A prospective randomized trial comparing patient-controlled sedation using propofol and alfentanil and physician-administered sedation using diazepam and pethidine during transvaginal ultrasound-guided oocyte retrieval

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BACKGROUND: This open label study compared the effectiveness of patient-controlled sedation (PCS), with physician-administered sedation (PAS) during transvaginal ultrasound-guided oocyte retrieval (TUGOR).

METHODS: A total of 106 patients was randomized using a computer model to receive either PCS (n = 51) or PAS (n = 55). Intra-operative sedation and co-operation were measured on a 5-point scale while severity of pain, and doctor and patient satisfaction were assessed using a 100 mm visual analogue scale. Number of oocytes retrieved and fertilization, cleavage and clinical pregnancy rates were also recorded. RESULTS: Levels of sedation and co-operation were similar between groups. The pain score was higher in the PCS group during (mean ± SD, 53 ± 23 versus 35 ± 24; P < 0.01) and 2 h after the procedure (29 ± 27 versus 17 ± 22; P < 0.05). Doctors were less satisfied with PCS than PAS (62 ± 25 versus 71 ± 26; P < 0.05) while patients were highly satisfied with both methods (76 ± 23 versus 74 ± 21; not significant). There were no oversedation or peri-operative complications. Fertility outcomes were similar. Patients tended to prefer PCS when given the choice of sedation method. CONCLUSION: Although PCS provides less analgesia then PAS during TUGOR, it is safe, satisfactory and accepted by patients.

Key words: anaesthesia/conscious sedation/IVF/oocyte retrieval/patient-controlled sedation

Introduction

Transvaginal ultrasound-guided oocyte retrieval (TUGOR) is one of the most stressful components of assisted reproductive treatment. Conscious sedation producing intra-operative amnesia and analgesia is highly desirable (Trout et al., 1998). Traditionally, doses of sedative and analgesic are calculated according to the average requirement in healthy adults. However, pain tolerance, drug response and patient anxiety vary among individuals. Therefore, standard doses may result in either oversedation or inadequate pain relief in different patients.

Patient-controlled sedation (PCS) allows the patients to take control of drug administration. The principle of PCS is based on the concept of patient-controlled analgesia (PCA) for post-operative pain relief. While PCA allows self-administration of i.v. analgesics according to individual needs, PCS enables self-titration of sedation in a similar fashion. Thus, a desired level of sedation and pain relief may be achieved with a customized minimal effective dose of sedative and analgesic (Herrick, 1996; Roseveare et al., 1998). Furthermore, patient participation in dose titration may improve their sense of self-control and result in better patient satisfaction and operating conditions (Lefcourt, 1973; Girdler et al., 2000).

Previous reports have shown that the use of PCS during TUGOR is safe and effective (Zelcer et al., 1992; Dell and Cloote, 1998). However, it is not known whether PCS is more effective than conventional physician-administered sedation (PAS). In this randomized controlled trial, we compared the effectiveness and safety of PCS using propofol-alfentanil admixture with PAS for conscious sedation during TUGOR.

Materials and methods

This study was approved by the Clinical Research Ethics Committee of the local university and all patients gave written informed consent. All patients undergoing IVF in a university-affiliated assisted reproductive technology unit were invited to join the study. Only patients
with fewer than three dominant follicles (for whom oocyte retrieval would not be performed), or who had a history of cardio-respiratory disease or known allergy to the drugs used in this study were excluded. All patients received a standardized ovarian stimulation regimen (Yim et al., 2001). Premedication was not prescribed. Following measurement of baseline haemodynamic parameters, patients were randomly allocated to receive either PCS or PAS using computer-generated random numbers concealed in opaque envelopes.

Patient-controlled sedation

PCS was provided by a commercially available PCA pump (Model 3300, Graseby Medical, Watford, Herts, UK). A mixture of propofol (10 µg/ml) and alfentanil (50 µg/ml) was prepared. The PCA pump was programmed to deliver a bolus dose of 1 ml at 200 µl/h on patient’s demand and the pump took 18 s to deliver the bolus, during which time it would not respond to a further demand. Thus, the effective lockout time was 18 s. After randomization and before the procedure, patients were instructed clearly on how to use the pump and were encouraged to press the demand button as often as required. The total number of PCS requested (total demands) and the number of demands that resulted in successful bolus delivery were recorded. We also calculated the demand/delivery ratio to indicate the effectiveness of PCS (McCoy et al., 1993). In this regard, patients with inadequate sedation or analgesia would be expected to make frequent requests over a short period of time. These requests may occur during the effective lockout period, resulting in unsuccessful demands and an increase in demand/delivery ratio. A ratio equal to one represents the most effective PCS system.

Physician-administered sedation

Patients assigned to the PAS group received an i.v. bolus of pethidine 1.5 mg/kg and diazepam 0.1 mg/kg 5–10 min prior to the procedure. Additional doses of pethidine 0.5 mg/kg were given when necessary as judged by the attending physician or upon the patient’s request. This technique represents the standard method of sedation used for TUGOR in this unit.

All procedures were performed by L.P.C. or D.L.W.C. During operation, non-invasive arterial pressure, heart rate and pulse oximetry were measured at 5 min intervals. Intra-operative sedation and co-operation were scored according to 5-point sedation and co-operation scales respectively, as shown in Table I (Dell and Cloote, 1998). Difficulty in retrieving oocytes was recorded as follows: easy to mildly difficult, moderately difficult or very difficult. During the procedure and 2 h afterwards, all patients were asked to evaluate the severity of pain and nausea using a 100 mm visual analogue scale (VAS; 0 mm = nil, 100 mm = worst imaginable). At the end of the procedure, both the patient’s satisfaction and doctor’s perception towards adequacy of pain and sedation control were rated using a similar VAS (0 mm = most dissatisfied, 100 mm = most satisfied). Patients who had previous oocyte retrievals under PAS and were currently randomized to PCS were also asked about their preferred type of sedation.

Before being discharged, patients were asked to complete an 8-item client satisfaction questionnaire (CSQ-8) (Larsen et al., 1979) which is a simple assessment of patient attitude towards new treatment. A maximum possible score of 32 indicates greatest satisfaction, whereas the lowest score of 8 reflects a most dissatisfied patient.

During retrieval of the last two oocytes, venous blood and follicular fluid were collected for the measurement of propofol and alfentanil concentration using high-pressure liquid chromatography (Gin et al., 1991) and radioimmunoassay (Michiels et al., 1983) respectively. Venous blood samples were stored at 4°C while follicular fluid was immediately centrifuged at 1800 g for 10 min to eliminate cellular components and frozen at −20°C until assay. The between-batch coefficients of variation for propofol and alfentanil were 6.7 and 4.6% respectively. The limit of detection was 2 ng/ml for propofol and 0.1 ng/ml for alfentanil.

IVF parameters including the number of oocytes retrieved, cycles with ICSI, fertilization rate, cleavage rate, number of embryos transferred or frozen and clinical pregnancy rate were recorded.

Statistics

Prospective power analysis was based on our pilot study of 30 patients undergoing TUGOR with conventional PAS. Given that the mean (± SD) pain score was 36 ± 16, we calculated that 47 patients per group would provide 90% power at 5% significance level to detect a 30% change in pain. With an estimated 10% drop-out rate, we based our study on a total sample size of 110. Data from this pilot study were not included in the final analysis.

Statistical analysis was performed with Statistical Packages of Social Sciences for Windows 10.1 (SPSS, Inc., Chicago, IL, USA). Categorical data were compared between groups using χ2-test and continuous data were analysed by Mann–Whitney U-test. To test the validity of demand/delivery ratio as a measure of PCS effectiveness, we compared the ratio with the severity of pain, CSQ-8 score, and doctor and patient satisfaction using linear regression. P < 0.05 was taken to indicate statistical significance.

Results

Between March and August 2001, 120 women fulfilling the recruitment criteria were invited to join the study. Ten women refused to participate and thus 110 patients were randomized into the study. Four patients in the PCS group were excluded before the start of the procedure. Of these, three withdrew consent due to personal reasons; another patient was excluded because of PCA pump failure. None of these patients received the allocated medications (propofol-alfentanil) and their data were excluded from further analysis. Therefore, a total of 51 women in the PCS group and 55 in the PAS group completed the study (Figure 1).

Patient characteristics are listed in Table II. Patients receiving PCS were on average 2 years younger than those in the PAS group (P = 0.01). However, no differences were noted with respect to body weight, cause of infertility or number of previous IVF cycles.

TUGOR was completed in all patients. The duration of the procedure was similar between the two groups. There were no
Figure 1. Flow diagram of subject progress through the phases of the randomized trial. PCS refers to patient-controlled sedation and PAS refers to physician administered sedation.

Table II. Patient characteristics. Values are mean ± SD or n (%) of which seven (range 3–17) demands were actually delivered. The median demand/delivery ratio was 1.5 (range 1–5.5). This positively correlated with intra-operative pain score (Pearson correlation coefficient, r = 0.45, P = 0.001) and negatively correlated with CSQ-8 score (r = −0.59, P < 0.001), physician satisfaction (r = −0.61, P < 0.001) and patient satisfaction scores (r = −0.65, P < 0.001, Figure 2). The mean (± SD) total propofol and alfentanil consumed during the procedure was 83.5 ± 33.2 mg and 418 ± 166 µg respectively. Neither propofol nor alfentanil was detected in any of the follicular fluid samples collected from

Table III. IVF outcomes in patients receiving patient-controlled sedation (PCS) or physician-administered sedation (PAS) during transvaginal ultrasound-guided oocyte retrieval. Values are mean ± SD or n (%)

*P = 0.01.

peri-operative complications and all patients were discharged within 4 h of the procedure. There was no difference in the IVF parameters measured between the two groups (Table III).

Three women in the PAS group required additional pethidine for pain relief during vaginal puncture. The mean (± SD) total doses of pethidine and diazepam were 76 ± 6 and 5 ± 1.1 mg respectively. However, there was marked variation in dose administration for patients receiving PCS. The median number of PCS demands was 13 (range 3–63),
Figure 2. Correlation of patient-controlled sedation (PCS) demand/delivery ratio with intra-operative pain ($r = 0.45$, $P = 0.001$), doctor satisfaction ($r = -0.61$, $P < 0.001$), patient satisfaction ($r = -0.65$, $P < 0.001$) and client satisfaction scores (CSQ) ($r = -0.59$, $P < 0.001$). The lines of best fit given by linear regression are shown as solid lines and the 95% confidence intervals of the regressions are shown as dashed lines.

Table IV. Quality of sedation and analgesia after patient-controlled sedation (PCS) and physician-administered sedation (PAS)

<table>
<thead>
<tr>
<th></th>
<th>PCS</th>
<th>PAS</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of procedure (min)</td>
<td>18.2 ± 7.5</td>
<td>15.9 ± 5.5</td>
<td>NS</td>
</tr>
<tr>
<td>Number of vaginal puncturesa</td>
<td>3 (3–4)</td>
<td>3 (2–4)</td>
<td>NS</td>
</tr>
<tr>
<td>Degree of difficulty perceivedb</td>
<td>Easy or mildly difficult</td>
<td>14 (30)</td>
<td>21 (39)</td>
</tr>
<tr>
<td></td>
<td>Moderately difficult</td>
<td>22 (48)</td>
<td>21 (40)</td>
</tr>
<tr>
<td></td>
<td>Very difficult</td>
<td>10 (22)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Co-operation scorea</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>NS</td>
</tr>
<tr>
<td>Sedation scorea</td>
<td>1 (1–3)</td>
<td>1 (1–2)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During oocyte retrieval</td>
<td>53 ± 23</td>
<td>35 ± 24</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td>2 h after oocyte retrieval</td>
<td>29 ± 27</td>
<td>17 ± 22</td>
<td>$&lt; 0.05$</td>
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<tr>
<td>Nausea score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During oocyte retrieval</td>
<td>5 ± 9</td>
<td>9 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>2 h after oocyte retrieval</td>
<td>7 ± 1</td>
<td>13 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Satisfaction score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctor’s satisfaction score</td>
<td>62 ± 25</td>
<td>71 ± 26</td>
<td>$&lt; 0.05$</td>
</tr>
<tr>
<td>Patient’s satisfaction score</td>
<td>76 ± 23</td>
<td>74 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>CSQ-8 scores</td>
<td>27 ± 3</td>
<td>27 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>89.1 ± 12.0</td>
<td>85.4 ± 11.3</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74.6 ± 12.4</td>
<td>82.5 ± 10.9</td>
<td>$&lt; 0.05$</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, amedian (range), b$n$ (%) where appropriate. NS = not significant.

the first 10 cases. Therefore, we abandoned further follicular fluid collection in the subsequent patients.

The quality of sedation and analgesia after PCS and PAS is summarized in Table IV.

Sedation and co-operation scores did not differ between groups and all patients responded readily to commands throughout the procedure. However, intra-operative pain scores were significantly higher in the PCS group compared with the PAS group (53 ± 23 versus 35 ± 24; $P < 0.01$). No patients required post-operative analgesia, but the pain score 2 h after the procedure was significantly higher in the PCS group (29 ± 27 versus 17 ± 22; $P < 0.05$). There was no difference in the degree of nausea. Doctors’ perceptions towards adequacy of pain and sedation control were better with PAS than PCS (71 ± 26 versus 62 ± 25; $P < 0.05$) whereas no differences were found in patient satisfaction scores or CSQ-8 scores. Nineteen women in the PCS group had undergone previous oocyte retrieval with PAS. When given the option, more patients preferred PCS (11 or 57.9%) than PAS (8 or 42.1%) but the difference was not statistically significant.

Haemodynamic parameters did not change during the operation. However, heart rate in the PAS group was significantly higher than in the PCS group ($P < 0.01$) and this may be related to the intrinsic vagolytic property of pethidine. Oxygen saturation was well maintained in all patients.

Discussion

PCS appears to be an effective alternative to PAS for TUGOR. Although pain scores were higher in patients receiving PCS than PAS, the pain was modest and well tolerated by the patients. Similar findings have been reported when PCS was used for colonoscopy (Roseveare et al., 1998). Furthermore, patients were equally satisfied with PCS and PAS, and 57.9%
of patients with experience of both methods expressed a preference for PCS. Such a high preference rate has been observed in other procedures performed under PCS (Roseveare et al., 1998; Zacharias et al., 1998; Girdler et al., 2000). The acceptance and preference of PCS probably depend on factors other than pain control alone because patient behaviour towards pain control can be unpredictable. A recent report indicated that 38% of patients pressed the demand button only when pain became intolerable (Chumbley et al., 1998). Similarly, Hawkins and Price showed that patients were reluctant to eliminate their pain even when they were constantly encouraged to do so (Hawkins and Price, 1993). We believe that patient participation and the sense of self-control account for the favourable response in patients receiving PCS (Lefcourt, 1973; Girdler et al., 2000).

In the present study, PCS was delivered as frequent small boluses upon request. Thus, a desired level of sedation could be achieved rapidly if the demand button was pressed sufficiently often. We did not set a lockout interval between consecutive boluses. However, the time taken to infuse each dose imposed a brief refractory period (18 s) to the PCS system. We believe this effective lockout time protects patients from stacking of PCS demands and unintentional drug overdose. Only a third of the patient’s demands were rejected by the PCS system, resulting in a demand/delivery ratio of 1.5. Given that the ratio correlated with patient satisfaction, these findings indicated that our current PCS setting was efficient in fulfilling patient requests. Any future modification of the PCS dose regimen should aim to achieve a demand/delivery ratio <1.5 in order to produce a better patient response.

It should be emphasized that neither the patient nor the physician was blinded to the treatment group. In this regard, patients may be less critical of their performance when given the option of controlling drug administration. Similarly, physicians’ attitudes towards PCS may have altered patient’s response. However, patient participation and physician interaction are key to the success of PCS. Thus, a double-blinded trial would not be feasible. Nevertheless, the endpoints were clearly defined and all investigators were familiar with the measurement scales; therefore, differences between the groups cannot be attributed entirely to treatment bias or measurement error. We used a mixture of propofol and alfentanil to provide sedation and analgesia respectively. Both drugs are fast in action are key to the success of PCS. Thus, a double-blinded trial would not be feasible. Nevertheless, the endpoints were clearly defined and all investigators were familiar with the measurement scales; therefore, differences between the groups cannot be attributed entirely to treatment bias or measurement error.

We used a mixture of propofol and alfentanil to provide sedation and analgesia respectively. Both drugs are fast in onset but short acting, making them easy for dose titration and a popular combination for PCS. However, anaesthetics per se may adversely affect fertilization outcome. In mice, embryo cleavage was inhibited at propofol 10 ng/ml (Tatone et al., 1998), significant parthenogenetic activation was noted at 50 ng/ml (Janssenswillen et al., 1997) and in-vitro maturation was suppressed at 10 000 ng/ml (Alsalili et al., 1997). There are no data on the fecundability of oocytes during alfentanil administration. Although the embryo cleavage characteristics and fertilization in human oocytes were shown to be similar between propofol-alfentanil anaesthesia and paracervical blocks (Christiaens et al., 1998) as well as in oocytes exposed to propofol (Ben-Shlomo et al., 2000), it would be prudent to minimize the amount of anaesthetic delivered. PCS may be useful in reducing drug dosage. Accordingly, patients reduce their drug consumption as the desired level of sedation is achieved. Thus, the total drug consumed represents the minimal effective dose of sedative required. In this regard, Girdler et al. were able to reduce propofol administration by 30% using PCS in anxious dental patients (Girdler et al., 2000). In the present study, the total propofol and alfentanil consumption (1.5 mg/kg and 7.9 μg/kg respectively) was less than that generally recommended for PAS (Sa Rego and White, 2000). Consequently, the resultant concentrations of propofol and alfentanil were low in plasma and were not detected in follicular fluid samples and this is unlikely to produce any detrimental effect on the oocytes. Although we found no difference in the IVF parameters, including pregnancy outcomes between the two groups, our study was not primarily aimed at and was not powered for comparing pregnancy rates.

In summary, PCS using propofol and alfentanil can be a satisfactory and effective alternative to conventional diazepam-pethidine based PAS during TUGOR. Our results also demonstrate that PCS is safe and simple to administer and is associated with high patient satisfaction.

Acknowledgements

The authors wish to thank Ms Pat Tan for her assistance in performing drug assays and the nurses in the IVF unit for their help during the study.

References


Submitted on March 22, 2002; accepted on May 2, 2002