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CLINICAL INVESTIGATIONS

Remifentanil Infusion and Paracervical Block Combination for Transvaginal Ultrasound Guided Oocyte Retrieval

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Abstract: The optimal anesthetic technique for transvaginal ultrasound guided oocyte retrieval (TUGOR) is not known. We present a case series of patients having TUGOR under intravenous remifentanil infusion and paracervical block (PCB). One hundred four unpremedicated patients were included in our study. After monitoring heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2) and end tidal CO_2 ($ETCO_2$), a remifentanil infusion of 0.25 μg kg^{-1} min^{-1} was started. PCB (10 ml 1% lidocaine) was performed under remifentanil infusion. As soon as the patient felt dizzy, the remifentanil infusion was decreased to 0.15 μg kg^{-1} min^{-1}. Sedation was evaluated according to a 5 - point scale (1: Patient sleeps and cannot be awakened, 2: Patient sleeps and can be awakened with difficulty, 3: Patient sleeps and can be easily awakened, 4: Patient is cooperative, oriented, and tranquil 5: Patient is anxious and agitated). Pain intensity was assessed with an 11-point numerical pain rating scale (NPRS) (0 = no pain while 10 = most severe pain). Patient satisfaction was assessed by asking whether they would prefer the same anesthesia protocol should they need to undergo a similar procedure in future. Side effects were recorded. ANOVA was used to assess differences in time and $P < 0.05$ was considered significant. HR and MAP decreased significantly from pre-procedure values but they were not clinically significant. Sedation scores remained between 3 and 4 and satisfactory analgesia was achieved in all patients. The most frequent side effects were fatigue (43.3%), nausea (34.6%) and pruritus (28.8%). Most of the patients were satisfied with the anesthetic technique. Remifentanil infusion in combination with PCB under monitored anesthesia care provided satisfactory analgesia without any major adverse effects in patients undergoing TUGOR.

Key Words: Oocyte retrieval, paracervical block, remifentanil

Introduction

Transvaginal ultrasound guided oocyte retrieval (TUGOR), which is considered a short painful procedure, requires anesthesia and/or analgesia. Several anesthetic techniques, mainly general anesthesia and central blocks, were used when TUGOR was first introduced (1-4). Since then, sedoanalgesia, paracervical block in combination with several opioids, benzodiazepines or hypnotics as well as electroacupuncture have been used in an attempt to reduce the perception of pain and discomfort during this procedure under monitored anesthesia care (1,5-12). Although remifentanil, a rapid and ultra-short acting opioid analgesic, has been used with either propofol or midazolam or as a sole agent (7,8,13), it has not been used in combination with paracervical block for TUGOR procedures. Therefore, we present our preliminary observational results using IV remifentanil infusion with paracervical block.

Materials and Methods

One hundred four unpremedicated patients having American Society of Anesthesiologists (ASA) class I or II physical status scheduled to undergo TUGOR between October 2002 and July 2003 at the Assisted Conception Unit in our hospital were included in the study. After we obtained approval from the local research ethics committee, all patients were informed about the procedure and the anesthetic technique. Then informed written consent was obtained from each patient.

In order to assess the intensity of pain, the numerical pain rating scale (NPRS) was explained to the patients before the procedure (0 corresponding to no pain and 10 to the most severe pain). Patients were told to indicate the degree of their pain by NPRS, when they were asked to evaluate the intensity of their pain.

Heart rate (HR), non-invasive mean arterial pressure (MAP) (Hewlett Packard M10258, Denmark), respiratory rate (RR), pulse oximetry (SpO_2) and end tidal carbon dioxide ($ETCO_2$) (Odam Physiogard SM785, France) were recorded prior to remifentanil infusion (baseline value), when the patient complained of dizziness, at the time of 1st (right) and 2nd (left) ovarian punctures, at the end of the procedure and 10, 20 and 30 min postprocedure (post.) and at the time of discharge.

Normal saline solution (5 ml kg^{-1} h^{-1}) was infused via an IV 22 G catheter. All patients received 3 l min^{-1} oxygen through one of the nostrils while measuring $ETCO_2$ from the other nostril during spontaneous ventilation.

Patients were positioned in dorsal lithotomy position. Betadine was applied for vaginal disinfection and the vagina was washed with a warm saline solution by the obstetrician. Then, remifentanil 0.25 µg kg^{-1} min^{-1} was infused via a perfusor (IVAC 770, San Diego, USA). As soon as the patient felt dizzy which was considered a clinical sign of opioid administration, 10 ml of 1% lidocaine was injected deeply at 3 and 9 o'clock positions of the cervix (14). Afterwards the remifentanil infusion was decreased to 0.15 µg kg^{-1} min^{-1}, followed by the retrieval procedure. Sedation scale according to 5 - point scale (1: Patient sleeps and cannot be awakened, 2: Patient sleeps and can be awakened with difficulty, 3: Patient sleeps and can be easily awakened, 4: Patient is cooperative, oriented, and tranquil 5: Patient is anxious and agitated) and the intensity of pain by NPRS were recorded every 5 min during the procedure and particularly at the time of PCB, ovarian punctures of each site (1st and 2nd punctures) and at the end of the procedure. Adverse effects were recorded.

The intravenous infusion of remifentanil was stopped after successful puncture of the last follicule. When NPRS was higher than 3, remifentanil infusion was increased by 0.05 µg kg^{-1} min^{-1} until complete pain relief occurred. In the case of deep sedation; i.e. RR < 8 breath min^{-1}, SpO_2 less than 94% and $ETCO_2$ higher than 50 mmHg, remifentanil infusion was decreased by 0.05 µg kg^{-1} min^{-1}. Switch on and off times of remifentanil infusion and surgical duration were recorded.

Patient satisfaction was assessed by asking whether they would prefer the same anesthesia protocol should they need to undergo a similar procedure in future.

Puncture sites were reexamined to make sure there was no bleeding. Patients moved to the transport table without any support and they were transferred to the recovery room. All of the parameters except $ETCO_2$ and RR were recorded every 10 min during the first 30 min postoperatively. Patients who were free from nausea and vomiting and had stable vital signs and were able to walk without any help were discharged after being observed for a maximum of 2 h.

Statistical Analysis: The results of the present study were expressed as mean ± standard deviation (mean ± SD) or n (%) where appropriate. HR, MAP, SpO_2, RR and $ETCO_2$ were analyzed by repeated measures ANOVA. $P < 0.05$ was considered significant.

Results

Demographic variables, ASA physical status, anesthesia and surgical duration are presented in Table 1.

During the study period the initial remifentanil infusion of 0.25 µg kg^{-1} min^{-1} was decreased to 0.2, 0.15, 0.1 and 0.05 µg kg^{-1} min^{-1} as required. Sufficient analgesia was provided but, 0.15 and 0.1 µg kg^{-1} min^{-1} in 47 (45.9%) and 41 patients (39.42%), respectively. There was a requirement for 0.2 µg kg^{-1} min^{-1} in 11 patients (10.57%) due to aspiration from the pouch of Douglas and puncture of the mobile follicles being stabilized by pressing from outside the abdomen. The minimum remifentanil infusion dose was 0.05 µg kg^{-1} min^{-1} in 1 patient (0.96%), whereas the maximum dose was 0.3 µg kg^{-1} min^{-1} in 1 patient (0.96%).

Hemodynamic changes are shown in Figure 1. There were statistically significant decreases in all MAP values except for the value measured at the time of dizziness, compared to the baseline values ($P < 0.05$), but those changes were not clinically significant. The IV fluid infusion was increased and 5 mg of IV ephedrine was

Table 1. Demographic properties, and operation and anesthesia duration (mean ± SD)(minimum-maximum values).

Age (year)	33.4 ± 5.2 (18-45)
Height (cm)	161.0 ± 5.7 (145-175)
Weight (kg)	65.5 ± 12.1 (38-110)
ASA I/II (n)	101/3
Operation duration (min)	28.3 ± 8.6 (10-64)
Anesthesia duration (min)	38.4 ± 9.1 (18-64)

administered to treat hypotension in only 1 (0.96%) patient. Significant changes were observed in the HR at the time of feeling dizzy, postoperative 10, 20 and 30 min compared to baseline values ($P < 0.05$), which were within clinical limits (Figure 1).

Peripheral oxygen saturation values determined from the second ovarian puncture to discharge showed a statistically significant decrease versus baseline values, but they were not clinically significant (Figure 2). Although there were significant increases in the $ETCO_2$ values with respect to baseline values ($P < 0.05$), none of them exceeded 50 mmHg (Figure 2).

There were significant decreases in the RR starting from the time of dizziness until the end of post. 20 min with respect to baseline values ($P < 0.05$). RR decreased below 8 breath min^{-1} in 12 patients (11.5%); 7 out of 12 (6.7%) had 7 breath min^{-1}, 3 out of 12 (2.9%) had 6 breath min^{-1} and 2 out of 12 (1.9%) had 5 breath min^{-1}. RR returned to normal values on the verbal command to breath deeply and the remifentanil infusion was decreased. The decrease in RR below 8 breath min^{-1} was generally observed before the punctures.

Most of the patients did not complain of any pain (NPRS = 0) at the time of PCB (n = 97, 93%), at the time of 1st puncture (n = 93, 89%), at the time of 2nd puncture (n = 83, 79%) or at the end of the procedure (n = 97, 93%). Fewer patients had NPRS between 1 and 3 as shown in Figure 3. None of the patients had NPRS higher than 3 at the time of PCB. However, more patients had NPRS scores higher than 3 at the time of the 2nd ovarian puncture (Figure 3). At the end of the procedure, NPRS scores became zero except one patient whose score was 4 (Figure 3).

Sedation scores of the patients were 4 before TUGOR, they remained between 3 and 4 during the procedure and returned to 4 during transfer to the recovery room.

The side effects are presented in Table 2. The most frequent side effects were fatigue (43.3%), nausea (34.6%) and pruritus (28.8%). Three (2.9%) patients out of 36 (34.6%) who were complaining of nausea vomited; 1 (0.96%) of them vomited during the procedure and the remaining 2 (1.9%) patients vomited after the procedure. Thirty-one patients (29.8%) were treated with 10 mg of metochlopramide and recovered, but the remaining 5 patients (4.8%) were additionally treated with 4 mg of IV ondansetron. Another frequent adverse effect was pruritus, particularly observed on the face, which was associated with the opioid, remifentanil.

Most of the patients [102 (98.1%)] stated that they would prefer the same anesthesia protocol should they need to undergo a similar procedure in future, while [2 (1.9%)] patients would not because of vomiting.

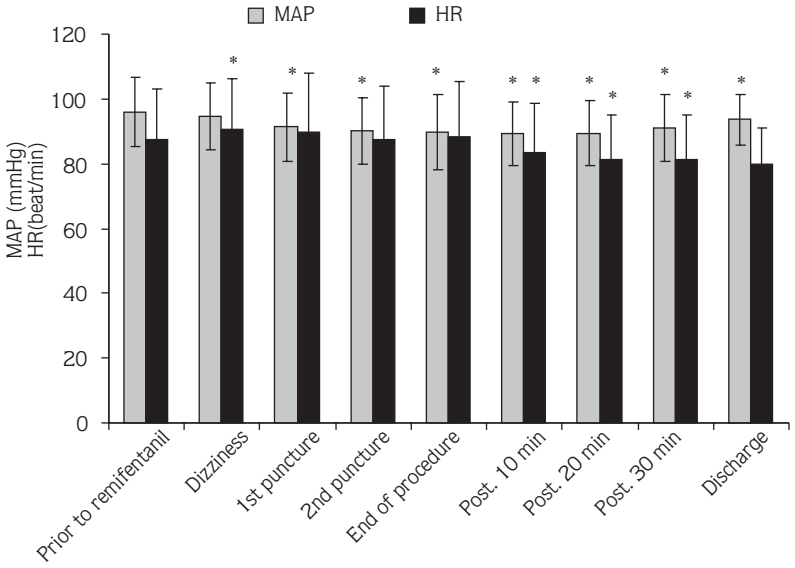

Figure 1. Mean arterial pressure (MAP) and heart rates (HR) of the patients (mean ± SD). *P < 0.05 versus prior to remifentanil administration (control) for each variable.

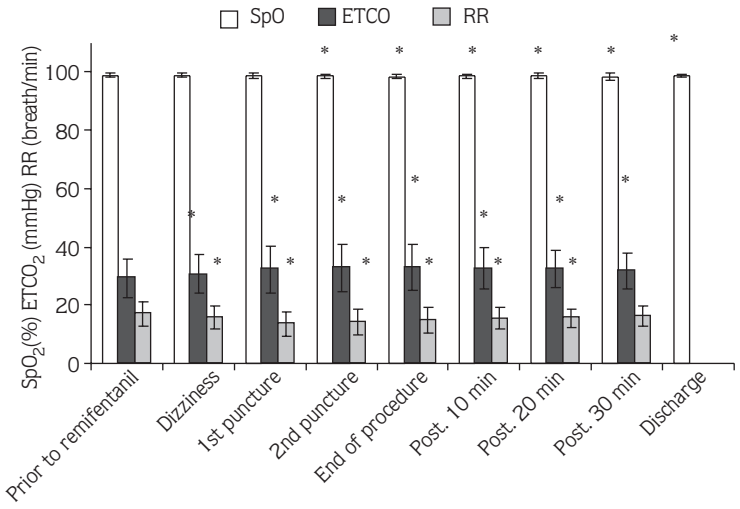

Figure 2. Peripheral oxygen saturation (SpO_2), end tidal carbon dioxide ($ETCO_2$) levels and respiratory rates (RR) of the patients (mean ± SD). *P < 0.05 versus prior to remifentanil administration (control) for each variable.

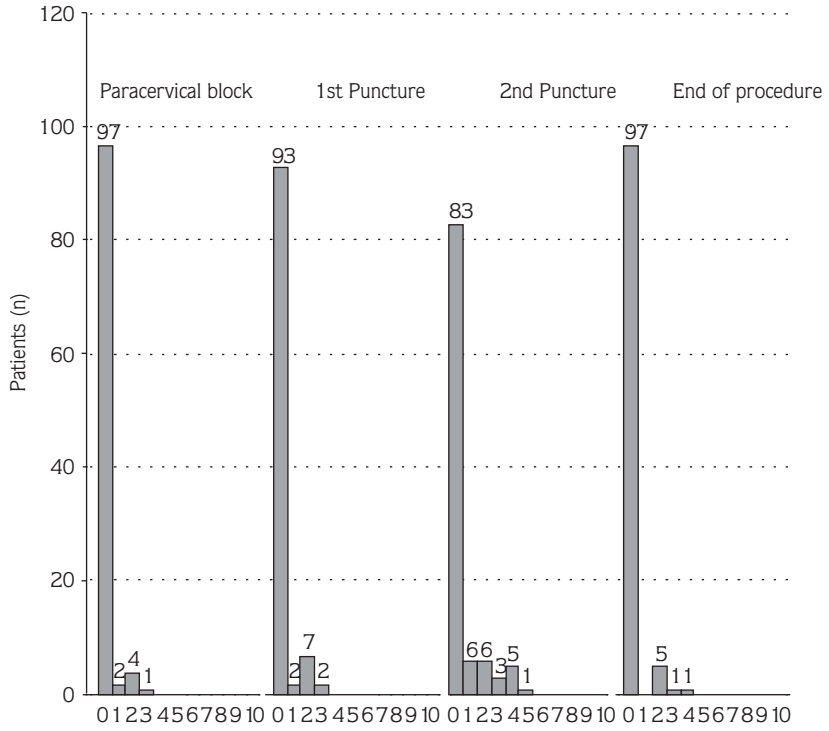

Figure 3. Distribution of numeric pain rating scale (NPRS) during paracervical block, 1st and 2nd ovarian punctures and at the end of the procedure.

Table 2. Incidence of side effects n(%).

	Yes	No
Nausea-vomiting	36 (34.6)	68 (57.7)
Dizziness	104 (100)	-
Dysphagia	4 (3.8)	100 (96.2)
Feeling warm	22 (21.2)	82 (78.8)
Pruritus	30 (28.8)	74 (71.2)
On face	28 (26.9)	-
On body	2 (1.9)	-
Fatigue	45 (43.3)	59 (56.7)
Headache	4 (3.8)	100 (96.2)
Shivering	14 (13.5)	90 (86.5)
Nystagmus	2 (1.9)	102 (98.1)
Muscle rigidity	-	104 (100)

Discussion

The present anesthesia protocol, IV remifentanil infusion plus PCB, resulted in a high patient satisfaction rate and few side effects (fatigue) without clinically significant changes in blood pressure, heart rate or peripheral oxygen saturation. The combination of PCB with IV remifentanil infusion under monitored anesthesia care provided satisfactory analgesia with satisfactory sedation scores in TUGOR.

A major disadvantage of TUGOR without general anesthesia is the variable degree of pain experienced by the patients. Therefore, we demonstrated that TUGOR could be performed without general anesthesia and its attendant risks. Remifentanil infusion in combination with PCB in patients undergoing TUGOR to relieve the pain and discomfort due to the procedure was proved to be successful in terms of hemodynamic and respiratory parameters as well as the patients' satisfaction associated with fewer adverse effects due to the present technique.

Many sedative-hypnotics and opioid analgesics have been frequently used in providing patient comfort, sedation, anxiolysis or supplemental analgesia during TUGOR performed with or without PCB under monitored anesthesia care (6,9,15,16).

Remifentanil, a piperidine derivative, is a potent mu-opioid receptor agonist with a rapid onset and a short half-life (3.8-8.3 min). It is rapidly metabolized by non-specific blood and tissue esterases to remifentanil acid which is about 800-2000 times less potent (17). Remifentanil has become widespread because of its rapid onset and elimination, and the ease of administrating it by continuous infusion. After it was shown that remifentanil had no effect on the development of frozen thawed rat embryo blastocytes, it was used in TUGOR procedures in combination with propofol and midazolam (7,8,18). Remifentanil was first used as a sole agent in TUGOR and sufficient analgesia was achieved by 0.25 μg kg^{-1} min^{-1} in 70% of patients by Wilhelm et al. (19). In parallel to that study we used the same initial remifentanil infusion dose of 0.25 μg kg^{-1} min^{-1}. According to our results, following initial dosing, the infusion dose was found to be ≤ 0.2 μg kg^{-1} min^{-1}. The remifentanil infusion rate was increased to 0.3 μg kg^{-1} min^{-1} in only 1 patient (0.96%) and total remifentanil consumption was 407.5 ± 123.2 μg.

Most of the drugs used for TUGOR were determined in follicular fluid (9,20,21). Achwal et al. (7) showed that small amounts of remifentanil were detected in the follicular fluid when compared to fentanyl. Although opioids used in TUGOR procedures were detected in the follicular fluid, it did not affect the pregnancy rates (13).

Wilhelm et al. (19) used a Stanpump program to determine peak bood concentration of remifentanil and concluded that the plasma remifentanil concentration decreased to 2 ng ml^{-1} and 1 ng ml^{-1} 5 and 10 min after stopping the infusion, respectively. We think that the peak blood concentration of remifentanil should have been even lower in our study both during and after the procedure, since we could easily decrease the infusion rate of remifentanil even ≤ 0.15 μg kg^{-1} min^{-1} in 89 (85.5%) patients because of sufficient analgesia.

It was stated that intravenous remifentanil infusion at doses of 0.025 μg $kg^{-1}min^{-1}$ was sufficient to cause adverse effects on the respiratory system (22). Furthermore it was noted that SpO_2 decreased to 87% in one patient that received remifentanil as a sole agent (13). Bolus doses of remifentanil with or without sedatives and hypnotics might result in muscle rigidity and respiratory depression (8,23). In contrast to those findings , we did not observe any muscle rigidity. None of our patients had SpO_2 values below 96% although the respiratory rate decreased below 8 breath min^{-1} in 12 patients (11.5%). As their sedation scores were found to be 3 and 4, their respiratory rates returned to normal ranges. However, we prepared for any emergent situation against probable muscle rigidity and respiratory depression.

Increased $ETCO_2$ may result in hypercapnia, leading to respiratory arrest, hypertension and cardiac arrhythmias (24). For that reason we suggest it is necessary to use a capnograph in addition to pulse oximeter if remifentanil infusion is used in monitored anesthesia care.

Wilhelm et al. (13) reported a stable hemodynamic profile in TUGOR. Although we observed statistically significant differences in cardiovascular parameters (heart rate, mean arterial pressure) compared to baseline values ($P < 0.05$), those changes were not clinically significant and only one hypotensive patient required treatment.

The incidence of nausea varied between 26% and 36%, whereas it was 10-21% for vomiting in TUGOR studies (15,18,25). We observed that 34.6% of our patients suffered from nausea and 2.9% of the patients vomited. In our opinion, the IV remifentanil infusion and PCB combination provided good recovery characteristics and none of the patients had any adverse effects on discharge.

The incidence of pruritus was 28.8%, which was higher than the 22% observed by Gold et al. (25). The most frequent side effect in the present study was fatigue (43.3%). Both fatigue and pruritus ameliorated.

Paracervical block has not only been widely used in dilatation and curettage and hysteroscopies by obstetricians, but also in assisted conception units with or without premedication in combination with opioids, hypnotics, benzodiazepines and electroacupuncture (12,26,27). PCB is effective in reducing the perception of pain arising from the vaginal mucosa to the peritoneal layer (vaginal pain), but there is a need for other analgesics for the pain arising from the peritoneal layer (abdominal pain). We were able to reduce the vaginal pain with PCB and the abdominal pain by remifentanil infusion. Combining PCB with IV remifentanil infusion might have resulted in lower remifentanil consumption, leading to a lack of muscle rigidity and respiratory depression in this study. It was reported that remifentanil infusion resulted in respiratory difficulties in 10% (13), whereas remifentanil in combination with midazolam caused a mild muscle rigidity in 13% of patients (8).

Several doses varying from 50 to 200 mg of lidocaine have been studied (9,10,28). No significant differences in pain scores, fertilization, implantation or pregnancy rates were found with lidocaine at doses of 150 and 200 mg. In a recent randomized double-blind study comparing 50, 100 and 150 mg of lidocaine doses, no significant differences in pain scores were found (29). Severe bradycardia and bradypnea were reported while applying PCB with 400 mg of mepivacaine (30). Therefore, the clinically safe limits of local anesthetics should not be exceeded.

In conclusion, remifentanil infusion in combination with PCB not only reduced the perception of pain and discomfort but also provided better sedation scores with high patient satisfaction. Remifentanil because of its rapid onset and elimination, allowing us easy dose titration by IV continuous infusion, used in combination with PCB in monitored anesthesia care proved to be successful in TUGOR with comparable side effects.

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References

1. Hammadeh ME, Wilhelm W, Huppert A et al. Effects of general anesthesia vs. sedation on fertilization, cleavage and pregnancy rates in an IVF program. Arch Gynecol Obstet 263: 56-9, 1999.
2. Manica VS, Bader AM, Fragneto R et al. Anesthesia for in vitro fertilization: a comparison of 1.5% and 5% spinal lidocaine for ultrasonically guided oocyte retrieval. Anesth Analg 77: 453-6, 1993.
3. Botta G, D'Angelo A, D'Ari G et al. Epidural anaesthesia in an in vitro fertilization and embryo transfer program. J Assist Reprod Genet 12: 187-90, 1995.
4. Martin R, Tsen LC, Tzeng G et al. Anesthesia for in vitro fertilization: The addition of fentanyl to 1.5% lidocaine. Anesth Analg 88: 523-6, 1999.
5. Bein T, Klapproth CE. Analgosedierung mit midazolam und fentanyl als alternative zur allgemeinnarkose bei transvaginaler follikelpunktion im rahmen der in-vitro-fertilization. Anaesth Intensivther Notfallmed 24: 77-80, 1989.
6. Trout SW, Vallrand AH, Kemmann E. Conscious sedation for in vitro fertilization. Fertil Steril 69: 799-808, 1998.

7. Achwal M, Abuzeid M, Bowenschen JL et al. Remifentanil and fentanyl concentrations in follicular fluid during transvaginal oocyte retrieval. Anesthesiology 90: A16, 1999.

8. Casati A, Valentini G, Zangrillo A et al. Anaesthesia for ultrasound guided oocyte retrieval. Midazolam/remifentanil versus propofol/fentanyl regimens. Eur J Anaesthesiol 16: 773-8, 1999.

9. Soussis I, Bower S, Boyd O et al. Follicular fluid levels of midazolam, fentanyl, and alfentanil during transvaginal oocyte retrieval. Fertil Steril 64: 1003-7, 1995.

10. Ng EHY, Tang OS, Chui DKC et al. 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: 2783-7, 1999.

11. Ng EHY, Tang OS, Chui DKC et al. Comparison of two different doses of lignocaine used in paracervical block during oocyte collecting in an IVF programme. Hum Reprod 15: 2148-51, 2000.

12. Stener-Victorin E, Naldenström U, Nilsson L et al. A prospective randomized study of electro-acupuncture versus alfentanil as anaesthesia during oocyte aspiration in in-vitro fertilization. Hum Reprod 14: 2480-4, 1999.

13. Wilhelm W, Hammadeh ME, White PF et al. General anesthesia versus monitored anesthesia care with remifentanil for assisted reproductive technologies: Effect on pregnancy rate. J Clin Anesth 14: 1-5, 2002.

14. Stubblefield PG. Control of pain in women undergoing abortion. Int J Gynaecol Obstet 3: 131-40, 1989.

15. Avramaov MN, Smith I, White PF. Interactions between midazolam and remifentanil during monitored anesthesia care. Anesthesiology 85: 1283-9, 1996.

16. Rosenblatt M, Bradford C, Bodian C et al. The effect of propofol based sedation technique on cumulative embryo scores, clinical pregnancy rates, and implantation rates in patients undergoing embryo transfers with donor oocytes. J Clin Anesth 9: 614-7, 1997.

17. Glass PS, Gan TJ, Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanil. Anesth Analg 99: S 7-14, 1999.

18. Brennan G, Yarmush, Stein D et al. The effect of remifentanil on the percentage of frozen-thawed mouse embryos that proceed to the blastocyst stage. J Soc Gynecol Invest 4: 173, 1997.

19. Wilhelm W, Biedler A, Hammadeln ME et al. Infusionanalgesia mit remifentanil. Anaesthesist 48: 698-704, 1999.

20. Endler GC, Srour M, Magyar DM et al. Follicular fluid concentrations of thiopental and thiamylal during laparoscopy for oocyte retrieval. Fertil Steril 48: 828-33, 1987.

21. Imoedemhe DAG, Sigue AB, Abdul-Ghani I et al. An evaluation of the effect of the anaesthetic agent propofol (Diprivan) on the outcome of human in vitro fertilization. J Assist Reprod Genet 9: 488-91, 1992.

22. Amin HM, Sopchak AM, Esposito BF et al. Naloxane-induced and spontaneous reversal or depressed ventilatory responses to hypoxia during and after continuous infusion of remifentanil or alfentanil. J Pharmacol Exp Ther 274: 34-9, 1995.

23. Hogue CW, Bowdle TA, O'Leary C et al. A multicenter evaluation of total intravenous anesthesia with remifentanil and propofol for elective in patient surgery. Anesth Analg 83: 279-85, 1996.

24. Freeman ML. Sedation and monitoring for gastrointestinal endoscopy. Gastrointest Endosc Clin N Am 3: 485-99, 1994.

25. Gold MI, Waykins WD, Sung YF et al. Remifentanil versus remifentanil/midazolam for ambulatory surgery during monitored anesthesia care. Anesthesiology 875: 51-7, 1997.

26. Phair N, Jensen J, Nicols N. Paracervical block and elective abortion: the effect of waiting between injection and procedure pain. Am J Obstet Gynecol 186: 1304-7, 2002.

27. Cicinelli E, Didonna T, Schonauer LM et al. Paracervical anesthesia for hysteroscopy and endometrial biopsy in postmenopausal women: a randomized, double-blind, placebo-controlled study. J Reprod Med 43: 1014-8, 1998.

28. Wikland M, Evers H, Jakobsson AH et al. The concentration of lidocaine in follicular fluid when used for paracervical block in a human IVF-ET programme. Hum Reprod 5: 920-3, 1990.

29. Ng EHY, Miao B, Ho PC. A randomized double-blind study to compare the effectiveness of three different doses of lignocaine used in paracervical block during oocyte retrieval. J Assist Reprod Genet 20: 8-12, 2003.

30. Ayestaran C, Matorras R, Gomez S et al. Severe bradycardia and bradypnea following vaginal oocyte retrieval: a possible toxic effect of paracervical mepivacaine. Eur J Obstet Gynecol Reprod Biol 91: 71-3, 2000.