Article

Pain relief during oocyte retrieval – exploring the role of different frequencies of electro-acupuncture

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Abstract

Electro-acupuncture has previously proven its analgesic effect in oocyte retrieval for IVF. The aim of the present prospective randomized study was to explore the optimal frequency for analgesia when electro-acupuncture was applied a few minutes prior to oocyte retrieval. A total of 152 patients were prospectively randomized to receive either a combination of high (80 Hz) and low frequency (2 Hz), 3 s each, a so-called mixed frequency, or a fixed frequency of 20 Hz during oocyte retrieval. In addition to electro-acupuncture, both groups had a paracervical block and manual acupuncture. No differences in pain before, during or after oocyte retrieval between the two groups were seen. In the fixed frequency group, however, a higher level of anxiety ($P < 0.05$) before oocyte retrieval was seen, and a higher level of nausea after aspiration of one ovary ($P < 0.01$) was seen in the mixed frequency group. No differences were seen regarding clinical outcome parameters. Contrary to previous reports on acute and chronic pain, the analgesic effect of the mixed frequency and the fixed frequency was similar when used for short duration electro-acupuncture.

Keywords: *electro-acupuncture, frequency, IVF, oocyte retrieval, pain relief*

Introduction

Acupuncture, a method of treatment, dating back at least 3000 years, is an integral part of traditional Chinese Medicine. Over the last decade, it has become increasingly integrated into Western medicine. This integration has primarily been promoted by patients. Due to the increasing demand by patients, acupuncture has also found its way into fertility treatment. Few topics, however, are as controversial as acupuncture, especially within the scientific community, primarily due to the lack of well-designed randomized studies to assess the efficacy of the procedure. The dearth of proper scientific documentation and the fact that mechanisms are not fully understood in physiological terms increases scepticism, but whether or not acupuncture results in analgesia is a compelling area for the scientific community to investigate.

Acupuncture with needle penetration of the skin and underlying muscles, followed by stimulation of the needles by manual rotation or by electrical stimulation, so-called electro-acupuncture, excites afferent nerve fibres (Kniffki *et al.*, 1981).

Electro-acupuncture with different frequencies of electrical stimulation has been shown to stimulate the release of opioid peptides in the central nervous system (CNS) in animal studies. The analgesia induced by different frequencies of electro-acupuncture in animals can be blocked by an opioid antagonist (naloxone) or by the use of various opioid receptor subtype-specific antagonists, indicating that electro-acupuncture releases opioid peptides (Han, 2003, 2004). Low frequency (1–4 Hz) electro-acupuncture stimulates the release of β-endorphin (μ-receptor) and enkephalin (δ-receptor), whereas high frequency (80–120 Hz) stimulates the release of dynorphin (κ-receptors) (Han, 2003, 2004). In animals,

an alternate frequency, i.e. a mixed frequency with 3 s of automatic shifting between low and high frequency electro-acupuncture stimulation, has been shown to induce a more potent analgesic effect than that induced by a constant, i.e. fixed, frequency. These observations have subsequently been confirmed in controlled clinical studies on acute pain (Wang *et al.*, 1997; Hamza *et al.*, 1999b) and chronic pain (Hamza *et al.*, 1999a, 2000).

Conscious sedation, including premedication with benzodiazepine, application of a paracervical block and administration of intravenous (i.v.) fast-acting opiates, still appears to be the most commonly used type of sedation (Trout *et al.*, 1998; Stener-Victorin, 2005) during oocyte retrieval for IVF.

Previously, the pain relieving effect of electro-acupuncture was explored in combination with a paracervical block during oocyte retrieval in a number of studies (Stener-Victorin *et al.*, 1999, 2003; Humaidan and Stener-Victorin, 2004). Electrical stimulation techniques, as well as the premedication given, however, vary in these studies, i.e. different frequencies, intensity, duration of stimulation and presence or absence of premedication.

As 40% of patients currently choose electro-acupuncture for oocyte retrieval in combination with a paracervical block instead of conventional medical analgesia (CMA), it was thought important to elucidate the most optimal electrical stimulation regimen. In a previous study (Humaidan and Stener-Victorin, 2004), a fixed frequency of 20 Hz was used for electrical stimulation in a new short duration protocol. The aim of the present study was to compare the pain relieving effect of a mixed frequency of 2–80 Hz and a fixed frequency of 20 Hz, when electro-acupuncture was used in the short duration protocol. The primary end-point of the study was pain relief, and the hypothesis was 'non-inferiority' between the two arms of the study. Secondary end-points were anxiety, nausea and hospitalization time.

Materials and methods

Setting, study design, participants and randomization

The present prospective randomized study was performed between August 2004 and May 2005 at the Fertility Clinic, Viborg Hospital (Skive), Denmark. The CONSORT guidelines for randomized trials were followed. All patients included in the IVF programme were informed about the study approximately 1 week to 3 days before oocyte retrieval. Patients with chronic pelvic pain were excluded from the study. Each patient gave her written informed consent before participating in the study, and contributed data from one cycle only. Randomization was performed by a nurse on the day of the last ultrasound examination before oocyte retrieval, using sealed, unlabelled envelopes, each containing a unique study number. Doctors and patients were blinded to the arm of treatment. A total of 432 patients were assessed for eligibility and 160 patients were willing to participate, giving an acceptance rate to the trial of 37%, which approximates to the use, in the clinic, of acupuncture in the oocyte retrieval situation of 40% of cases. Patients were randomly allocated to the mixed frequency group or the fixed frequency group. The participants were informed that they could discontinue the study at any time. The local Ethics Committee of Viborg County, Denmark approved this prospective, randomized study.

Analgesic protocol

Paracervical block

Both study groups received a paracervical block of 10 ml lidocaine (5 mg/ml) lidocaine hydrochloride (Lidocain®; SAD, Amternes lægemiddelregistreringskontor I/S, Denmark). Lidocaine was injected where the aspiration needle was intended to pass through the vaginal wall. The paracervical block was applied about 1–2 min after the electro-acupuncture procedure started.

Electro-acupuncture

The acupuncture needles (CARBO; AcuPharma A/S, Ballerup, Denmark; size 0.22 × 25 mm and 0.22 × 40 mm) were inserted 15–25 mm intramuscularly into the acupuncture points (**Table 1**) a few minutes before oocyte retrieval. In the mixed frequency group, the needles in the abdominal muscles and in the hands were connected to an electrical stimulator (CEFAR ACUS 4; Cefar, Lund, Sweden) and stimulated with an alternating frequency of 80 Hz and 2 Hz, 3 s each, and a pulse duration of 0.18 ms. In the fixed frequency group, the needles in the abdominal muscles and in the hands were connected to an electrical stimulator (Agistim Duo®; Sedatelec, Irigny, France) and stimulated with a fixed frequency of 20 Hz and a pulse duration of 0.5 ms. The stimulation intensity was as high as possible, just under pain threshold. The stimulation intensity of the needles was adjusted continuously during the procedure. Well-trained nurses administered the acupuncture. At the end of the procedure, the acupuncture needles were removed.

In addition to electro-acupuncture, both groups received manual acupuncture, using the acupuncture point governor vessel (GV) 20 for stimulation (**Table 1**). Needles were stimulated every 10th minute during oocyte retrieval.

No premedication was administered to either group. If sufficient pain relief was not obtained by electro-acupuncture alone, patients were supplemented with i.v. alfentanil (0.25 mg) (Rapifen; Janssen-Cilag A/S, Birkeröd, Denmark). After the procedure, patients were offered additional pain relief as required in the form of either Pamol (paracetamol; Nycomed, Roskilde, Denmark) or Diclon (Diclofenac; DuraScan Medical Products AS, Odense, Denmark) in tablet form.

Outcome variables

Pain and anxiety assessment

A visual analogue scale (VAS) (McCormack *et al.*, 1988) is a rating scale consisting of a 10 cm line oriented vertically on a paper (Stener-Victorin *et al.*, 1999, 2003; Humaidan *et al.*, 2004; Greco *et al.*, 2005). Before oocyte retrieval, VAS was used to evaluate the level of anxiety, nausea and abdominal pain. Furthermore, after aspiration of one ovary, patients were asked to rate pain and nausea. Directly after aspiration, another rating was performed to assess the mean and maximum pain

Table 1. Acupuncture points, anatomical position and innervation, used together with a paracervical block during the oocyte retrieval procedure.

Points	*Stimulation*	*Segmental innervation*	*Muscle localization*
ST 29 bilaterally	EA	(Th7–12, L1)	Mm. obliquus externus, abdominis internus
LI 4 bilaterally	EA	Nn. ulnaris, medianus (C8, Th1)	Mm. interosseus dorsalis I, lumbricalis II, adductor pollicis
SP 6 bilaterally		Nn. tibialis (L4–5, S1–2)	Mm. flexor digitorum longus, tibialis posterior
GV 20	Manual	Nn. trigeminus (V), occipitalis minor (C2), occipitalis major (C2–3)	Aponeurosis epicranii

EA = electro-acupuncture; GV = governor vessel; LI = large intestine; SP = spleen.

levels during oocyte retrieval. At this point, nausea was not rated. Moreover, ratings were performed 30 min after aspiration and when the patients left the clinic. The questionnaire had the following end-points: for anxiety, no anxiety and unbearable anxiety; for abdominal pain, mean pain and maximum pain, no pain and unbearable pain. Finally, 30 min after aspiration, patients were asked to evaluate the pain relief as a whole during the procedure.

Recorded medication, time consumption and IVF parameters

In cases where patients needed additional analgesics during the aspiration, the dosage of alfentanil was recorded. Moreover, additional pain relief after the procedure was recorded. The time interval from the end of the oocyte retrieval until the patient left the clinic was recorded and referred to as time to discharge. Clinical parameters, including number of oocytes retrieved, number of embryo transfers, number of positive pregnancy tests per embryo transfer, and number of clinical pregnancies, were recorded.

A positive pregnancy test was defined by a plasma β-HCG concentration >10 IU/l, 12 days after embryo transfer. The ongoing clinical pregnancy rate was defined as an intrauterine pregnancy with a heartbeat 8 weeks after a positive β-HCG test (i.e. 10 weeks of pregnancy).

Statistics

Sample size was calculated based on a one-sided alternative hypothesis and 'non-inferiority' between the two arms. With a power of 80% and a level of significance of 0.05, a total of 51 patients were needed per arm to confirm the hypothesis. In order to account for possible dropouts, it was planned to include a total of 150 patients. The Mann–Whitney *U*-test was used to compare differences between the groups concerning the VAS ratings. The chi-squared test was used to compare differences among groups concerning, pregnancy rate per embryo transfer and clinical pregnancy rate. Student's *t*-test for independent samples was used to compare differences between the groups concerning time from the oocyte retrieval until leaving the clinic. $P < 0.05$ was considered significant.

Results

Cancellations

One hundred and sixty patients were randomized. Eighty-one patients were allocated to treatment with a mixed frequency and 79 patients were allocated to treatment with a fixed frequency. In the mixed group, five patients withdrew from the study on the day of oocyte retrieval. In the fixed group, three patients withdrew from the study on the day of oocyte retrieval. Seventy-six patients received treatment with a mixed frequency and 76 patients received treatment with a fixed frequency.

Patient characteristics

No demographic differences were seen between the two groups. All participants were Caucasians (**Table 2**).

Visual analogue scale (VAS)

The fixed frequency group had a higher anxiety rating before oocyte aspiration as compared with the mixed frequency group ($P < 0.05$) (**Table 3**). Moreover, women undergoing their first IVF/ICSI treatment (55.3%) had a significantly higher anxiety rating ($P < 0.01$) as compared with women with previous IVF failure (44.1%). There were, however, no differences regarding numbers of previous IVF attempts between the two groups (data not shown). After aspiration of one ovary, the mixed frequency group experienced a higher level of nausea as compared with the fixed frequency group ($P < 0.01$) (**Table 3**). No differences were seen regarding pain at any rating point (**Table 3**). No differences were seen regarding the duration of oocyte retrieval and hospitalization time (data not shown).

A total of three patients (4%) in the mixed frequency group were supplemented with 0.5 mg alfentanil during oocyte retrieval versus four patients (5%) in the fixed frequency group. After the procedure, 38 (50%) patients in the mixed frequency group were supplemented with either 1 g of paracetamol or 100 mg of a non-steroidal anti-inflammatory drug (diclofenac) versus

33 patients (43%) in the fixed frequency group. No difference in the need for supplementation was seen according to the cause of infertility. No side effects were reported.

Clinical outcome

In both the mixed and fixed frequency groups, 76 patients underwent oocyte retrieval and 62 patients had an embryo transfer. The reasons for not performing embryo transfer were: (i) no fertilization (mixed: 5, fixed: 4), (ii) no development/ stagnation/fragmentation (mixed: 9, fixed: 10). There were no significant differences between the mixed group and the fixed group regarding number of follicles aspirated, number of oocytes, number of embryos transferred, number of positive HCG tests, and clinical pregnancy rates (**Table 4**).

Table 2. Demographic data for patients given mixed or fixed frequency electro-acupuncture during oocyte retrieval.

Characteristics	*No. of women*	
	Mixed frequency (n = 76)	*Fixed frequency (n = 76)*
Age[a] (years)	32.0 (4.4)	31.3 (3.7)
Body mass index[a]	23.2 (4.9)	23.7 (3.4)
Cause of infertility		
Male	22	23
Tubal disease	17	12
Endometriosis	2	4
Anovulation	7	13
Unexplained	27	24
Other causes	1	0
Two causes	4	5

[a]Mean (SD). There were no statistically significant differences between the two groups.

Table 3. Visual analogue scale (VAS) ratings on vertical, 10-cm lines expressed as median (minimum–maximum) and mean (SD) in patients given mixed or fixed frequency electro-acupuncture during oocyte retrieval.

Scale and end-point definitions (0–10)	*VAS rating (cm)*				*P-value*
	Mixed frequency (n = 76)		*Fixed frequency (n = 76)*		
	Median (min–max)	*Mean (SD)*	*Median (min–max)*	*Mean (SD)*	
Before oocyte aspiration					
Anxiety: no anxiety and unbearable anxiety	0.8 (0–7.2)	1.6 (1.8)	2.0 (0–9)	2.3 (2.1)	<0.05
Nausea: no nausea and unbearable nausea	0 (0–5.8)	0.3 (0.9)	0 (0–8.3)	0.3 (1.1)	NS
Abdominal pain: no pain and unbearable pain	0 (0–6.1)	0.4 (1.0)	0 (0–8)	0.5 (1.3)	NS
After aspiration of one ovary					
Pain: no pain and unbearable pain	1.5 (0–9.0)	1.9 (1.8)	1.6 (0–5.0)	1.7 (1.3)	NS
Nausea: no nausea and unbearable nausea	0 (0–7.3)	0.3 (1.1)	0 (0–1.7)	0.06 (0.3)	<0.01
Pain directly after oocyte aspiration					
Maximum pain during oocyte retrieval: no pain and unbearable pain	4.4 (0–10.0)	4.6 (2.5)	4.9 (0–8.9)	4.5 (2.1)	NS
Mean pain during oocyte retrieval: no pain and unbearable pain	2.6 (0–8.5)	2.8 (1.8)	2.8 (0–6.1)	2.8 (1.5)	NS
Pain 30 min after oocyte aspiration					
Abdominal pain: no pain and unbearable pain	1.4 (0–7.5)	1.9 (1.7)	1.4 (0–8.2)	1.8 (1.8)	NS
Pain when leaving the clinic					
Abdominal pain: no pain and unbearable pain	0.4 (0–7.4)	0.8 (1.2)	0.5 (0–9.0)	0.7 (0.7)	NS

The Mann–Whitney *U*-test was used to compare differences in the VAS ratings between the groups. NS = not statistically significant.

Table 4. Oocytes retrieved and pregnancy outcome in patients given mixed or fixed frequency electro-acupuncture during oocyte retrieval.

	Mixed frequency (n = 76)	*Fixed frequency (n = 76)*
Oocytes retrieved, mean no. (SD)	8.2 (4.5)	8.4 (4.9)
Embryo transfer, no.	62	62
Positive HCG, no.	27	29
Positive HCG, % per embryo transfer	43.5	46.8
Ongoing pregnancies, % per embryo transfer (no.)	29 (18)	32 (20)

Using the chi-squared test there were no statistically significant differences between the two groups.

Discussion

This is, so far as is known, the first study exploring the pain relieving effect of different frequencies of electrical stimulation, when short-time electro-acupuncture was used for oocyte retrieval. In this study, a comparison was made between a fixed frequency of 20 Hz and an alternating frequency of 2 and 80 Hz, so-called mixed frequency. Both groups of patients received a paracervical block and manual acupuncture in addition to electro-acupuncture. In contrast to previous clinical reports on acute and chronic pain, no difference in pain relieving effect was found between the two modes of electrical stimulation when short-time electro-acupuncture was used. The mixed frequency group, however, experienced a significantly higher ($P < 0.01$) level of nausea.

In previous clinical studies, low frequency (2 Hz) or high frequency (80–100 Hz) electro-acupuncture has been compared with a mixed frequency. The overall conclusion was that the mixed frequency produces a significantly stronger analgesic effect than that produced by a fixed frequency (Han, 2003). From experimental data, it can be postulated that the mixed frequency of 2 and 80 Hz activates both the μ/δ and κ opioid system inducing a synergistic analgesic effect (Han, 2003). Thus, the mixed frequency has been used as a standard mode of stimulation in studies investigating optimal stimulation intensity.

In the previous study (Humaidan and Stener-Victorin, 2004), a fixed frequency of 20 Hz at a continuous pulse duration of 0.5 ms in a short duration electro-acupuncture protocol was used. Maximum pain ratings during oocyte retrieval were 4.6 in the electro-acupuncture arm. In the study by Stener-Victorin *et al.* (2003), comparing electro-acupuncture to alfentanil, a combination of 2 Hz in the hands and 80 Hz in the abdominal muscles was used in a 30 min electro-acupuncture protocol. Maximum pain ratings were 4.6 in the electro-acupuncture arm and 4.5 in the alfentanil arm, showing similar pain relief with electro-acupuncture and alfentanil. In the present study, maximum pain ratings were 4.6 and 4.5 in the mixed and fixed frequency group respectively, and no significant differences were found in the pain ratings at any time when the mixed frequency electro-acupuncture was compared to the fixed frequency electro-acupuncture group. This is in opposition to previous reports on the pain relieving effect of alternating frequencies (Hamza *et al.*, 1999a, 2000), but could be explained by the fact that most studies used a fixed low (2 Hz) or a fixed high (100 Hz) frequency. With a fixed frequency of 20 Hz, as in the present study, one could postulate that as well the δ opioid system, the κ opioid system is also activated, thereby inducing a similar analgesic effect as the mixed frequency electro-acupuncture. In addition, Go and Yaksh (1987) showed that other neuropeptides, such as substance P, are released by 20 Hz electro-acupuncture stimulation. The anti-nociceptive effect, however, of the release of substance P is unclear.

Interestingly, the mixed frequency electro-acupuncture group experienced a significantly higher ($P < 0.01$) level of nausea compared with the fixed frequency electro-acupuncture group after aspiration of the first ovary. One possible explanation of the positive effect of fixed electro-acupuncture stimulation with a frequency of 20 Hz on nausea might be that it modulates the autonomic nervous system, which is involved in the control of the antiemetic centre in the brain stem (Lin *et al.*, 1998; Lin and Fu 2000).

A total of 4% of patients in the mixed frequency group versus 5% in the fixed frequency group were supplemented with alfentanil during oocyte retrieval, proving the pain-relieving efficacy of the short duration protocol. However, it still remains to be investigated whether there are any differences in the pain relieving effect between the short duration protocol and the 30 min protocol, when different frequencies (mixed/fixed) of electrical stimulation are applied.

Taken as a whole, this study revealed pain levels in the electro-acupuncture arms similar to pain levels previously reported (Stener-Victorin *et al.*, 1999, 2003) when oocyte retrieval was performed with alfentanil, contrasting with the findings of others (Gejerwall *et al.*, 2005). Moreover, the analgesic effect of short duration electro-acupuncture with a fixed frequency of 20 Hz was similar to that of a mixed frequency of 2–80 Hz during oocyte retrieval. On the other hand, the degree of nausea was significantly lower ($P < 0.01$) in the fixed frequency electro-acupuncture group, after aspiration of the first ovary.

There is no consensus regarding the optimal method of pain relief for oocyte retrieval. Pain is subjective to each individual

and pain relief, therefore, should be tailored to the individual concerned. The scientific community is encouraged to embark upon future prospective randomized trials to further elucidate the effects of acupuncture.

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