Comparison of the effects of 2 different doses of remifentanil infusion for sedation during in-vitro fertilization procedure

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ABSTRACT

الأهداف: عمل مقارنة بين الجرعتين المختلفتين من تسريب الريميفينتانيل (remifentanil) المُضاف إليه البروبوفول في عملية التلقيح المجهري وذلك على أساس مستوى التخدير المهدئ، وتأثيره على ديناميكية الدم، ورضا المرضى والأطباء عن هاتين الجرعتين.

الطريقة: أُجريت هذه الدراسة الاستطلاعية العشوائية المغشاة في قسم التخدير والنساء والولادة، كلية الطب التابعة لجامعة دوكوز إيلول، إيزمير، تركيا، واستمرت خلال الفترة من نوفمبر 2006م إلى أغسطس 2008م. شملت الدراسة 86 مريضة من الفئة 1 ـ 2 حسب تصنيف جمعية أطباء التخدير الأمريكية، وتتراوح أعمارهم ما بين 18–40 عاماً واللاتي سيخضعن لعملية التلقيح المخبري. لقد تم تقسيم المشاركات في الدراسة إلى مجموعتين وهما: المجموعة ر1 وتلقت 0.1 ميكروغرام / كلغ / د من تسريب الريميفينتانيل، والمجوعة ر2 وتلقت 0.15 ميكروغرام / كلغ / د من نفس المخدر المهدئ. وبعد ذلك قمنا بتسجيل البيانات التالية: الآثار الجانبية، ومجموع الجرعات المُعطاة من الريميفينتانيل والبروبوفول، ومعدل نبضات القلب، وقيم ضغط الدم الانقباضي والانبساطي. وأخيراً قمنا بمقارنة معدلات العقم، والانقسام، والحمل مع التنبؤ بنسبة الحمل المتوقعة.

النتائج: أشارت نتائج الدراسة إلى عدم ظهور فروق واضحة بين المجموعتين وذلك في معدل نبضات القلب ومتوسط ضغط الشرايين (p=0.281). ولقد كان رضا أطباء التخدير عن نتائج المجموعة ر1 أعلى من رضاهم عن المجموعة ر2 (p=0.009)، فيما كنا رضا الجراحيين عن نتائج المجموعة ر2 أعلى من رضاهم عن المجموعة ر1 (p=0.01). وأسفرت النتائج في كلتي المجموعتين عن رضا المرضى (p=0.31)، كما لم يكن هناك اختلافاً بين المجموعتين عندما قمنا بمقارنة كلاً من: معدلات الحمل، والانقسام، والعقم، والتنبؤ بنسبة الحمل المتوقعة (p>0.05).

خاتمة: أثبتت الدراسة بأن كلتي الجرعتين من الريميفينتانيل قد كان لهما دوراً في استقرار ديناميكية الدم مع سرعة الإفاقة من التخدير ومن دون أية مشاكل مترتبة.

Objectives: To compare the sedation level, hemodynamic effects, patient and physician satisfactions following sedation achieved by 2 different doses of remifentanil (R) infusion with additional bolus infusions of propofol for in vitro fertilization (IVF) procedure.

Methods: A double-blind prospective randomized study was implemented on 86 ASA I-II grade female patients, 18-40 years of age that underwent IVF procedure. This study was performed in the Department of Anesthesiology and Obstetrics and Gynecology, School of Medicine, Dokuz Eylül University, Izmir, Turkey between November 2006 to August 2008. Group R1 received 0.1µg/kg/min while Group R2 received 0.15 µg/kg/min infusion dose remifentanil. Side effects, total doses of remifentanil and propofol administered, heart rate (HR), systolic arterial pressure and diastolic arterial pressure values have been recorded. Fertilization, cleavage, and pregnancy rates together with prognosis of pregnancies were compared.

Results: Groups did not show statistically significant differences for hemodynamic parameters of HR and MAP (p=0.281). Comparison of the satisfaction levels of 2 groups showed that anesthesiologist satisfaction was superior in R1 (p=0.009) whereas surgeon satisfaction was superior in R2 (p=0.01). Both groups reported good patient satisfaction levels (p=0.31). There were no differences between the groups in terms of fertilization, cleavage, pregnancy rates and prognosis of pregnancies (p>0.05).

Conclusion: Both doses of remifentanil provided stable hemodynamics along with fast and uncomplicated recovery.

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In vitro fertilization (IVF) is an assisted reproductive method used for the treatment of infertility. Assisted reproductive methods are costly procedures that have physiologic and psychological effects on patients and put the doctor at risk of failure.[1-5] In vitro fertilization is an uncomfortable and painful procedure that requires anesthesia and analgesia.[1] Methods of anesthesia used for in vitro fertilization include general, regional, or local anesthesia, sedation, and acupuncture.[1-7] The ideal agent for in vitro fertilization should have no toxic potential for oocyte fertilization and the gamete or the embryo; and preserve respiratory and hemodynamic stability throughout the procedure and allow rapid recovery at the end of the procedure.[4-7] Several studies have shown that most of the anesthetic agents disturb reproductive physiology.[5-8] The purpose of the present study was to compare the hemodynamic effects, sedation level, patient and doctor satisfaction, and IVF outcomes of 2 different doses of remifentanil infusion used for IVF patients.

Methods. This prospective double blind and randomized study was performed after approval of Ministry of Health's Ethical Committee and informed consent. Eighty-six patients American Society of Anesthesiologist Physical Status Classification (ASA status I-II) between 18-40 ages subjected to elective IVF were included into the study. This study was performed in the Department of Anesthesiology and Obstetrics and Gynecology, Dokuz Eylül University School of Medicine, Izmir, Turkey from November 2006 to August 2008.

Exclusion criteria were use of drugs that affect central nervous system, history of allergic reaction to study drugs, chronic use of sedatives or opioid analgesics, and presence of a psychiatric disorder. Patients scheduled for day-care IVF in the IVF unit were taken into the operating room and monitored by non-invasive blood pressure, electrocardiogram, pulse oximeter, and respiratory rate. A 20 gauge intravenous catheter was placed to dorsum of the hands of all patients and 0.9% saline infusion was started. Remifentanil (Ultiva® GlaxoSmithKline, Belgium) was prepared at a concentration of 40 µg/ml. Patients were randomized into 2 groups as Group R1 and Group R2 by sealed envelope. Patients, surgeon and postoperative observers were blind to the group application. Patients received 6 L/min oxygen by face mask during the in vitro fertilization procedure. Baseline values, heart rate (HR), systolic arterial pressure, diastolic arterial pressure, mean arterial pressure (MAP), arterial oxygen saturation (SpO_2), respiration rate (RR) and Ramsay Sedation Scores (RSS) were recorded. These measurements were repeated every 2 minutes for the first 10 minutes following the start of remifentanil infusion and at every 5 minutes until the end of the IVF procedure. Average of the first 3 values of the parameters (HR, RR, SpO_2) were recorded as the baseline values and 20 µg/kg midazolam intravenous (IV) (Dormicum ampule, Roche Pharmaceuticals, Istanbul, Turkey) was administered. Patients in Group R1 received 0.1 µg/kg/min remifentanil infusion during the procedure. Patients in Group R2 received 0.15 µg/kg/min remifentanil infusion during the procedure. Propofol 1 mg/kg (Propofol 1% Fresenius® Fresenius Kabi, Sweden) was administered as bolus doses via IV route to both groups at the second minute of remifentanil infusion. Sedation score of 3-4 was aimed; additional 0.5 mg/kg bolus doses of propofol were given when required and surgical procedure was allowed to start. Anesthesia was maintained at a sedation level of 3-4 by remifentanil infusion and additional 0.5 mg/kg bolus doses of propofol. Remifentanil infusion and bolus doses of propofol were stopped when hemorrhage control was started subsequently to aspiration of the oocyte and patients who returned to sedation score of 2 were sent to recovery unit.

Lidocaine 0.04 mg (Aritmal 2% ampoule, Biosel Drug Industry, Istanbul, Turkey) was added for 1 mg of propofol to eliminate the pain of injection.[9] The RSS:[10] patient anxious, agitated or restless, cooperated, oriented, sedated, but responds to verbal stimulation, patient is asleep, responds to glabellar tap or loud noise, responds to nail bed compression, does not respond to nail bed compression. Doses of remifentanil and propofol administered during the in vitro fertilization were recorded. Any side effects including hypoventilation (<8 breaths/min), apnea (absence of respiration for more than 20 seconds), airway obstruction, hypotension (reduction in MAP by >30% compared to basal values, MAP <60 mm Hg), hypertension (increase of MAP by >30%), arrhythmia, bradycardia (<50 beat/min), SpO_2 <95% were recorded and treated as required. Oxygen flow was increased to 8 L/min in case of hypoventilation (<8 breath/min) or SpO_2 <95% and the patient was warned to take deep breathes. Remifentanil infusion and bolus doses of propofol were stopped in case of hypoxemia (SpO_2 <90%) or apnea (absence of respiration for more than 20 seconds), jaw thrust maneuver was performed and manual ventilation with bag mask was started if necessary. In case of hypotension (reduction in MAP by >30% compared to baseline values or MAP <60 mm Hg), remifentanil infusion was reduced by half and 100 ml intravenous fluid was administered. During the hypotension period systemic arterial pressure was measured at 1 minute intervals, if hypotension persisted (>3 min) remifentanil was stopped and administration of remifentanil infusion and propofol intravenous bolus doses were suspended until MAP was >60 mm Hg. In case of bradycardia (<50 beats/min), 0.5 mg atropine (Atropin ampule,

Biosel Drug Industry, Istanbul) was administered intravenously. Anesthesiologist and surgeon satisfaction in both groups were investigated and noted. The satisfaction of the obstetrician/anesthesiologist applying IVF was evaluated and recorded at the end of IVF. The choices "poor", "fair", "well" and "very well" were for evaluation. Patients with RSS of 2 were transferred from IVF room to recovery room and followed by Modified Alderete Scores (MAS)[11] at every 5 minutes for the first 30 minutes and every 15 minutes for the second 30 minutes. Patients with MAS of 9 or higher were allowed to go home with a companion and informed not to drive for 24 hours. Fertilization rate, cleavage rate and pregnancy rates of both groups recorded by the obstetrics team of the IVF unit were retrieved and compared.

Statistical analysis was performed by Statistical Package for Social Sciences for Windows program version 11.0 (SPSS, Chicago, IL, USA). Data are presented as means ± standard deviation (means ± SD). The difference a=0.05 between the average propofol dose used 0.75 mg were considered and 90% power calculated as the total number of cases at least 64 (n=32) was found. Student T test, Chi-square test, and Mann-Whitney U test was used for comparison of the groups. Level of significance was set as $p<0.05$.

Results. Groups did not show significant difference for etiological distribution, mean age, mean body weight, ASA physical status classification, and mean operation time (**Table 1**). The MAPs and mean heart rates of the groups before and after the operation did not show statistically significant difference. Mean values of peripheral oxygen saturation during and after the operation did not show significant difference between the groups (p=0.267). Comparison of mean respiratory rates of the groups at 15, 20, 25, 40, and 45 minutes of the operation showed significant difference (p=0.02) (**Figure 1**). There was no significant difference between the mean respiratory rates of the groups after the operation (p=0.13). Mean RSS measured during and after the procedure did not show statistically significant difference (p=0.317). Modified Aldrete Scores measured after the procedure did not show statistically significant difference either (p>0.05). Statistical analysis was also performed for the respiratory adverse effects during anesthesia. Although desaturation and hypopnea were lower in Group R1, it did not reach statistical significance (p=0.38). Apnea was significantly higher in the Group R2 (p=0.02). Therefore, significantly more patients in Group R2 required additional treatment for respiratory depression. Although the need for increased oxygen flow and jaw thrust maneuver was higher in this group, the difference was not statistically significant (p=0.13). Need for mechanical ventilation was significantly higher in Group R2 (p=0.01). Statistically significant difference was observed between the anesthesiologist and surgeon satisfaction of the groups (p=0.009). Anesthesiologist satisfaction was "good" in Group R1, whereas surgeon satisfaction was "good" in Group R2. Patient satisfaction was "good" in both groups (p=0.01) (**Figure 2**). There was no significant difference between the groups for amount of propofol used (p=0.218), whereas amount of remifentanil used was significantly higher in Group R2 (p=0.01) (**Figure 3**). No significant difference was

Table 1 - Demographic data of patients and procedure time (N=86).

Variables	Group R1	Group R2	P value
Age (year)	31 ± 5	32 ± 4	0.58
Weight (kg)	66 ±12	62 ± 8	0.80
ASA (I/II)	36/7	37/6	0.70
Procedure time (min)	16 ± 6	17 ± 5	0.20

*p>0.05, ASA - American Society of Anesthesiologist Physical Status Classification

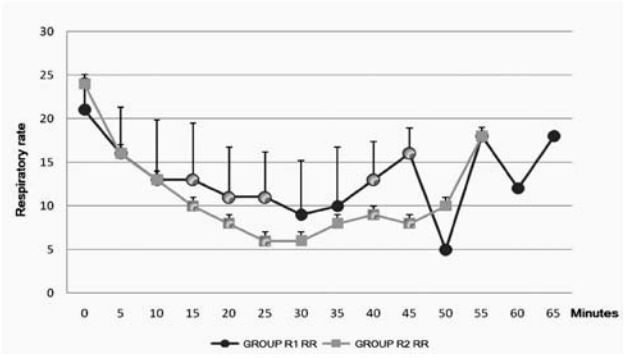

Figure 1 - Mean respiratory rates of the groups during the procedure. In Group R1, difference between the mean respiratory rates at 15, 20, 25, 40, and 45 minutes were statistically significant (p=0.02). In Group R2, difference between the mean respiratory rates at 15, 20, 25, 40, and 45 minutes were statistically significant (p=0.001).

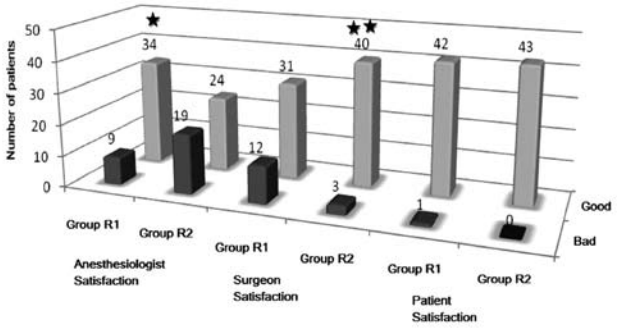

Figure 2 - Satisfaction levels in the groups during sedation. *Anesthesiologist satisfaction was significantly higher in Group R1, p=0.009. **Surgeon satisfaction was significantly higher in Group R2, p=0.01.

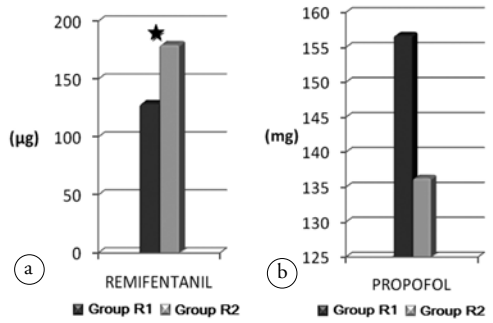

Figure 3 - Mean amount of a) remifentanil and b) propofol used during the procedure. Mean amount of remifentanil used was significantly higher in Group R2, *(p=0.01).

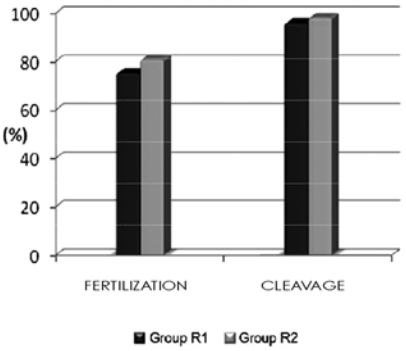

Figure 4 - Fertilization and cleavage rates of the groups.

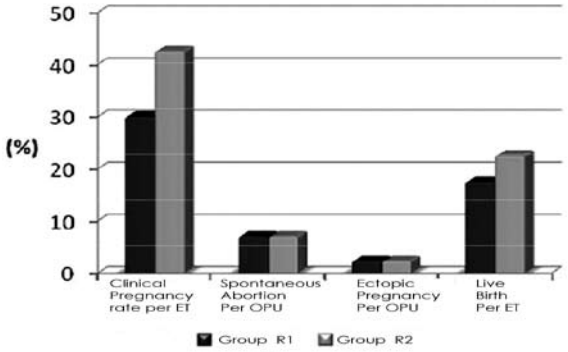

Figure 5 - Pregnancy rates of groups after IVF procedure [Oocyte pick-up (OPU), embryo transfer (ET)].

observed between the fertilization and cleavage rates of the groups (p=0.315). Mean fertilization rate was 75.2% in Group R1, and 80.7% in Group R2; mean cleavage rate was 95.8% in Group R1, and 98% in Group R2 (**Figure 4**). Analysis of IVF revealed that clinical pregnancy/embryo transfer (ET) rate was 30% in group R1 and 42.5% in Group R2 (p=0.215). No difference was observed between the pregnancy rates of the two groups (p=0.321). Groups were comparable in terms of spontaneous abortion, ectopic pregnancy, and live birth rates (**Figure 5**).

Discussion. Use of sedation or other methods of anesthesia during IVF procedure offers convenience both for the patient and the surgeon.[12] At present, an ideal method of anesthesia for assisted reproductive techniques has not been defined.[13] It should be remembered that the method of anesthesia and the agents' chosen may influence the success rate of IVF. Studies have shown that using short acting anesthetic agents at a relatively low dose and frequency had a beneficial effect on success rate of IVF.[14,15] In the present study, we selected remifentanil as a short acting agent and combined 2 different infusion doses of remifentanil with propofol. Hein et al[16] compared 2 methods of intravenous sedation technique by using propofol or methohexital. In the propofol group, pregnancy, and birth rates were significantly higher compared to methohexital group whereas nausea, vomiting and uncomfortable side effects were significantly lower. Numerous studies have confirmed propofol as the safest agent for assisted reproductive techniques.[17-19] Amin et al[20] have found that 0.025 µg/kg/min infusion doses of remifentanil altered spontaneous respiratory activity in healthy, unstimulated individuals that received no surgical stimulus. This effect was more prominent in higher doses i.e.0.1 µg/kg/min.[21] In a study where they have used remifentanil infusion analgesia during transvaginal follicle aspiration under USG guidance, Wilhelm et al[15] recommended close monitoring of respiratory function. Infusion dose of patients that developed respiratory depression was reduced in our study. Amin et al,[20] administered remifentanil infusion to healthy individuals with no surgical stimulus and stated that infusion should be ceased and antagonization with naloxone should be started in case of a critical respiratory depression. They have reported that naloxone rapidly and safely reversed the respiratory function. They recommended the use of both methods if one method alone fails to correct the situation.

Wilhelm et al,[15] in their study where remifentanil infusion analgesia was used alone, also reported no considerable change in mean blood pressure, mean HR, and mean spontaneous RR. These findings supported that remifentanil can be adjusted according to requirements of analgesia and provides sufficient analgesia. Thus, they have suggested remifentanil infusion alone, as an alternative to other methods of analgesia and anesthesia for relieve of pain in transvaginal follicle puncture within an IVF program.[15] In our study, no significant difference was observed between the groups in terms of hemodynamic parameters of MAP and HR during the procedure and the recovery period. This finding was attributed to comparable amounts of the propofol used, similarity of the need for anesthesia due to homogeneity

of the groups, performers, and the technique. Analysis of side effects observed during anesthesia revealed that desaturation and hypopnea were more frequent in Group R2, although difference was not statistically significant. However, apnea was significantly higher in Group R2. This finding was attributed to the higher dose of remifentanil infusion in Group R2. Therefore, ventilation by bag-valve mask system was more frequently used in this group. Increased flow of oxygen and jaw thrust maneuver was more frequently used in the Group R2 although difference was not statistically significant. These actions corrected the desaturation, therefore, cessation of remifentanil infusion or antagonizing with naloxone was not required.

Total doses of propofol did not show statistically significant difference between the groups. This finding was attributed to use of fixed doses of propofol and to similarity of mean body weights of the groups which were used for calculation of propofol dose. Mean amount of remifentanil used was higher in Group R2 due to higher dose of infusion. Higher dose of remifentanil infusion in Group R2 reduced the need for propofol in this group.

Our study demonstrated significant difference between the anesthesiologist and surgeon satisfaction rates. Anesthesiologist satisfaction was defined as 'good' in Group R1. Anesthesiologist satisfaction may have been affected by intraoperative respiratory complications. Lower rate of complications in Group R1 might contribute to increased anesthesiologist satisfaction. However, performers that were blind for the group that patient belonged to, reported that the procedure became easier in the period of hypopnea or apnea due to reduced abdominal movements and expressed their satisfaction thereof. Correspondingly, surgeon satisfaction was higher in Group R2, where respiratory complications were more common and controlled respiration was frequently used. Patient satisfaction was 'good' for both groups in which same anesthetic agent combination was used, and similar levels of sedation were maintained. Patients expressed that they were highly satisfied because they "felt no discomfort and fell asleep easily".

In our study, postoperative hemodynamic parameters of the patients remained stable and no side effects were observed. Patients achieved MAS of 9 or higher at approximately 8 minutes of the recovery period. This finding is consistent with the previous studies in the literature[19] and suggests that remifentanil provides a safe, rapid, and predictable postoperative recovery. In the literature, it has been stated that preemptive postoperative treatment of pain is not required for follicular puncture under general anesthesia.[15] Thus, we have not inquired our patients for pain during the postoperative follow-up period. Anesthetic agents used in these procedures may impede human oocyte fertilization or embryo implantation. Besides, exposure of peritoneum to carbon dioxide, duration of the procedure, duration of respiratory depression, dose of the drug, use of different combinations, mother's age and many other factors may affect the success of IVF.[11] Our results showed no difference between the fertilization, cleavage and clinical pregnancy rates and pregnancy outcomes of the groups. Similarity of factors such as age, etiological distribution, used sedative drugs and exposure time of the groups was considered to play role in the similarity of IVF outcomes. Technique employed, patient demographics and diverse responses to stress were pointed as the causes of different results observed in several studies.[2] A study in which propofol-fentanil or propofol-remifentanil was used for transvaginal follicle puncture has resulted in lower diffusion of opioid to follicular fluid with remifentanil compared to fentanil.[22,23] However, we did not measure remifentanil and propofol concentrations in the follicular fluid. Imoedemhe et al[22] have studied the reproductive effects of intravenous propofol that is distributed into the follicular fluid. They observed no significant difference between the propofol concentrations of the follicular fluid of fertilized and non-fertilized oocytes. Similarly no difference was detected between the propofol concentrations of the first and last aspirated oocytes. Presence of this agent in the follicular fluid was shown not to affect IVF outcomes or ET.[22] A meta-analysis concerning the effects of general and regional anesthesia during in vitro fertilization on reproductive outcomes showed no difference for cleavage and pregnancy rates.[2] Another clinical study that compared general anesthesia and sedation suggested general anesthesia using remifentanil without nitrogen protoxide as an appropriate alternative to sedative procedures for in vitro fertilization.[2] Another study has examined in vitro the effects of fentanil on fertilization of sea urchin oocytes.[23] Results from this study have shown that fentanil delayed and precluded fertilized membrane formation, thus led to polyspermia. Use of fentanil in clinical practice was discouraged because of these effects.[23] Hammadeh et al[3] compared sedation by propofol with general anesthesia by propofol and remifentanil in 202 female patients that underwent ultrasonography-guided oocyte aspiration. They reported a higher number of oocytes collected but lower fertilization rate in the general anesthesia group. Higher number of oocytes collected was attributed to comfort provided by general anesthesia both to patient and the obstetrician; but lower fertilization rates could be due to numerous factors (such as age of the patient, IVF indication, ovarian stimulation protocol, estradiol response, diameter of the needle used, aspiration pressure employed, culture media). This study proposed general anesthesia with remifentanil–propofol combination as an

alternative method to sedation.[2] A study by Wilhelm et al[13] found higher success of pregnancy with "monitored anesthesia care" technique using remifentanil compared to 'balance' general anesthesia during ultrasonography-guided transvaginal oocyte collection. However, it was also noted that differences in pregnancy rates between the groups should not be completely ascribed to the anesthetic agents.

Most important aspect of anesthesia technique to be used for in vitro fertilization is selection of an agent that would both increase the IVF success rate and allow day care anesthesia. Having these 2 features, remifentanil is one of the agents that can be used for the "appropriate anesthesia method" in patients that will undergo follicular puncture during IVF procedure.[15]

Drugs or drug combinations selected that will be used for optimum sedation should have sedative-hypnotic, anxiolytic, amnestic properties with lower incidence of perioperative side effects and should be easily titrated to provide intended level of sedation along with rapid awakening.[24,25] We believe that these characteristics preferred for the ideal sedation are met by 0.1µg/kg/min infusion dose of remifentanil. Sedation achieved by 2 different doses of remifentanil infusion used in our study provided stable hemodynamic parameters along with rapid and uneventful recovery and had minimal effect on IVF outcomes. However, we believe that 0.1µg/kg/min dose of remifentanil infusion is a safer alternative as it offers more stable respiratory function during the IVF procedure.

One limitation of this study, is the lack of the determination of propofol and remifentanil levels in the follicular fluid. This could show us if it diffuses into the follicle and effects the fetus. Another limitation is that we didn't monitored the sedation level with Bispectral index (BIS), which could give us more objective data for the sedation level. Further research with the lacking parts of our study could contribute to the literature about anesthesia methods for IVF.

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