Human Reproduction vol.14 no.10 pp.2480–2484, 1999

A prospective randomized study of electro-acupuncture versus alfentanil as anaesthesia during oocyte aspiration in in-vitro fertilization

Elisabet Stener-Victorin[1,4], Urban Waldenström[2], Lars Nilsson[1], Matts Wikland[3] and Per Olof Janson[1]

[1]Department of Obstetrics and Gynaecology, Göteborg University, SE-413 45 Göteborg, [2]IVF Center Falun, SE-791 82 Fallun, [3]Fertility Centre Scandinavia, SE-402 29 Göteborg, Sweden

[4]To whom correspondence should be addressed at: Department of Obstetrics and Gynaecology, Kvinnokliniken, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden

The aim of the present study was to evaluate the anaesthetic effect during oocyte aspiration of a paracervical block (PCB) in combination with either electro-acupuncture (EA) or intravenous alfentanil. In all, 150 women undergoing in-vitro fertilization (IVF) and embryo transfer were randomized to receive either EA plus PCB or alfentanil plus PCB. Visual analogue scales (VAS) were used to evaluate subjective experiences during oocyte aspiration, and IVF outcome parameters were recorded. No differences in pain directly related to oocyte aspiration, adequacy of anaesthesia during oocyte aspiration, abdominal pain, or degree of nausea were found between the two groups in the VAS ratings. Before oocyte aspiration, the level of stress was significantly higher in the EA group than in the alfentanil group ($P < 0.05$), and the EA group experienced discomfort for a significantly longer period during oocyte aspiration ($P < 0.01$). Compared with the alfentanil group, the EA group had a significantly higher implantation rate ($P < 0.05$), pregnancy rate ($P < 0.05$), and take home baby rate ($P < 0.05$) per embryo transfer. In conclusion, EA has been shown to be as good an anaesthetic method as alfentanil during oocyte aspiration, and we suggest that EA may be a good alternative to conventional anaesthesia during oocyte aspiration.

Key words: alfentanil/anaesthesia/electro-acupuncture/implantation rate/oocyte aspiration

Introduction

During the last decade, the vaginal ultrasound transducer has dramatically facilitated the oocyte aspiration procedure in in-vitro fertilization (IVF) and embryo transfer. This technique for follicle puncture causes little trauma and few side-effects. Transvaginal follicle puncture often requires the application of local anaesthesia paracervically and implies either one or two needle perforations of the vaginal wall (Wikland *et al*., 1987). The pain experienced during the transvaginal follicle puncture procedure varies from individual to individual. The pain is often described as an intense menstrual pain, which ceases fairly quickly, after which a tenderness is experienced in the abdomen.

Anaesthesia during oocyte aspiration is given according to the experience of each centre. In Sweden anaesthesia consists of a local anaesthetic administered as a paracervical block (PCB) and either i.v. opioids administered during oocyte aspiration or different combinations of premedication in the form of sedatives and i.v. opioids before the oocyte aspiration procedure. Conventional anaesthetic methods involve a number of side-effects such as tiredness, nausea and confusion (Whitwam, 1995; Meert, 1996; Yeo *et al*., 1997). Alfentanil has been found in the follicular fluid shortly after an i.v. injection, but it is not known whether opioids and sedatives negatively affect the follicles, the oocytes, and/or endometrial receptivity (Alahuhta *et al*., 1993; Soussis *et al*., 1995; Giroux *et al*., 1997).

Electro-acupuncture (EA) is a pain-relieving method (Lundeberg *et al*., 1988) that activates endogenous opioid systems (Andersson and Lundeberg, 1995) and has few negative side-effects. Acupuncture has previously been reported to give acceptable pain relief both intra-operatively and post-operatively (Hollinger *et al*., 1979; Kho *et al*., 1990, 1991, 1993), and we thought that it may serve as an alternative or complement to conventional anaesthetic methods during the transvaginal follicle puncture procedure.

The aim of the study was to compare EA and a fast-acting opioid with regard to pain relief, discomfort, stress, nausea, and IVF outcome parameters during oocyte aspiration.

Materials and methods

Subjects and design

This study was a prospective, randomized, multicentre trial. It was approved by the Ethics Committees of Göteborg and Uppsala Universities, Sweden.

The study was performed between September 1996 and May 1997 and was conducted at three IVF centres in Sweden (the IVF Unit at Sahlgrenska University Hospital in Göteborg, Fertility Centre Scandinavia in Göteborg, and the IVF Center in Falun). The women were informed about the study ~3 days before the oocyte aspiration procedure: ultrasound-guided transvaginal follicle puncture as previously described (Wikland *et al*., 1987). A total of 150 women was recruited (50 per IVF centre), all of them willing to use EA if randomized to that group. Each centre randomized its patients using sealed, unlabelled envelopes. Each woman gave her written informed consent before beginning the study. Seventy-five women aged 25–42 years (mean 33.3) were randomized into the EA group and given EA + PCB using lidocaine hydrochloride (Xylocain®; Astra, Södertälje, Sweden) and 75 women aged 25–46 years (mean 34.4) were

Table I. The acupuncture points—their anatomical position and their innervation—used together with a paracervical block as premedication for the oocyte aspiration procedure

Points	Stimulation	Segmental innervation	Muscle localization
LI 4 bilateral	EA, 2 Hz	Nn. ulnaris, medianus (C8, Th1)	Mm. interosseus dorsalis I, lumbricalis II, adductor pollicis
TE 5 bilateral	EA, 2 Hz	N. interosseus posterior (C7–8)	M. extensor digiti minimi
ST 29 bilateral	EA, 100 Hz	N. thoracicus (Th6–12)	M. rectus abdominis
GV 20	Manual	Nn. trigeminus (V), occipitalis minor (C2), occipitalis major (C2–3)	Aponeurosis epicranii
ST 36 bilateral	Manual	N. peroneus profundus (L4–5)	M. tibialis anterior

EA = electro-acupuncture; LI = large intestine; TE = triple energizer; ST = stomach; GV = governor vessel.

Table II. The numbers of women with the different causes of infertility and the number of previous in-vitro fertilization treatments in the two anaesthetic groups

Characteristics	No. of women (%)	
	EA + PCB (n = 75)	Alfentanil + PCB (n = 74)
Cause of infertility		
male	23 (30.7)	20 (27.0)
tubal disease	26 (34.7)	29 (39.2)
endometriosis	6 (8.0)	8 (10.8)
unexplained	16 (21.3)	16 (21.6)
other causes	4 (5.3)	1 (1.4)
No. of previous IVF treatments		
1	28 (35.4)	35 (47.3)
2	28 (35.4)	19 (25.7)
3	8 (10.1)	10 (13.5)
4	4 (5.1)	5 (6.8)
5	8 (10.1)	4 (5.4)
6	2 (2.5)	0 (0)
8	1 (1.3)	1 (1.4)

EA = electro-acupuncture; PCB = paracervical block.

randomized into the alfentanil group and given alfentanil (Rapifen®; Janssen-Cilag, Sollentuna, Sweden) + PCB as an anaesthetic during oocyte aspiration. They could discontinue the study at any time.

One woman in the alfentanil group was excluded because she had received premedication; a total of 149 women was analysed.

Anaesthesia

The acupuncture procedure was performed as follows: EA was begun at least 30 min before oocyte aspiration and the PCB was placed at the start of the procedure and terminated directly after oocyte aspiration. The needles (Hegu; Hegu AB, Landsbro, Sweden) were made of stainless steel and were inserted i.m. to a depth of 15–35 mm. They were then rotated to evoke the needle sensation of 'de qi', often described as variable feelings of tension, numbness, tingling, and soreness and reflecting activation of muscle-nerve afferents (A delta and possibly C fibres) (Lundeberg *et al*., 1988; Haker and Lundeberg, 1990). The location and type of stimulation were the same in all women in the EA group (Table I). The needles in the abdominal muscles were attached to an electrical stimulator (CEFAR Acus; Cefar, Lund, Sweden) and stimulated with continuous square wave pulses, alternating polarity, pulse duration of 0.2 ms, 'high frequency' 100 Hz. The intensity was high, giving non-painful paraesthesia. The needles in the hands were also electrically stimulated, with a low burst frequency of 2 Hz. Individual pulses within the burst frequency were square wave pulses, alternating polarity, pulse duration of 0.2 ms, 80 pulses per second (pps). The intensity was sufficient to cause non-painful local muscle contractions. The needles not stimulated electrically were manually stimulated every tenth minute (Table I).

The alfentanil group received 0.25–0.5 mg alfentanil and 0.25 mg atropine (Atropin NM Pharma; NM Pharma AB, Stockholm, Sweden) i.v. directly before oocyte aspiration and placement of the PCB.

Both groups received PCB, and it was supplied using 10 ml of lidocaine (5 mg/ml at the IVF Center in Falun and 10 mg/ml at both the IVF Unit at Sahlgrenska University Hospital and the Fertility Centre Scandinavia, Göteborg) before oocyte aspiration was begun.

Both groups received an electric heating pad on the abdomen during oocyte aspiration. No premedication was administered in any group. If EA or the initial dose of alfentanil did not result in sufficient pain relief, additional alfentanil was administered.

Measurements

The outcome of the study was measured using visual analogue scales (VAS) (McCormack *et al*., 1988). Six different VAS, each consisting of a 100 mm line oriented vertically on a paper, were used to evaluate the subjective experience (0–100) during oocyte aspiration. The six variables had the following endpoints. Abdominal pain: no pain and unbearable pain; pain directly related to oocyte aspiration: no pain and unbearable pain; adequacy of anaesthesia: enough and would have needed much more; stress: not at all stressed and very stressed; time of discomfort: never and all the time; nausea: no nausea and unbearable nausea. The ratings were performed ~30 min before oocyte aspiration, directly after oocyte aspiration, and 2 h after oocyte aspiration. In addition, the following IVF outcome parameters were recorded: number of intracytoplasmic sperm injection (ICSI) cycles, number of standard IVF cycles, number of oocytes retrieved, fertilization rate, number of embryo transfers, total number of embryos transferred, number of gestational sacs, number of pregnancies, and number of miscarriages before 16th week. The implantation, pregnancy and take-home baby rates per embryo transfer were calculated.

Statistics

The Mann–Whitney *U*-test was used to compare differences between the groups concerning the VAS ratings, the number of oocytes retrieved and the fertilization rate (Altman, 1996). Fisher's exact test was used to compare differences between the groups concerning miscarriage before the 16th week, implantation rate, pregnancy per embryo transfer, and take home baby rate. $P < 0.05$ was considered significant. The mean and SD were calculated when possible.

Table III. Means (SD) for visual analogue scale (VAS) ratings in two groups of women under different anaesthetic regimes for oocyte aspiration

Questions (VAS; 0–100)	EA + PCB mean (SD) (n = 75)	Alfentanil + PCB mean (SD) (n = 74)
Approximately 30 min before oocyte aspiration		
Stress:		
not at all stressed and very stressed	36.6 (25.2)[a]	29.1 (25.9)
Abdominal pain:		
no pain and unbearable pain	13.4 (16.9)	12.5 (16.6)
Nausea:		
no nausea and unbearable nausea	4.2 (8.2)	5.8 (11.7)
Directly after oocyte aspiration		
Worst pain directly related to oocyte aspiration:		
no pain and unbearable pain	48.6 (23.1)	43.6 (28.5)
Mean pain directly related to oocyte aspiration:		
no pain and unbearable pain	30.1 (19.4)	26.6 (22.0)
Pain now:		
no pain and unbearable pain	26.7 (26.1)	20.6 (22.1)
Time of discomfort during oocyte aspiration:		
never and all the time	27.0 (19.7)[b]	20.7 (23.9)
Nausea:		
no nausea and unbearable nausea	6.7 (16.2)	5.7 (12.8)
Two hours after oocyte aspiration		
Abdominal pain:		
no pain – unbearable pain	21.8 (21.4)	22.9 (23.4)
Adequacy of anaesthesia during oocyte aspiration:		
adequacy – would have needed much more	17.4 (21.5)	19.1 (25.9)
Nausea:		
no nausea and unbearable nausea	3.0 (7.2)	4.1 (8.0)

EA = electro-acupuncture; PCB = paracervical block.
[a]$P < 0.05$, [b]$P < 0.01$ for comparisons between the two anaesthetic groups.
The Mann–Whitney *U*-test was used to compare differences between the groups concerning the VAS ratings at three different times during the procedure.

Results

The reasons for infertility did not differ between the two groups (Table II). A total of 13 (17.3%) of the women in the EA group and 21 (28.4%) of the women in the alfentanil group were given additional alfentanil i.v.

No significant differences between the groups in the VAS ratings made before, directly after, and 2 h after oocyte aspiration were found with respect to pain directly related to oocyte aspiration, adequacy of anaesthesia during oocyte aspiration, abdominal pain, and degree of nausea (Table III). Before oocyte aspiration, the level of stress was significantly higher in the EA group than in the alfentanil group ($P < 0.05$). Compared with the alfentanil group, the EA group experienced discomfort for a significantly longer period of time ($P < 0.01$) during oocyte aspiration.

In the EA group, 75 women underwent oocyte aspirations and 61 embryo transfer; in the alfentanil group 74 underwent oocyte aspirations and 67 embryo transfer (Table IV). The reasons for not performing embryo transfer did not differ between the two groups: absence of fertilization, no oocytes or spermatozoa found on the day of aspiration, or embryo degeneration. Compared with the alfentanil group, the EA group showed a significantly higher implantation rate (27.2% versus 16.3%, $P < 0.05$), pregnancy rate (45.9% versus 28.3%, $P < 0.05$) and take home baby rate (41% versus 19.4%, $P < 0.05$) per embryo transfer. Six of the 28 (21.4%) women in the EA group and four of the 19 (21.1%) women in the alfentanil group who became pregnant received additional anaesthesia during oocyte aspiration. Three (10.7%) women in the EA group miscarried, compared with six (31.6%) in the alfentanil group (not significantly different). No significant difference was found between the EA group and the alfentanil group in mean (SD) number of oocytes retrieved [9.9 (5.2) versus 8.7 (4.8)] and in fertilization rate [59.9% (30.7) versus 65.9% (28.4)]. Detailed IVF outcome data are presented in Table IV.

Table IV. In-vitro fertilization (IVF) outcome data in the two anaesthetic groups

Variable	EA + PCB (n = 75)	Alfentanil + PCB (n = 74)
No. of ICSI cycles	34	32
No. of standard IVF cycles	41	42
No. of embryo transfers	61	67
Total no. of embryos transferred	125	135
Total no. of gestational sacs	34	22
No. of pregnancies	28	19

EA = electro-acupuncture; PCB = paracervical block; ICSI = intracytoplasmic sperm injection.

Discussion

The main result of the present study is that we found no difference between the EA group and the alfentanil group

in the women's ratings of pain experienced during oocyte aspiration.

Support for our findings that EA gives sufficient relief of visceral pain during minor surgery has recently been reported (Wang *et al*., 1992, 1997). These studies showed that EA, used for pain relief during colonoscopy, was as effective as conventional anaesthesic methods but with fewer side-effects. They attributed the EA effect to activation of the central descending pain inhibitory systems, involving the secretion of endogenous opioids. The idea that EA might give an acceptable pain relief during oocyte aspiration is also supported by physiological models explaining the mechanisms in the treatment of both acute and chronic pain conditions (Andersson and Lundeberg, 1995). Sympathetic outflow and nociceptive input from viscera may be inhibited at the segmental level. For this reason, acupuncture points were selected, as far as possible, in somatic segments according to the innervation of the ovary and uterus (Th10–12, L1–2, S2–4). In addition, well-known general pain-relieving points were selected. The aims of the electrical and manual stimulation were to activate both the segmental pain inhibitory system, involving the so-called gate control mechanism (Melzack and Wall, 1965) and the central pain inhibitory system, involving secretion of endogenous opioids (Bloom, 1983; Cuello, 1983; Smyth, 1983; Akil *et al*., 1984). Whether the choice of acupuncture points and the method of stimulation in this study are optimal remains to be elucidated.

The significantly greater stress before oocyte aspiration and the significantly longer time of discomfort in the EA group during oocyte aspiration may possibly be associated. It is well known that high levels of stress may decrease the pain threshold, counteract analgesia, and increase discomfort (Widerström-Noga *et al*., 1998). The majority of the women were unfamiliar with the EA procedure. This could be one possible explanation for the greater stress reported before oocyte aspiration and the longer period of discomfort reported directly after oocyte aspiration. However, both these ratings appear to be temporary since the majority of women ~2 h after oocyte aspiration reported that they had received adequate pain relief.

There is a possible bias in the study in that some of the women in the EA group were administered additional alfentanil during oocyte aspiration. The ideal situation would have been to compare EA alone in all women in that group against alfentanil. However, from an ethical point of view this ideal situation was not possible to achieve and additional alfentanil was administered in both the EA group and the alfentanil group (17.3% and 28.4% of patients respectively).

Other clinical observations (not statistically proven or presented in the results) were that the women in the EA group compared with the women in the alfentanil group appeared to be more alert, were less tired, and could leave the clinic soon after oocyte aspiration. In addition, it seems that women who received EA had less bleeding during and after oocyte aspiration.

No negative effects on endometrial receptivity, follicles, or oocytes during IVF–embryo transfer treatment have been reported following administration of synthetic opioids during oocyte aspiration. Elevated concentrations of alfentanil in the follicular fluid during transvaginal oocyte aspiration have been found (Soussis *et al*., 1995) but the number of patients was too small for evaluation of pregnancy rates. These authors, however, did recommend that the time taken to collect the oocytes should be kept to a minimum to avoid any potentially harmful effects of the drugs reaching the follicular fluid. The dose of alfentanil used in the present study was different in the three IVF centres involved in the study. There was no indication that this had any influence on the VAS ratings or on the IVF outcome parameters.

EA involves biological activation of the endogenous pain inhibiting systems (Andersson and Lundeberg, 1995). It is unlikely that EA could influence the follicular fluid or the oocyte in any negative way. In addition to this, we showed in a previous study that repeated EA treatments decrease the pulsatility index in the uterine arteries (Stener-Victorin *et al*., 1996), and it is possible that this improves endometrial receptivity (Steer *et al*., 1992, 1995).

An interesting observation was the significantly higher implantation rate in the EA group. It should be noted, however, that the number of patients was small and hence the power of the findings too low for these observations to be considered scientifically proven. A study with a larger number of patients is currently in progress to further clarify this point.

In conclusion, this study has shown that EA is as good an anaesthetic method as alfentanil during oocyte aspiration. The women in this study were positive to the idea of using EA. We therefore suggest that EA may be a good alternative to conventional anaesthesia during oocyte aspiration.

Acknowledgements

We would like to thank the midwives who performed the EA and collected data: Birgitta Josefsson and Elisabeth Bergqvist (IVF Unit, Sahlgrenska University Hospital, Göteborg), Margareta Hammar and Elisabeth Nilsson (Fertility Centre Scandinavia, Göteborg), and Ragna Törnqvist (IVF Center of Falun). Without their invaluable help, this study could not have been completed. It was partly supported by grants from the Foundation for Acupuncture and Alternative Biological Treatment Methods, Swedish Medical Research Council (Project no. 4982).

References

Akil, H., Watson, S.J., Young, E. *et al.* (1984) Endogenous opiods: biology and function. *Annu. Rev. Neurosci*., **7**, 223–255.

Alahuhta, S., Rasanen, J., Jouppila, P. *et al.* (1993) Epidural sufentanil and bupivacaine for labor analgesia and Doppler velocimetry of the umbilical and uterine arteries. *Anesthesiology*, **78**, 231–236.

Altman, D.G. (1996) *Practical Statistics for Medical Research*. Chapman & Hall, pp. 194–198.

Andersson, S. and Lundeberg, T. (1995) Acupuncture—from empiricism to science: functional background to acupuncture effects in pain and disease. *Med. Hypoth*., **45**, 271–281.

Bloom, F.E. (1983) The endorphins. A growing family of pharmacologically pertinent peptides. *Annu. Rev. Pharmacol. Toxicol*., **23**, 151–170.

Cuello, A.C. (1983) Central distribution of opioid peptides. *Br. Med. Bull*., **39**, 11–16.

Giroux, M., Teixera, M.G., Dumas, J.C. *et al*. (1997) Influence of maternal blood flow on the placental transfer of three opioids–fentanyl, alfentanil, sufentanil. *Biol. Neonate*, **72**, 133–41.

Haker, E. and Lundeberg, T. (1990) Acupuncture treatment in epicondylalgia: A comparative study of two acupuncture techniques. *Clin. J. Pain*, **6**, 221–226.

Hollinger, I., Richter, J.A., Pongratz, W. and Baum, M. (1979) Acupuncture anesthesia for open heart surgery: a report of 800 cases. *Am. J. Chin. Med*., **7**, 77–90.

Kho, H.G., van Egmond, J., Zhuang, C.F. *et al*. (1990) The patterns of stress response in patients undergoing thyroid surgery under acupuncture anaesthesia in China. *Acta Anaesthesiol. Scand*., **34**, 563–571.

Kho, H.G., Eijk, R.J.R., Kapteijns, W.M.M.J. and van Egmond, J. (1991) Acupuncture and transcutaneous stimulation analgesia in comparison with moderate-dose fentanyl anaesthesia in major surgery. Clinical efficacy and influence on recovery and morbidity. *Anaesthesia*, **46**, 129–135.

Kho, H.G., Kloppenborg, P.W.C. and van Egmond, J. (1993) Effects of acupuncture and transcutaneous stimulation analgesia on plasma hormone levels during and after major abdominal surgery. *Eur. J. Anaesthesiol*., **10**, 197–208.

Lundeberg, T., Hurtig, T., Lundeberg, S. and Thomas, M. (1988) Long-term results of acupuncture in chronic head and neck pain. *Pain Clinic*, **2**, 161–164.

McCormack, H.M., de L. Horne, D.J. and Sheather, S. (1988) Clinical applications of visual analogue scales: a critical review. *Psychol. Med*., **8,** 1007–1019.

Meert, T.F. (1996) Pharmacotherapy of opioids: present and future developments. *Pharm. World Sci*., **18**, 1–15.

Melzack, R. and Wall, P.D. (1965) Pain mechanism: A new theory. *Science*, **150**, 971–979.

Smyth, D.G. (1983) Beta-endorphin and related peptides in pituitary, brain, pancreas and antrum. *Br. Med. Bull*., **39**, 25–30.

Soussis, I., Boyd, O., Paraschos, T. *et al*. (1995) Follicular fluid levels of midazolam, fentanyl, and alfentanil during transvaginal oocyte retrieval. *Fertil. Steril*., **64**, 1003–1007.

Steer, C.V., Campbell, S., Tan, S.L. *et al*. (1992) The use of transvaginal colour flow imaging after *in vitro* fertilization to identify optimum uterine conditions before embryo transfer. *Fertil. Steril*., **57**, 372–376.

Steer, C.V., Tan, S.L., Dillon, D. *et al*. (1995) Vaginal color Doppler assessment of uterine artery impedance correlates with immunohistochemical markers of endometrial receptivity required for the implantation of an embryo. *Fertil. Steril*., **63**, 101–108.

Stener-Victorin, E., Waldenström, U., Andersson, S.A. and Wikland, M. (1996) Reduction of blood flow impedance in the uterine arteries of infertile women with electro-acupuncture. *Hum. Reprod*., **11**, 1314–7.

Wang, H.H., Chang, Y.H. and Liu, D.M. (1992) A study in the effectiveness of acupuncture analgesia for colonoscopic examination compared with conventional premedication. *Am. J. Acupunct*., **20**, 217–221.

Wang, H.H., Chang, Y.H., Liu, D.M. and Ho, Y.J. (1997) A clinical study on physiological response in electroacupuncture analgesia and Meperidine analgesia for colonoscopy. *Am. J. Chin. Med*., **25**, 13–20.

Whitwam, J.G. (1995) Co-induction of anaesthesia: day-case surgery. *Eur. J. Anaesthesiol*., **12** (Suppl.), 25–34.

Widerström-Noga, E., Dyrehag, L.-E., Börglum-Jensen, L. *et al*. (1998) Pain threshold responses to two different modes of sensory stimulation in patients with orofacial muscular pain: Psychological considerations. *J. Orofacial Pain*, **12**, 27–34.

Wikland, M., Hammarberg, K., Nilsson, L. and Enk, L. (1987) Use of a vaginal transducer for oocyte retrieval in an IVF/ET program. *J. Clin. Ultrasound*, **13**, 245–251.

Yeo, W., Lam, K.K., Chan, A.T. *et al*. (1997) Transdermal fentanyl for severe cancer-related pain. *Palliat. Med*., **11**, 233–239.

Received on January 25, 1999; accepted on July 2, 1999