Turk J Med Sci
36 (2006) 105-111

CLINICAL INVESTIGATION

Remifentanil Infusion and Paracervical Block Combination Versus Remifentanil Infusion Alone During In Vitro Fertilisation (IVF)

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Received: July 06, 2005

Abstract: The aim of this study is to compare two accepted techniques; intravenous (IV) remifentanil infusion versus its combination with paracervical block (PCB) in patients undergoing transvaginal ultrasound guided oocyte retrieval (TUGOR). One hundred unpremedicated patients were divided into two groups to receive either IV remifentanil (Group R) or IV remifentanil plus PCB (Group R+PCB). After monitoring cardiopulmonary parameters, remifentanil infusion of 0.25 μg kg^{-1} min^{-1} was started in both in groups. Additionally, when the patient felt dizzy, PCB with 10 ml 1% lidocaine was performed only in Group R+PCB followed by remifentanil infusion reduction to 0.15 μg kg^{-1} min^{-1}. Hemodynamic and respiratory parameters, adequacy of analgesia by Simple Numerical Rating Scale (SNRS), total amount of remifentanil used, pregnancy rates and side effects were recorded. Hemodynamic changes remained within clinical limits.There were clinically insignificant changes in peripheral oxygen saturation (SpO_2) and end tidal carbon dioxide ($ETCO_2$) and they returned to baseline at the end of the procedure. SNRS higher than 3 at the time of 1st ovarian puncture was observed in 6 and 0 patients, in Groups R and R+PCB, respectively ($P < 0.05$). The total amount of remifentanil used (μg) was significantly higher in Group R (571.8 ± 167.4) than in Group R+PCB (357.2 ± 93.6). Pregnancy rates were 60% and 48% for Groups R and R+PCB, respectively ($p = 0.048$). The incidence of nausea+vomiting was higher in Groups R (42%) than in Group R+PCB (20%) ($P < 0.05$). Addition of PCB to IV remifentanil infusion was found to be superior in pain relief during 1st ovarian puncture and reduced the incidence of nausea-vomiting with respect to IV remifentanil infusion alone.

Key Words: Paracervical block; lidocaine, remifentanil; IVF

Introduction

Transvaginal ultrasound guided oocyte retrieval (TUGOR) is a relatively invasive procedure generally performed under light anesthesia with local anaesthesics, opioids, hypnotics or benzodiazepines (1). In recent years several opioids, such as, meperidine, alfentanil, fentanyl and recently remifentanil, have been used as a part of conscious sedation/monitored anesthesia care (2, 3).

Remifentanil is a μ opioid agonist, which can be administered by intravenous IV infusion. Short elimination half life and increased metabolism by blood and tissue esterases make remifentanil a suitable agent for outpatient procedures such as IVF (4). After Brennan et al. (5) showed that there were no toxic effects of remifentanil in freeze and thawed mouse embryos, remifentanil has been administered either as a sole agent or in combination with propofol or midazolam in IVF (6-8).

Paracervical block (PCB) has been used in combination with opioids, hypnotics, sedatives, and acupuncture with or without premedication during TUGOR (9-16). We have recently used the IV remifentanil infusion and PCB combination and presented our preliminary observational results (17). However, addition of PCB to IV remifentanil infusion has not yet been compared with IV remifentanil infusion. Therefore, we aimed to compare two accepted techniques; (IV) remifentanil infusion versus its combination with (PCB) in patients undergoing (TUGOR).

Materials and Methods

One hundred unpremedicated patients, having American Society of Anesthesiologists (ASA) class I or II physical status and scheduled to undergo TUGOR, were included in this prospective observational comparative study. After we obtained approval from the local hospital ethics committee, all patients were informed about the procedure. Informed written consent was then obtained from each patient.

Patients were selected to have an IVF attempt with various etiologies (Table 1). Inclusion criteria consisted of first IVF attempt, age under forty, and normal responders. Induction of ovulation consisted of controlled ovarian hyperstimulation with subcutaneous leuprolide acetate 1 mg day^{-1} (Lucrin, Abboth, Turkey) for 14 days followed by a reduced dose of 0.5 mg day^{-1} leuprolide acetate throughout the cycle. Controlled ovarian hyperstimulation was achieved with gonadotrophins, either recombinant follicle stimulating hormone (Gonal F-Serono, Puregon Organon, Turkey) or in combination with human menopausal gonadotropin (Menogon, Erkim, Turkey). The initial dose for each patient was adjusted individually according to day 3 FSH levels, basal antral follicle count and ovarian volume (150-450 IU day^{-1}). Cycle monitorization was done by serial measurement of serum E_2 levels and ovarian folliculometry. Gonadotropin dose was adjusted individually according to the follicular growth. Ova collection was scheduled to be performed within 36 hours of injection of human chorionic gonadotropin (hCG) 10.000 IU (Profaci, Serono, Turkey).

Table 1. Demographic characteristics and etiologies of infertility (Mean ± SD).

	Group R (n = 50)	Group R+PCB (n = 50)
Age (years)	32.7 ± 5.9	33.5 ± 4.8
Height (cm)	159.7 ± 5.9	159.1 ± 5.5
Weight (kg)	61.8 ± 8.1	63.3 ± 13.4
Primary Infertility Rate	10/50 (20%)	10/50 (20%)
Living Child	1/50 (2%)	1/50 (2%)
Infertility Causes		
Tuboperitoneal	6 (12%)	4 (8%)
Male-borderline	6 (12%)	3 (6%)
Male-severe	21 (42%)	18 (24%)
Anovulation	3 (6%)	6 (12%)
Unexplained	14 (28%)	12 (24%)
Mixed	-	7 (14%)
Type of treatment ICSI	50 (100%)	50 (100%)

ICSI: Intracytoplasmic sperm injection.

In order to assess the intensity of pain, 11-point Simple Numerical Rating Scale (SNRS) 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 by the SNRS when they were asked to evaluate the intensity of pain.

Heart rate (HR), non-invasive mean arterial pressure (MAP) (Hewlett Packard M10258, Denmark), respiratory rate (RR), peripheral oxygen saturation (SpO_2) and end tidal carbon dioxide ($ETCO_2$) were measured continuously (Odam Physiogard SM785, France) but recorded at specific time points such as; before the induction, at the time of feeling dizzy, 1st and 2nd ovarian punctures, at the end of the procedure, 10, 20 and 30 min after the procedure and on discharge. All patients received 3 l min^{-1} oxygen through one of the nostrils while measuring $ETCO_2$ from the other nostril during spontaneous ventilation. Physiologic saline (0.9% NaCl) 5 ml kg^{-1} h^{-1} was infused to the patients during the procedure.

The patients were allocated into two groups to receive either IV remifentanil infusion (Group R, n=50) or IV remifentanil infusion+PCB (Group R+PCB, n=50). Patients were told to indicate when they started to feel dizzy before the onset of remifentanil infusion. Both groups received IV remifentanil (2 mg diluted in 20 ml saline) infusion of 0.25 µg kg^{-1} min^{-1} via perfusor (IVAC 770, San Diego, U.S.A.) under the control of an anesthesiologist. As soon as the patient told that she felt dizzy, the remifentanil dose of 0.25 µg kg^{-1} min^{-1} was continued in Group R and onset of retrieval procedure was allowed to continue. In Group R+PCB, the same remifentanil regimen followed by the PCB with 10 ml 1% lidocaine injection was divided between 3 and 9 o'clock positions of the cervix by the obstetricians (18). After PCB, remifentanil infusion was decreased to 0.15 µg kg^{-1} min^{-1} followed by the onset of retrieval procedure. Remifentanil dose adjustment was performed according to sedation and respiratory parameters.

Degree of sedation was evaluated according to a five point scale (1: Patient sleeps and can not be awakened, 2:

Patient sleeps and can be awakened with difficulty, 3: Patient sleeps and can be easily awakened, 4: Patient is co-operative, oriented, and tranquil 5: Patient is anxious and agitated).

Sedation score and SNRS were measured every 5 min but particularly recorded at the time of PCB, ovarian punctures of right and left sites (1st and 2nd ovarian punctures) and at the end of the procedure. Remifentanil infusion was discontinued when the procedure was over.

When the sedation score was less than 3, RR less than 8 breath min^{-1}, SpO_2 less than 94% and $ETCO_2$ higher than 50 mmHg, remifentanil infusion was reduced by 0.05 µg kg^{-1} min^{-1} incrementally. Meanwhile when the SNRS was higher than 3, remifentanil infusion was increased by incremental doses of 0.05 µg kg^{-1} min^{-1} in 1 min intervals up to the dose of 0.25 µg kg^{-1} min^{-1}. The total amount of remifentanil used and duration of the procedure and side effects were recorded.

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

Patients were allowed to pass to the transport table without any support and they were transferred to the recovery room. Patients free from side effects with stable vital signs and able to walk without any help were discharged after being observed for maximum 2 hours.

All retrieved ova were processed for intracytoplasmic sperm injection. All embryos were cultured until day three and the best quality embryos transferred. The mean number of transferred embryo was 3.4 ± 0.8 and all embryo transfers were performed under ultrasound guidance. All patients received luteal support with vaginal progesterone (Crinone, Serono, Turkey) for 14 days, or 10th week of pregnancy. A β hCG above 10 mIU ml^{-1} was considered as pregnancy and a positive fetal heart beat was considered as clinical pregnancy.

Statistical Analysis

The results of the present study were expressed as mean ± standard deviation (Mean ± SD) or n (%) where appropriate. Demographic variables, duration of anesthesia and procedure, amount of remifentanil consumption and number of collected oocytes were compared by t-test. HR, MAP, SpO_2, RR and, $ETCO_2$ were analyzed by repeated measures ANOVA followed by Bonferroni correction. Chi square and Fischer's exact tests were used to assess differences in the incidence of sedation score, side effects, causes of infertility, IVF rates and patient numbers having SNRS higher than 3 between the groups. $P < 0.05$ was considered as significant.

Results

Demographic variables of the groups were comparable and infertility causes of the patients were shown in Table 1.

The duration of procedure and anesthesia were comparable in both groups (Table 2). Remifentanil consumption was significantly lower in Group R+PCB than in Group R ($P < 0.05$, Table 2). The number of oocytes picked up were similar in both groups. Rates of fertilization and retrieval were not significantly different between the groups. Pregnancy rate per cycle ($p = 0.048$) and embryo transfer ($p = 0.026$) were significantly higher in Group R than in Group R+PCB, respectively. Fertilization was done by ICSI in all of the retrieved ova (Table 2).

There were no significant differences in MAP and HR both within and between the groups and they remained within normal clinical limits throughout the procedure (data not shown).

There were clinically insignificant fluctuations in SpO_2 and $ETCO_2$ values but they returned to clinically normal limits at the end of the procedure (Figure 1). The number of patients having RR < 8 breath min^{-1} were 12 and 8 in groups R and R+PCB, respectively ($P > 0.05$).

Table 2. Characteristics of anesthesia and procedure in the groups (Mean ± SD).

	Group R (n = 50)	Group R+PCB (n = 50)
Duration of procedure (min)	35.9±10.9	30.2±8.3
Duration of anesthesia (min)	45.4±12.2	39.0±9.0
Remifentanil consumption (µg)	571.8±167.4	357.2±93.6*
Number of oocytes picked up	13.3 ± 7.1	11.8 ± 6.1
Retrieval rate (%)	86.3	91.4
Fertilization rate (%)	69.8	73.3
Pregnancy rate per cycle (%)	60	48*
Pregnancy rate per embryo transfer (%)	62.5	51.1*

*: $P < 0.05$ (between the groups)

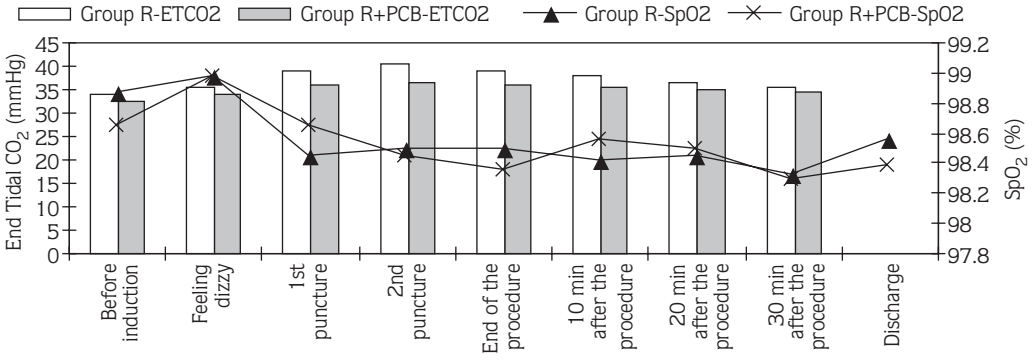

Figure 1. The distribution of peripheral oxygen saturation (SpO_2) and end tidal carbondioxide (ET CO_2) concentration of the groups recorded at specific time points. *:P < 0.05 (between the groups).

The number of patients having SNRS higher than 3 at the time of 1st ovarian puncture in Group R was significantly higher than in Group R+PCB (P < 0.05), but there were no significant differences in the number of patients having SNRS higher than 3 at other time points between the groups (Table 3). Sedation scores of the patients were 4 (co-operative and oriented) until the 1st ovarian puncture in both groups. Although it remained stable at 4 in Group R+PCB, it varied between 3 to 4 in Group R.

The incidence of side effects; nausea, dysphagia, shivering and headache were higher in Group R than in Group R+PCB (P > 0.05). Only the incidence of nausea+vomiting was significantly lower in Group R+PCB than in Group R (P < 0.05, Table 4) and these patients were treated with 10 mg IV metochlopromide. Although the incidence of pruritus was less in Group R than in Group R+PCB, it was not significantly different between the groups (P > 0.05, Table 4) and it recovered spontaneously without treatment. Muscle rigidity was not observed in any of the groups (Table 4).

Table 3. Simple numeric rating scale (SNRS) of patients higher than 3 (n).

	Group R (n = 50)	Group R+PCB (n = 50)
Paracervical block	0	0
1st ovarian puncture	6*	0
2nd ovarian puncture	3	3
End of procedure	0	1

*: P < 0.05 between the groups

Table 4. Incidence of side effects [n (%)].

	Group R (n=50)	Group R+PCB (n=50)
Nausea	26 (52)	18 (36)
Nausea + vomiting	21 (42)	10 (20)*
Dysphagia	6 (12)	2 (4)
Pruritus	18 (36)	20 (40)
Headache	4 (8)	3 (6)
Shivering	10 (20)	7 (14)
Nystagmus	2 (4)	2 (4)
Muscle rigidity	0 (0)	0 (0)

*: P<0.05 between the groups

Patient satisfaction rate did not differ significantly between the groups; 47 out of 50 (94%) versus 48 out of 50 (96%) in Groups R and R+PCB, respectively. Since patients were highly satisfied with the anesthesia technique, they stated that they would prefer the same anesthesia protocol should they need to undergo a similar procedure in future.

Discussion

In the present study either remifentanil infusion alone or remifentanil infusion plus PCB produced high patient satisfaction rate and similar side effects except nausea+vomiting. No clinically significant changes were observed in blood pressure, heart rate, peripheral oxygen saturation, and end tidal carbondioxide pressure. The combination of PCB with remifentanil resulted in lower remifentanil consumption leading to less nausea +

vomiting and more pain relief during the 1st ovarian puncture of TUGOR.

Remifentanil and lidocaine were traced in follicular fluid (7, 9, 20). No adverse effects of these drugs on pregnancy rates have been reported (21). Hammadeh et al (22) combined remifentanil with hypnotics and benzodiazepines and reported no adverse effects on fertilization, cleavage and pregnancy rates, with better rates than general anesthesia. Therefore, we used both drugs in our anesthesia protocols.

The lidocaine dose used for PCB may vary (11). It has been reported that the efficiency of different lidocaine doses on fertilization, cleavage and pregnancy rates were similar in TUGOR (15,16). A higher pregnancy rate has been achieved with electroacupuncture and PCB with respect to alfentanil use (9) . When Gonen et al (10) compared local anesthesia plus sedation, epidural anesthesia and general anesthesia including nitrous oxide, they reported that the pregnancy rates were similar. Jensen et al (23) compared intravenous sedation and general anesthesia and found that the longer the general anesthesia duration the lower the fertilization rate, but not with local anesthesia. In contrast to the study recommending that 10 ml of 0.5% (50 mg) lidocaine was the lowest effective dose in PCB in TUGOR (11), in the present study we divided 1% 10 ml (100 mg) lidocaine between two injection sites in our unpremedicated patients. In the study of Ng et al (11), the reason for finding 50 mg lidocaine in PCB to be effective should be the heavy premedication (im 50 mg of pethidine and 25 mg of prometazine followed by IV 5 mg of diazepam and 25 mg of pethidine) administered prior to intravenous sedatives and/or analgesics. The local anesthetic agents were supposed to pass promptly to the intravascular space due to increased structures at the apex of the vagina causing high blood peak levels. However, the lidocaine (100 mg) dose we used is within recommended doses in clinical practice (50-200 mg) (16, 19).

We have recently reported that IV remifentanil infusion and PCB combination was effective in relieving pain during TUGOR (17). In that preliminary observational study, 104 patients received the same protocol as Group R+PCB of the present study. However, this combination was not compared with IV remifentanil infusion alone in regard to side effects. Concerning both groups of the present study, significantly less nausea+vomiting was observed in Group R+PCB (20%) than in Group R (42%). The total amount of remifentanil used was significantly lower in the Group R+PCB (357.2 ± 93.6 μg) than in Group R (571.8 ± 167.4 μg.). When remifentanil infusion+PCB groups of both studies were taken into account, the incidences of nausea+vomiting were comparable (34.6% versus 20%) and the corresponding amounts of remifentanil used were comparable also (407.5±123.2 μg vs 357.2±93.6 μg for our previous and the present studies, respectively) as well. The side effects, such as pruritus which was observed in 36% and 40% of patients in Groups R and R+PCB respectively in this study, were less frequent (54%) with respect to Wilhelm et al (6) who used remifentanil as a single agent for oocyte retrieval.

The contribution of PCB in this technique not only reduced side effects but also provided excellent analgesia especially during the 1st ovarian puncture, which was one of the most painful stages of the TUGOR procedure.

The hemodynamic and respiratory side effects of remifentanil are dose dependent (4). We observed clinically insignificant changes in MAP, HR, SpO_2 and $ETCO_2$ levels with respect to baseline values according to our preliminary results (17). In the present study MAP and HR did not differ within and between the groups and SpO_2 and $ETCO_2$ levels showed fluctuations due to dose adjustment of remifentanil but those fluctuations were within clinically acceptable limits.

Wilhelm et al (6) administered remifentanil alone and stated that the remifentanil infusion doses higher than 0.25 μg kg^{-1} min^{-1} may cause respiratory depression. In our study, after the onset of retrieval procedure, initial remifentanil dose was reduced to maintain conscious sedation, but when patients' SNRS became 3, incremental increase was carried out to provide adequate analgesia. Therefore, we did not need to use remifentanil doses higher than the initial dose (0.25 μg kg^{-1} min^{-1}). We found that mean SpO_2 and $ETCO_2$ levels did not exceed normal clinical limits at any time point. However, the limitation of measuring $ETCO_2$ by a nasal canula gives only a rough estimation of $PaCO_2$ which is not always reliable in diagnosing respiratory depression. The number of patients having RR < 8 breath min^{-1} were 12 and 8 in groups R and R+PCB, respectively. Patients were told to take a deep breath since they were cooperative and able to obey verbal commands in this situation.

Casati et al (8) reported moderate muscle rigidity in patients receiving midazolam and remifentanil together. Arnt et al (24) reported mild thorax rigidity in patients premedicated with midazolam receiving IV remifentanil. Although Wilhelm et al (6) observed respiratory difficulty in 10% of the patients, they reported no muscle rigidity. We also have not observed any muscle rigidity either in the present study in both groups or in our previous study (17) because we did not use benzodiazepins or hypnotics in premedication. The explanation for this finding could be the lack of premedication in both studies.

The number of follicules aspirated and number of oocytes retrieved and the rate of fertilization and cleavage in both groups, pregnancy rate per cycle and embryo transfer decreased significantly in Group R+PCB with respect to Group R. We think that this reduction is independent of our anesthesia technique because many factors related to patients and surgeons might have a role in fertility.

In conclusion, addition of PCB to remifentanil infusion reduced remifentanil requirement and side effects due to remifentanil use during TUGOR. The two anesthesic techniques, remifentanil plus PCB being superior, provided sufficient analgesia and patient comfort under monitored anesthesia care.

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