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

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The role of paracervical block in the pain relief during egg collection in in-vitro fertilization (IVF) is still not confirmed. In this prospective, double-blind and placebo-controlled study, 135 patients undergoing egg collection in their first IVF cycle were randomized to receive 10 ml of 1.5% lignocaine (group A) or normal saline (group B) in the paracervical block and no local injection (group C). No differences were seen among the groups in the demographic data, the ovarian response, the duration of egg collection, the number of follicles punctured, the pregnancy rates and the pain levels related to blood taking, scanning and insertion of an i.v. cannula. All patients experienced similar pain scores for vaginal puncture but patients in group A experienced significantly less abdominal pain during egg collection, compared with those in group B and group C (P = 0.009 and P = 0.001 respectively; Mann–Whitney U-test). When lignocaine was used, the abdominal pain scores were reduced by 38.9 and 51.4% compared with placebo and no local injection respectively. We recommend that paracervical block with lignocaine should be used in conjunction with i.v. sedation/analgesia during egg collection performed through the transvaginal route under ultrasound guidance (TUGOR) to reduce the pain of the procedure.

Key words: embryo transfer/IVF/lignocaine/pain relief/paracervical block

Introduction

In-vitro fertilization (IVF) with embryo transfer is a well established treatment for various causes of infertility. It involves ovarian stimulation to induce development of multiple follicles, egg collection and embryo transfer after fertilization. In the majority of IVF units, egg collection is performed through the transvaginal route under ultrasound guidance (TUGOR). During TUGOR, the needle has to pass through the vaginal wall in order to puncture the follicles in the ovary. The procedures are generally short, lasting about 20–30 min, but can still be painful without adequate anaesthesia or analgesia.

Conscious sedation is the most widely used method for the pain relief during TUGOR (Trout et al., 1998). Paracervical block has been used in some IVF units (Hammarberg et al., 1987; Ben-Shlomo et al., 1992; Godoy et al., 1993; Gohar et al., 1993; Gonen et al., 1995) to improve pain relief during oocyte retrieval. Its role in pain relief during TUGOR is, however, still not confirmed and there are very few studies in the literature addressing this issue. The aim of this prospective, randomized, double-blind and placebo-controlled clinical study was to assess the efficacy of paracervical block in pain relief during TUGOR in IVF cycles.

Materials and methods

Infertile patients attending the Assisted Reproduction Unit at Department of Obstetrics & Gynaecology, Queen Mary Hospital, Hong Kong, for IVF/embryo transfer treatment were recruited for study. Every patient gave a written informed consent prior to participating in the study, which was approved by the Ethics Committee, Faculty of Medicine, University of Hong Kong. Criteria for inclusion were: (i) the first IVF cycle proceeding to TUGOR; (ii) the presence of follicles in both ovaries and (iii) body mass index ≤30. Only patients undergoing the first cycle were chosen because pain scores during egg collection may be influenced by previous experience. Gohar et al. (1993) found that the second cycle was less painful than the first one.

Exclusion criteria included: (i) IVF cycles converted from ovulation induction or intrauterine insemination cycles because of excessive ovarian responses; (ii) general anaesthesia requested by patients; (iii) fewer than three dominant follicles present; (iv) the presence of dominant follicles in one ovary only and (v) any history of drug sensitivity to lignocaine.

The details of ovarian stimulation regimen used at our centre had been previously published (Ng et al., 1997). They followed the long protocol of ovarian stimulation regimen and a maximum of three normally cleaved embryos were replaced into the uterine cavity 48 h after the egg collection.

Counselling of patients

All patients had gone through a three-step counselling procedure prior to TUGOR: firstly, before they were enrolled into IVF treatment, they attended a group information session organized by a dedicated nurse and supported by video-tapes; secondly, 2–3 months prior to their first IVF cycle, they were invited to a counselling session and to become familiar with the facilities of the centre such as the minor operating theatre and the embryo laboratory; and thirdly they were all counselled individually about the procedure and possible risks of TUGOR by a medical doctor on the day of the human chorionic gonadotrophin (HCG) injection.

TUGOR and paracervical block

Patients were admitted into hospital early in the morning and an i.v. cannula was inserted in a convenient location in the forearm. Routine prophylactic antibiotics, 1 g ampicillin (Bristol-Meyers Squibb, New Jersey, USA) and 0.5 g metronidazole (McGaw Inc, Irvine, CA, USA) and prophylactic metronidazole (McGaw Inc, Irvine, CA, USA) and prophylactic metronidazole (McGaw Inc, Irvine, CA, USA) and prophylactic metronidazole (McGaw Inc, Irvine, CA,
USA), were given i.v. 1 h prior to TUGOR. All patients were pre-medicated with 50 mg pethidine (Antigen Pharmaceuticals Ltd., Roscrea, Ireland) and 25 mg promethazine (Phenergan®; M&B, Essex, UK) given i.m. 30 min prior to the retrieval. 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 three groups according to a computer-generated list of random numbers: group A = paracervical block with 1.5% lignocaine; group B = paracervical block with normal saline (0.9%); and group C = no local injection given.

Both the patient and the doctor carrying out the procedure were blind to the placebo and active agents because the drugs were prepared and randomized by the pharmacy. The codes were broken only after the completion of the study. The nurse assisting TUGOR was not involved in the recruitment criteria and 10 (6.0%) patients declined the invitation. Women had a mean age of 33.1 ± 2.8 years and a mean body mass index (BMI) (kg/m²) of 21.0 ± 2.6 kg/m². The mean duration of infertility was 4.8 ± 2.2 years and 80% had primary infertility. The causes of infertility were tuboperitoneal factors in 36 (26.7%) patients; male factors in 69 (51.1%) patients; endometriosis in 12 (8.9%) patients; unexplained in 15 (11.1%) patients and mixed in three (2.2%) patients.

Assessment of pain level

The pain levels were assessed by means of a 100 mm linear visual analogue scale (0 = none to 100 = intolerable). Prior to TUGOR, patients were asked by another nurse (not involved in the TUGOR procedure) to give pain levels related to blood taking, transvaginal scanning, the insertion of an i.v. cannula and the expected pain level during TUGOR. The doctor, upon completing the retrieval, gave the vaginal and abdominal pain scores independently. The maximum levels of vaginal and abdominal pain during TUGOR were rated by patients within 4 h after TUGOR. Patients were usually discharged from the hospital 4 h after TUGOR when the vital signs were stable. 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

Bhattacharya et al. (1997) reported that the pain level scored on a visual scale of 100 points during TUGOR after the use of i.v. sedation/analgeisa was 46.1 ± 21.3 (mean ± SD). Assuming that a 30% reduction of pain level from 46.1 to 32.3 was acceptable after paracervical block of lignocaine, the sample size required would be 45 in each arm of therapy to give a test of significance of 0.05 and a power of 0.8 (Sigmastat, Jandel Scientific, CA, USA). The primary measures of the outcome were levels of vaginal pain and abdominal pain scored by patients in different groups. Demographic data, data on the ovarian responses and the duration of TUGOR were also compared. Results were expressed as mean ± SD. Statistical tests were carried out by one-way analysis of variance (ANOVA) with multiple comparisons (Tukey HSD) for continuous data and χ² test for categorical data, where appropriate. Kruskal–Wallis test and Mann–Whitney U-test were applied for continuous data with unequal variance. Correlations were assessed by the Pearson method. P value (two-tailed) of < 0.05 was taken as significant.

Results

A total of 135 (81.3%) patients were recruited from 166 patients undergoing the first attempt of TUGOR between early July 1998 and mid February 1999. In all, 21 (12.7%) patients were excluded from the study because they did not fulfill the recruitment criteria and 10 (6.0%) patients declined the invitation. Women had a mean age of 33.1 ± 2.8 years and had a mean body mass index of 21.0 ± 2.6 kg/m². The mean duration of infertility was 4.8 ± 2.2 years and 80% had primary infertility. The causes of infertility were tubopelvic factors in 36 (26.7%) patients; male factors in 69 (51.1%) patients; endometriosis in 12 (8.9%) patients; unexplained in 15 (11.1%) patients and mixed in three (2.2%) patients. Conventional IVF was performed in 86 cycles whereas intracytoplasmic sperm injection (ICSI) was used in the remaining 49 cycles; microoepididymal sperm aspiration (MESA) or testicular sperm extraction (TESE) was used to obtain sperms in 24 of the latter group. The standard dosage of sedation/analgesia (5 mg valium/25 mg pethidine) was adequate in most cases, except one patient in group C who requested a repeated dose because of severe pain. Thirty-one patients were found to be pregnant: one biochemical pregnancy; two clinical abortions and 28 on-going pregnancies. The pregnancy and on-going pregnancy rates per retrieval cycle were 31/135 (23.0%) and 28/135 (20.7%) respectively. The multiple pregnancy rate was 14/31 (45.2%) with two sacs in 11 (35.5%) patients and three sacs in three (9.7%) patients.

The vaginal and abdominal pain levels during TUGOR scored by patients in group C, i.e. those who received i.v.
Table II. Comparison of ovarian stimulation and pregnancy. Values are mean with SD shown in parentheses

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUGOR duration (min)</td>
<td>16.1 (6.4)</td>
<td>15.2 (5.0)</td>
<td>15.9 (7.4)</td>
<td>0.790</td>
</tr>
<tr>
<td>No. of follicles punctured</td>
<td>18.2 (9.9)</td>
<td>15.7 (7.5)</td>
<td>18.6 (11.3)</td>
<td>0.310</td>
</tr>
<tr>
<td>No. of oocytes obtained</td>
<td>12.2</td>
<td>10.0 (5.4)</td>
<td>13.2 (9.5)</td>
<td>0.125</td>
</tr>
<tr>
<td>Retrieval rate (%)</td>
<td>67.4 (18.6)</td>
<td>66.6 (22.3)</td>
<td>71.2 (22.7)</td>
<td>0.546</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>64.0 (25.9)</td>
<td>57.5 (29.0)</td>
<td>60.3 (27.3)</td>
<td>0.527</td>
</tr>
<tr>
<td>No. of pregnancies(^a)</td>
<td>13</td>
<td>11</td>
<td>7</td>
<td>0.319(^b)</td>
</tr>
<tr>
<td>No. of multiple pregnancies(^a)</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>0.555(^b)</td>
</tr>
<tr>
<td>Implantation rate(^a)</td>
<td>20/98 (20.4%)</td>
<td>14/101 (13.9%)</td>
<td>13/96 (13.5%)</td>
<td>0.457(^b)</td>
</tr>
<tr>
<td>No. of on-going pregnancies(^a)</td>
<td>12</td>
<td>10</td>
<td>6</td>
<td>0.517(^2)</td>
</tr>
</tbody>
</table>

Egg collection performed through the transvaginal route under ultrasound guidance (TUGOR) for treatment; see Table I for treatment given to each group. ANOVA = analysis of variance.

\(^a\)No. of patients.

\(^b\)Mann-Whitney U-test.

Table III. Comparison of various pain levels scored by patient. Values are mean with SD shown in parentheses

<table>
<thead>
<tr>
<th>Pain levels</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before TUGOR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood taking</td>
<td>17.7 (17.8)</td>
<td>18.2 (17.9)</td>
<td>22.8 (18.3)</td>
<td>0.335</td>
</tr>
<tr>
<td>Transvaginal scanning</td>
<td>16.0 (16.9)</td>
<td>16.2 (18.5)</td>
<td>21.4 (19.9)</td>
<td>0.301</td>
</tr>
<tr>
<td>Insertion of i.v. cannula</td>
<td>29.9 (24.5)</td>
<td>28.1 (25.0)</td>
<td>34.4 (27.0)</td>
<td>0.489</td>
</tr>
<tr>
<td>Egg collection</td>
<td>61.3 (25.4)</td>
<td>58.9 (23.2)</td>
<td>64.4 (30.0)</td>
<td>0.615</td>
</tr>
<tr>
<td>After TUGOR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal punctures</td>
<td>24.1 (25.0)</td>
<td>27.1 (23.4)</td>
<td>33.5 (29.0)</td>
<td>0.221</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21.2 (23.1)</td>
<td>34.7 (26.3)</td>
<td>43.7 (32.0)</td>
<td>0.001(^a,b)</td>
</tr>
<tr>
<td>Before embryo transfer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal pain</td>
<td>11.2 (21.3)</td>
<td>6.5 (13.8)</td>
<td>11.6 (18.5)</td>
<td>0.374(^a)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>38.3 (27.3)</td>
<td>32.8 (26.9)</td>
<td>36.5 (29.6)</td>
<td>0.655</td>
</tr>
<tr>
<td>After embryo transfer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal transfer procedure</td>
<td>15.3 (15.3)</td>
<td>20.7 (23.8)</td>
<td>21.0 (22.9)</td>
<td>0.452</td>
</tr>
</tbody>
</table>

ANOVA = analysis of variance; TUGOR = transvaginal route under ultrasound guidance.

\(^a\)Kruskal-Wallis test.

\(^b\)Statistically significant.

sedation/analgesia only, were 33.5 ± 29.0 and 43.7 ± 32.0 respectively. No differences were observed among the groups in age, body mass index, the causes of infertility, the duration of TUGOR, the number of follicles aspirated, the retrieval rate and the fertilization rate (Tables I and II). Patients in different groups had similar pain levels related to blood taking, transvaginal scanning, insertion of an i.v. cannula and expected pain levels during TUGOR (Table III). The pain levels for vaginal puncture were also similar but patients in group A experienced significantly less abdominal pain during TUGOR compared with those in groups B and C (P = 0.001, Kruskal–Wallis test). Significant differences were only found between groups A and B and between groups A and C (P = 0.009 and P = 0.001 respectively, Mann–Whitney U-test). There was no difference between groups B and C (P = 0.185, Mann–Whitney U-test). Similar results were also observed in patients’ abdominal pain scored by surgeons (Table IV).

The levels of abdominal pain during TUGOR by patient’s assessment were significantly correlated with body mass index, number of follicles punctured, the duration of TUGOR, as well as the pain threshold which was reflected by the pain scores related to blood taking, transvaginal scanning, insertion of an i.v. cannula and the expected pain levels during TUGOR (Table V). There were also significant correlations between the levels of vaginal pain (r = 0.288) and between the levels of abdominal pain (r = 0.428) assessed by patient and surgeon.

Discussion

TUGOR may be the most painful component of IVF treatment but has attracted very limited attention in the literature. The
the majority of patients (90%) experienced very little pain or underwent the egg collection with paracervical block only and the pain levels during egg collection. There are, however, very pain to be >5 and the mean pain score was 4.7 on a scale of maturity of oocytes and the fertilization/cleavage rate (Hayes et al.).

Patients are not left with unpleasant memories about the pregnancy or live birth is achieved. Therefore, it is preferable that patients are not left with unpleasant memories about the procedure. Furthermore, patients may not remain stationary during TUGOR when they are in pain and this can lead to an increased risk of injuries or damage to the surrounding blood vessels and bowel. It may also explain poor recovery of oocytes in some patients.

The optimal anaesthetic method should provide rapid onset of anaesthesia with adequate anaesthesia during the procedure, followed by a rapid recovery. The methods include general anaesthesia and i.v. sedation with or without local anaesthesia. There is also concern that general anaesthesia may reduce the maturity of oocytes and the fertilization/cleavage rate (Hayes et al., 1987), leading to an adverse effect on IVF outcome (Gonen et al., 1995). The most widely used method is conscious i.v. sedation/analgesia (Trout et al., 1998). General anaesthesia is not routinely used in our centre because of the above-mentioned possible impairment of fertilization/pregnancy rates and the implications of cost.

In this study, the average score of abdominal pain during TUGOR was 43.7 when only i.v. sedation/analgesia was given (group C). This finding is comparable to the results of other studies (Gohar et al., 1993; Bhattacharya et al., 1997) using sedation/analgesia only. About 50% of patients estimated their pain to be >5 and the mean pain score was 4.7 on a scale of 1–10 (Gohar et al., 1993). Bhattacharya et al. (1997) found that the mean pain score was 46.1 on a 100 mm linear analogue scale when patients were given i.v. sedation/analgesia only. These findings suggest that the use of i.v. sedation/analgesia only does not provide adequate pain relief to patients during TUGOR.

Paracervical block has been used in some IVF units (Hammarberg et al., 1987; Ben-Shlomo et al., 1992; Godoy et al., 1993; Gohar et al., 1993; Gonen et al., 1995) to reduce the pain levels during egg collection. There are, however, very few studies in the literature addressing this issue. Hammarberg et al. (1987) reported that 70% of patients after pre-medication underwent the egg collection with paracervical block only and the majority of patients (90%) experienced very little pain or no pain at all during the procedure. In a recent prospective, randomized, double-blind and placebo-controlled trial (Corson et al., 1994), it was demonstrated that both vaginal and global pain scores were significantly lower for paracervical block than placebo. When compared with no injection, a trend of lower global pain was observed in the paracervical block but it did not reach statistical significance. A larger sample size may be required to show a statistically significant difference.

Despite similar pain scores for vaginal puncture in different groups, patients in group A experienced a significantly lower abdominal pain score, compared with groups B and C. Significant differences were only found between groups A and B and between groups A and C. There was no difference between groups B and C in abdominal pain levels. When paracervical block was used, the reduction in abdominal pain scores was 38.9 and 51.4% compared with placebo and no local injection respectively. This reduction in pain was not only observed in pain levels scored by patients but also in those scored by surgeons.

The results of this study were different from that of Corson et al. (Corson et al., 1994). In the present study, there was a trend of less pain for vaginal puncture when lignocaine was used in paracervical block although the difference did not reach statistical significance. The upper part of the vagina is remarkably insensitive to ordinary stimuli and the insensitivity is explained by the fact that the upper part of the vagina is supplied by autonomic and not somatic nerves (Tindall, 1987). This insensitivity is also reflected by the finding that transvaginal single follicle aspiration during natural cycle IVF can be performed without analgesia (Ramsewak et al., 1990).

The design of our study differed from that of Corson et al. (1994). Only patients with the presence of mature follicles in both sides undergoing the first attempt of TUGOR were recruited and pre-medication was given in all patients in our study. Bupivacaine 0.25% was used as the local anaesthetic agent in the Corson et al. study (Corson et al., 1994), whereas we used 1.5% lignocaine. These may explain the different results obtained.

The localization of pain is usually vague. Therefore, there was no attempt to ask patients to differentiate the pain over different sides. The levels of abdominal pain during TUGOR were significantly correlated with the body mass index, the duration of TUGOR and the number of follicles punctured and the pain thresholds although the correlation coefficients were low (Table V). The pain levels during TUGOR may be affected by a number of factors such as patients’ characteristics, operator’s skill and the techniques of TUGOR. Patients’ characteristics included the pain threshold, the level of anxiety, the position and the mobility of ovaries, and the number of follicles punctured.

Patients in this study could be assumed to have similar pain thresholds as reflected by similar pain levels related to blood taking, transvaginal scanning and insertion of cannula in all three groups. Despite extensive counselling in our programme, patients still expected significant pain associated with TUGOR as the average anticipatory pain score during TUGOR was 60. It would be interesting to explore the effects of different ways of reducing anxiety such as the use of music prior to TUGOR.
on pain relief. TUGOR will be more painful when the ovaries are very mobile or fixed by adhesion or when they are stuck at unfavourable sites such as the pouch of Douglas behind the uterus or on top of the uterus. These variables were not routinely recorded in the operation record.

TUGOR was performed on rotation by one of the three surgeons (E.H.Y.N., O.S.T. and D.K.C.C.) with similar skill and experience. The retrieval rates were comparable, being 69.1, 64.3 and 70.1% respectively over the past year. The omission of follicular flushing (Tan et al., 1992) and use of a smaller-sized aspiration needle for TUGOR (Awonuga et al., 1996) were associated with less pain during egg collection.

Paracervical block was first described in 1926 (Gellert, 1926) and then later (Kobak and Sadove, 1961). The block has been used for labour pain during vaginal delivery, ablation of the cervical transformation zone (Johnson et al., 1989), dilatation of the cervix and uterine curettage in therapeutic abortions (Wiebe, 1992) and hysteroscopy (Vercellini et al., 1994). It is postulated from the results of this study that lignocaine used in paracervical block anesthetized both the vaginal mucosa and the peritoneal membrane over the pouch of Douglas or the uterosacral ligaments. This can reduce the levels of abdominal pain during TUGOR. Pain intensity was shown to be significantly higher during laparoscopy under local anaesthesia when the pouch of Douglas or uterosacral ligaments werestimulated than following stimulation of uterus, oviducts or ovaries (Kominckx and Ramaekers, 1997). The ovaries were, in fact, the least sensitive among the parts stimulated.

Both the vaginal and abdominal pain levels on the day of embryo transfer were not different and this can be accounted for by the short half-life of lignocaine used. An increase in abdominal pain may be due to some blood in the peritoneal cavity or the effects of high serum oestradiol concentration in some women. Lignocaine has been found in the follicular fluid but it appears that the concentration in the follicular fluid after 50 mg lignocaine does not negatively affect fertilization of the human oocyte or early cleavage of the human embryo (Wikland et al., 1990). The fertilization, implantation and pregnancy rates in this study were similar in all groups. Although a maximum of three good-quality embryos were allowed for transfer in our programme, the multiple pregnancy rate remained high. This also suggests that implantation is unlikely to be affected by lignocaine used in paracervical block.

In conclusion, our study showed that the use of paracervical block significantly reduced the abdominal pain during TUGOR compared with placebo and no local injection although the pain levels for vaginal puncture were not statistically different. The fertilization, implantation and pregnancy rates appeared unaffected when 10 ml of 1.5% lignocaine was employed. It is recommended that paracervical block with lignocaine should be used in conjunction with I.V. sedation/analgesia during TUGOR to reduce the pain of the procedure.

References


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Use of paracervical block for pain relief during egg collection