**Lidocaine vaginal gel versus lidocaine paracervical block for analgesia during oocyte retrieval**

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**BACKGROUND:** Evidence from randomized trials suggests that pain relief during oocyte retrieval is superior when adjunctive paracervical block is used in addition to sedation alone. Vaginal application of lidocaine gel is a non-invasive alternative to lidocaine paracervical block. The goal of the present trial was to compare analgesia with lidocaine vaginal gel versus lidocaine paracervical block. **METHODS:** A parallel-group randomized trial of adjunctive lidocaine vaginal gel versus adjunctive lidocaine paracervical block (with sedation for both groups) was performed in participants undergoing oocyte retrieval. Measured outcomes were subjective pain experiences. Subjects provided self-reported ratings of pain and anxiety. Visual analogue scales were used to measure pain during different procedural stages. The McGill Pain Questionnaire was used to measure pain character and the total pain experience. **RESULTS:** During application of lidocaine, pain ratings were less for vaginal gel than paracervical block. In contrast, during insertion of the aspiration needle and aspiration of follicles, pain ratings were greater for lidocaine vaginal gel. Total pain experience was greater with lidocaine vaginal gel. **CONCLUSIONS:** Subjective measures of pain intensity and the total pain experience were greater with lidocaine vaginal gel compared with lidocaine paracervical block.

**Key words:** analgesia/lidocaine/oocyte retrieval/pain/sedation

**Introduction**

Sedation is the technique most often used for pain relief during oocyte retrieval in the UK and the USA (Ditkoff et al., 1997; Bokhari and Pollard, 1999). Evidence from randomized, controlled trials suggests that pain relief is superior when adjunctive paracervical block is used in addition to sedation alone (Corson et al., 1994; Ng et al., 1999). Although paracervical block is the most commonly used form of regional anaesthesia for oocyte retrieval in the UK, most centres using sedation do so without adjunctive regional anaesthesia (Bokhari and Pollard, 1999).

Barriers to use of adjunctive paracervical block are the invasive nature of administration of the block (compared with administration of lidocaine vaginal gel) and potential toxicity of absorbed lidocaine. An alternative form of adjunctive therapy is lidocaine vaginal gel, a minimally invasive administration with potential for lower reproductive toxicity.

In a preliminary randomized trial, there was a trend to lower follicular fluid lidocaine concentration with lidocaine as vaginal gel compared with paracervical block (Weeraklet et al., 1999). During paracervical block, some follicles may be exposed to high levels of lidocaine, possibly due to passage of the aspiration needle through lidocaine-infiltrated tissue. Follicular fluid lidocaine concentrations were as high as 118 μg/ml after paracervical block with 100 mg of lidocaine (Bailey-Pridham et al., 1990). Follicular fluid lidocaine concentrations as low as 1.0 μg/ml were associated with toxic effects on fertilization and embryo development in the murine model (Schnell et al., 1992). In human use, however, there is no evidence of adverse events associated with lidocaine paracervical block. Mean follicular fluid lidocaine concentration was 0.36 μg/ml after paracervical block with 50 mg of lidocaine (Wikland et al., 1990). Comparison of cohorts with and without paracervical block showed no adverse effects on fertilization, cleavage or pregnancy rates (Wikland et al., 1990).

Randomized trials of lidocaine gel in contexts other than assisted reproduction have produced results more generally
non-beneficial than beneficial. In gynaecological trials, application of intrauterine lidocaine gel showed no difference from placebo when used during endometrial aspiration (Kozman et al., 2001). In contrast, perineal application of 2% lidocaine gel was associated with a modest decrease in post-partum pain (Collins et al., 1994). In urological trials, intra-urethral or transrectal administration of lidocaine gel failed to show therapeutic benefit (Chang et al., 2001; McFarlane et al., 2001).

The purpose of the present trial was to compare the analgesic efficacy of two forms of adjunctive treatment to sedation for oocyte retrieval: lidocaine vaginal gel versus lidocaine paracervical block.

Materials and methods

Protocol
This parallel-group randomized trial was performed at London Health Sciences Centre, University Campus (formerly University Hospital) in London, Ontario, Canada between April 1997 and February 1998. The protocol was reviewed and approved by the Review Board for Health Sciences Research Involving Human Subjects of The University of Western Ontario, number 5737.

Sample size estimation was based on evidence from a previous randomized trial of lidocaine paracervical block (Corson et al., 1994) in which the authors used a pain score scale from 0 to 4. A pain score difference of 0.5 on the scale from 0 to 4 was considered relevant. Standard assumptions were \( \alpha = 0.05 \) and power = 0.8. A sample of 65 in each group was calculated to be needed for the present trial (Cohen, 1988).

Visual analogue scales for pain intensity are usually measured with a range from 0 to 10 and this range was chosen for the trial (Von Korff et al., 2000).

During the study interval, there were 331 patients who had oocyte retrieval. Superovulation patients converted to IVF (Nisker et al., 1994) \( (n = 91) \), as well as those who were allergic to lidocaine, were excluded. Patients undergoing primary treatment with IVF were asked to consider participation in the trial \( (n = 240) \) before starting treatment. A total of 150 participants gave consent (Figure 1).

Assignment
After giving written consent, treatment allocation was generated by an investigator (C.L.) using a random number table. There was no stratification and the sequence was not concealed. Treatment
assignment was made by the same investigator who then concealed the assignment in numbered, opaque, sealed envelopes. Enrolment and obtaining consent from participants was performed by staff nurses.

Masking
There was no masking. Participants were aware of their treatment assignment. The treating physician, who delivered the intervention with either vaginal gel or paracervical block, was also aware of treatment assignment.

Self-assessment of pain
Although other trials have employed physician assessment of pain, it was elected to confine outcomes to self-assessment. Patients undergoing fertility treatment may be highly motivated and reluctant to show their emotions. In an observational study, mean pain scores were lower with a physician observer assessment compared with self-assessment (Gohar et al., 1993).

Table I. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Paracervical block (n = 88)</th>
<th>Vaginal gel (n = 62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.9 ± 3.5</td>
<td>33.9 ± 4.2</td>
<td>0.99</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(32.8–34.9)</td>
<td>(33.1–34.6)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.9 ± 13.0</td>
<td>70.3 ± 13.2</td>
<td>0.51</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(66.0–73.6)</td>
<td>(66.1–71.6)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>25.1 ± 4.1</td>
<td>25.9 ± 4.1</td>
<td>0.27</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(25.8–26.9)</td>
<td>(25.2–26.0)</td>
<td></td>
</tr>
<tr>
<td>Previous cycles</td>
<td>0.97 ± 1.4</td>
<td>1.08 ± 1.4</td>
<td>0.61</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.7–1.4)</td>
<td>(0.7–1.3)</td>
<td></td>
</tr>
<tr>
<td>Aspiration needle insertions (95% CI)</td>
<td>2.50 ± 0.9</td>
<td>2.69 ± 1.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Oocytes retrieved (95% CI)</td>
<td>10.6 ± 4.9</td>
<td>11.4 ± 5.9</td>
<td>0.62</td>
</tr>
<tr>
<td>Duration retrieval (min) (95% CI)</td>
<td>13.8 ± 0.02</td>
<td>13.7 ± 0.01</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD.

Ratings of anxiety and pain before oocyte retrieval
Before oocyte retrieval, participants completed ratings indicating: current anxiety, degree of worry about oocyte retrieval and level of pain anticipated, on visual analogue scales that ranged from 0 to 10. For anxiety and worry, scale end-points ranged from 0 ‘not at all worried’ to 10 ‘extremely worried’. For anticipated pain, end-points ranged from 0 ‘no pain’ to 10 ‘pain as bad as it could be’.

Ratings of anxiety and pain after oocyte retrieval
After oocyte retrieval, participants rated pain during administration of lidocaine, pain during needle puncture of the vaginal wall, pain during oocyte aspiration and anxiety generally during oocyte retrieval.

Subjects were also asked to characterize the entire experience of oocyte retrieval by completing the McGill Pain Questionnaire, a standardized self-reported measure of subjective pain experience (Melzack, 1975). The questionnaire measures different aspects of the pain experience. Subjects chose words describing sensory and affective qualities of pain as well as evaluative words describing overall pain intensity. A pain rating index is calculated based on the rank value of words chosen from each category (Melzack, 1975). The pain rating index and total number of words chosen provide two measures of total pain experience. Ranks of each chosen word are added in each category and total score of all chosen words ranked. Total pain score is calculated by adding together ranks for all words chosen on the questionnaire. There is a supplementary category of words with four groupings that patients can choose from with words such as penetrating or piercing. Total pain score, therefore, may be greater than the sum of sensory, affective and evaluative scores if supplementary words are chosen.

Ovarian stimulation
A long luteal protocol for ovarian stimulation was used as previously described (Tummon et al., 1995). Gonadotrophin dosage was chosen individually, taking into account age, body mass index (BMI), basal FSH and previous response. Ovarian response was monitored with serum estradiol and transvaginal ultrasound. Ovulation was triggered using 10 000 IU of HCG. Transvaginal oocyte retrieval was done under ultrasound guidance with a single lumen aspiration needle (Swemed Lab, distributed by Scan-Med, Middle Grove, NY).

Lidocaine vaginal gel
For participants randomized to gel, lidocaine 80 mg was used (4 ml of 2% lidocaine gel, AstraZeneca Canada Inc., Mississauga, Ontario, Canada) inserted into the posterior vaginal fornix using an applicator 30 min before oocyte retrieval.

Paracervical lidocaine block
For participants randomized to paracervical block, lidocaine 75 mg was used (15 ml of 2% lidocaine, AstraZeneca Canada Inc., Mississauga, Ontario, Canada) injected at the 4 and 8 o’clock positions using a 21 gauge spinal needle, just before oocyte retrieval.

Sedative anaesthesia
All participants received i.v. fentanyl (Janssen-Ortho, Don Mills, Ontario, Canada) according to body weight. Subjects weighing 50–60 kg received 50 μg of fentanyl, participants weighing from 60 to 70 kg received 75 μg of fentanyl, while participants weighing >70 kg received 100 μg of fentanyl. No additional sedation was given to either intervention group.

Data analysis
Data were managed and analysed with Medcalc 7.2.0.2 (Mariakerke, Belgium). Means were compared using independent t-tests (Klugh, 1974). Analysis was by intention-to-treat. Multiple regression was used to examine whether independent variables of age, BMI, cycle, number of punctures, number of oocytes, physician operator or intervention group were related to total pain.

Results

Participant flow and follow-up (Figure 1)
A total of 150 participants registered for the trial and all were randomized. Sixty-two participants were allocated to receive intervention with lidocaine vaginal gel and 88 were allocated to receive intervention with lidocaine paracervical block. All participants received the interventions as allocated. No subject in either group withdrew from care or was lost to follow-up. All 150 participants completed the trial. Subjective pain experience records (the McGill Pain Questionnaire) were incomplete for one of the 62 participants in the lidocaine vaginal gel group and two of the 88 participants in the paracervical lidocaine block group. Demographic and clinical features of groups were similar, as shown in Table I.
Table II. Anxiety, worry and anticipated pain (0 to 10 scale)

<table>
<thead>
<tr>
<th>Anxiety parameter</th>
<th>Vaginal gel (n = 62)</th>
<th>Paracervical block (n = 88)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety before procedure</td>
<td>6.2 ± 4.2 (5.1–7.1)</td>
<td>7.0 ± 3.8 (6.2–7.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>Degree of worry about procedure</td>
<td>7.1 ± 4.4 (5.9–8.2)</td>
<td>7.3 ± 4.4 (6.3–8.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Pain anticipated before procedure</td>
<td>8.4 ± 3.1 (7.6–9.2)</td>
<td>7.6 ± 3.8 (6.8–8.4)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD.

Table III. Pain ratings during stages of procedures (0 to 10 scale)

<table>
<thead>
<tr>
<th>Pain parameter</th>
<th>Vaginal gel (n = 62)</th>
<th>Paracervical block (n = 88)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during application of lidocaine</td>
<td>1.2 ± 2.7 (0.6–1.9)</td>
<td>4.5 ± 3.5 (3.8–5.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>(as vaginal gel or paracervical block)</td>
<td></td>
<td></td>
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<tr>
<td>Pain when aspiration needle inserted</td>
<td>7.8 ± 4.6 (6.6–9.0)</td>
<td>5.8 ± 3.8 (5.1–6.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>through vaginal wall</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pain during aspiration of follicles</td>
<td>7.3 ± 4.5 (6.1–8.4)</td>
<td>4.7 ± 3.9 (3.9–5.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety during procedure</td>
<td>6.2 ± 4.4 (5.0–7.4)</td>
<td>5.8 ± 4.8 (4.9–6.8)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD.

Anxiety and pain ratings before procedures

Before oocyte retrieval, there were no differences in anxiety, worry or anticipated pain between intervention groups, as shown in Table II.

Pain and anxiety ratings during procedures

Pain during application of lidocaine as vaginal gel was less than administration of lidocaine as paracervical block (P = 0.001), as shown in Table III. In contrast, pain was greater with lidocaine vaginal gel compared with lidocaine paracervical block when the aspiration needle was inserted through the vaginal wall (P = 0.01). Pain was also greater with lidocaine vaginal gel compared with lidocaine paracervical block during follicular aspiration (P = 0.001). There was no difference in anxiety during procedures between intervention groups.

Subjective pain experience

Sensory qualities of pain, in terms of types of sensations experienced, such as time, space or pressure, were similar between groups. Affective qualities of pain experienced, in terms of tension or fear, were also similar between intervention groups. Intervention groups did not differ in number of words chosen. Evaluative qualities of pain and total pain experienced were greater with lidocaine vaginal gel compared with paracervical block, as shown in Table IV.

Other factors influencing pain

With total pain score as the outcome measure, factors other than adjunctive anaesthesia influenced outcome. Factors positively correlated with total pain were BMI (P = 0.001) and cycles (P = 0.01). Age was negatively correlated with total pain (P = 0.001). Factors unassociated with total pain were number of punctures, number of oocytes retrieved and the physician performing the procedure.

Adverse events

No important adverse events were observed in either intervention group.

Discussion

The goal of the present trial was to compare analgesia with lidocaine vaginal gel versus lidocaine paracervical block during oocyte retrieval. Intervention groups were similar in demographic characteristics, anxiety before treatment, pain anticipated before treatment, and anxiety during treatment. Intervention groups were different, however, in how they rated pain.

Subjects using lidocaine vaginal gel reported less pain with application of lidocaine and greater pain during insertion of the aspiration needle and follicular aspiration. Sensory and affective pain qualities were similar between intervention groups, but evaluative qualities of pain were greater with vaginal lidocaine gel compared with paracervical lidocaine block.

Participants using lidocaine vaginal gel also reported overall higher pain intensity and greater total pain experience. Apparently, the lesser degree of pain experienced during application of vaginal lidocaine gel did not compensate for the greater pain experienced during insertion of the aspiration needle and follicle aspiration.

A novel finding from the present trial was differentiation of pain between intervention groups at specific steps during oocyte retrieval. Outcome measures in previous trials did not differentiate between vaginal pain from administration of the paracervical block and insertion of the aspiration needle through the vaginal wall (Corson et al., 1994; Ng et al., 1999). On a note of caution, in the present trial, participants were asked to differentiate pain in a retrospective fashion. While the extent to which this distinction could be made reliably is unknown, there is no clear reason why recall should favour one treatment condition over another.
Factors other than adjunctive therapies also influenced the total pain experience in the present trial. Factors positively associated with increased total pain experience were younger age, higher BMI and a greater number of treatment cycles.

Generalizability
The external validity of the present trial is derived from wide general use of the techniques used. Sedation is the most common form of anaesthesia for oocyte retrieval in both the USA and the UK (Ditkoff et al., 1997; Bokhari and Pollard, 1999). In the UK, paracervical block is the most common regional technique used as adjunctive therapy to sedation (Bokhari and Pollard, 1999).

General interpretation
In the present trial, total pain experienced was greater with lidocaine vaginal gel compared with lidocaine paracervical block.

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References
Ng EH, Tang OS, Chui DK and Ho PC (1999) 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 14,2783–2787.

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