: Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974;2:656–659
14. Koninckx PR, Renaer M: Pain sensitivity of and pain radiation from the internal female genital organs. *Hum Reprod* 1997;12:1785–1788
15. Wikland M, Evers H, Jakobsson AH: The concentration of lidocaine in follicular fluid when used for paracervical block in a human IVF-ET programme. *Hum Reprod* 1990;5:920–923
16. British Medical Association and the Royal Pharmaceutical Society of Great Britain: British National Formulary. British Medical Association, London, UK, 2000, pp. 573–574
17. Scott DB: Maximum recommended doses of local anaesthetic drugs. *Br J Anaesth* 1989;63:373–374
18. Wiebe ER, Rawling M, Jannsen P: Comparison of 0.5% and 1.0% lidocaine for abortions. *Int J Gynecol Obstet* 1996;55:71–72
19. Grimes DA and Cates W Jr: Deaths from paracervical anesthesia used for first-trimester abortion, 1972–1975. *N Engl J Med* 1976;295:1397–1399
20. Schnell VL, Sacco AG, Savoy-Moore RT, Ataya KM, Moghissi KS: Effects of oocyte exposure to local anesthetics on in vitro fertilization and embryo development in the mouse. *Reprod Toxicol* 1992;6:323–327
21. Bailey-Pridham DD, Reshef E, Drury K, Cook CL, Hurst HE, Yussman MA: Follicular fluid lidocaine levels during transvaginal oocyte retrieval. *Fertil Steril* 1990;53:171–173