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Original Article

# Hemodynamic parameters and reproductive outcome after intracytoplasmic sperm injection and fresh embryo transfer in patients undergoing oocyte retrieval with general anesthesia using fentanyl, remifentanil or alfentanil – A randomized clinical trial

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ABSTRACT

*Objective:* Anesthesia for assisted reproductive technology is very important to provide less stressful and painful environment for patients, with minimal side effects on oocytes. In the present study, we aimed to evaluate hemodynamic parameters, recovery time and intracytoplasmic sperm injection (ICSI) outcome among patients underwent anesthesia with fentanyl, remifentanil or alfentanil.

*Material and methods:* This randomized double-blinded clinical trial was conducted in patients undergoing anesthesia for transvaginal ultrasound guided oocyte retrieval (TUGOR). Patients were randomly allocated to alfentanil (A; 15 μg/kg), fentanyl (F; 1.5 μg/kg) or remifentanil (R; 1.5 μg/kg) groups.

*Results:* Three hundred forty patients were assessed for eligibility and randomized for transvaginal oocyte retrieval following general anesthesia and 105 were lost to follow up. No statistically significant differences were noted among groups regarding basic characteristics. Although, time to respond to verbal command was significantly different among groups (A: 1.99 ± 1.64, F: 2.56 ± 1.72, R: 1.78 ± 1.34, P = 0.014). There were no significant differences among groups with respect to the first and second postoperative pain intensity, patient satisfaction, pre-induction and post-induction systolic and diastolic blood pressure (BP). Terminal systolic (A: 101.61 ± 9.15, F: 105.29 ± 12.61, R: 102 ± 12.91, P = 0.01) and diastolic (A: 59.97 ± 9, F: 65.63 ± 9.13, R: 63.69 ± 11.01, P = 0.003) BP was significantly different among groups. The fertilization rate was significantly different among groups (A: 51.6%, F: 54.4%, R: 62.2%, P = 0.018). Implantation rate, biochemical and clinical pregnancy rate was similar among groups.

*Conclusions:* The results of present study demonstrated that all three opioids have the same efficiency, in regards to patient satisfaction and pregnancy outcome. However, Anesthesia with alfentanil compared with fentanyl and remifentanil, seems to be inferior for TUGOR due to higher effect on fertilization rate and less hemodynamic stability.

*Registration number:* IRCT201410258677N4.



## Introduction

Transvaginal ultrasound guided oocyte retrieval (TUGOR) is a highly effective and less invasive procedure for assisted reproductive technology (ART) that requires anesthesia and/or analgesia [1,2]. Anesthesia for ART is very important to provide less stressful and painful environment for patients, with minimal side effects on oocytes.

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Several studies indicated that anesthetic drugs can enter the follicular fluids (FF) [3,4]. In general anesthesia, there is some concern about the anesthetic drugs accumulation in FF and their negative impacts on fertilization rate and embryo development [5,6]. These reverse outcome lead to the need for safe general anesthesia with rapid onset, fast recovery time, less postoperative pain that don't interfere with pregnancy outcome.

Several opioids have been used in anesthesia for ART procedures. Fentanyl is a lipophilic opioid with short onset and short duration of action with minimal penetration to FF [7]. Remifentanil is an opioid agonist that has a rapid onset of action and quickly achieves a steady state [8]. Alfentanil, analog of fentanyl is a short acting opioid and an appropriate alternative for in-vitro fertilization (IVF) procedure [9]. To the author's best knowledge, no evidence was identified to compare the mentioned drugs outcome in patients undergoing anesthesia for TUGOR and express the superiority of one opioid over others. The aim of present study was to evaluate hemodynamic parameters, recovery time and intracytoplasmic sperm injection (ICSI) outcome among patients undergoing anesthesia with fentanyl, remifentanil or alfentanil.

## Materials and methods

This randomized clinical trial was conducted at Mehr medical institute from November 2014 to April 2017. The trial registration code in Iranian Registry of Clinical Trial (IRCT) and ethical code were IRCT201410258677N4 and 1930382808 respectively. Written informed consent was obtained from all participants.

The inclusion criteria were: patients with less than two unsuccessful ICSI cycle, American Society of Anesthesiologist Physical Status (ASA-PS) I and II, age <40 years, basal FSH level <10 mIU/ml, no azoospermia, patients with no severe endometriosis and uterine anomalies, no history of cardiovascular disease, no history of chronic opioid use and allergic reactions to anesthetics agents. The exclusion criteria were patients with frozen/thawed embryo transfer and difficult embryo transfer.

Pituitary suppression was achieved with a single dose of gonadotropin-releasing hormone agonist (1.25 mg, Decapeptyl, Ferring, Germany) injection at the mid-luteal phase of previous cycle. Ovarian stimulation with recombinant FSH (rFSH) (Gonal-F, Merck Serono, Germany) and/or human menopausal gonadotrophin (hMG) (Menopur, Ferring, Germany) was commenced on day 2 of subsequent menstrual cycle and continued until the day of human chorionic gonadotrophin (hCG, Darou pakhsh, Iran) administration. The starting doses of gonadotropins were individualized (150–300 IU/day) according to ovarian reserve tests. Follicular growth was monitored with ultrasound scan and estradiol measurements. When at least 2 dominant follicles reached a mean diameter of 18–20 mm, 10,000 IU hCG were administrated and 36–39 h later, TUGOR under general anesthesia were done.

Patients were allocated in three groups with ratio of (1:1:1) with computerized block randomization. Each patient had an identification code (IC) which was placed in sealed envelope by researcher. Also, medications were placed in sealed containers with IC. The anesthesiologists and patients were blinded to group assignment. A total of 240 patients (80 in each study group) were required to achieve 80% power to detect a difference at significance level of 0.05. By considering the probability decrease to approximately 30% of sample size, 340 patients were allocated to alfentanil (n = 113, 15 μg/kg, Darou pakhsh, Iran), fentanyl (n = 113, 1.5 μg/kg, Darou pakhsh, Iran) or remifentanil (n = 114, 1.5 μg/kg, Mylan, France) groups. One hundred five patients were lost to follow up for frozen/thawed embryo transfer cycle (alfentanil (n = 28), fentanyl (n = 25), remifentanil (n = 27)), difficult embryo transfer (alfentanil (n = 2), fentanyl (n = 4), remifentanil (n = 3)) or embryo transfer failure (alfentanil (n = 5), fentanyl (n = 7) or remifentanil (n = 4)) at the end of cycle. Regarding the reasons for exclusion to follow up, the number of patients who completed the trial was similar among groups.

On arrival at operating theater, an intravenous cannula (20 gauge) was introduced to all participants. Lidocaine 40 mg (Iran hormone, Iran) was administrated to prevent the pain of propofol injection. According to the patient's IC, a sealed container filled by one of mentioned opioids was administrated. Patients received propofol 2 mg/kg (B-Braun, Germany) for induction of anesthesia. If surgical procedures took long, anesthesia was maintained with incremental boluses of propofol (30–50 mg). Patients were ventilated with 50% oxygen-enriched air via anesthesia face mask. The incidence of opioid induce cough were assessed before injection of propofol. Blood pressure (BP), heart rate (HR), respiratory rate and arterial oxygen saturation were monitored perioperatively. Ephedrine and atropine were administrated in bolus doses of 5–10 mg and 0.5 mg respectively (STEROP, Belgium and Caspian Tamin, Iran) in hypotensive patients, decreasing systolic BP more than 30% of baseline and in HR below 60 beats/min.

After TUGOR procedure, all patients were admitted to post-anesthesia care unit (PACU). Visual analog scale (VAS) (a 10 cm line with 0 indicating 'no pain' and 10 indicating maximum pain) were used for quantification of postoperative pain intensity and compared between first (on arrival to PACU) and second (30 min after first) interviews. Emerging from anesthesia was considered as responding to verbal commands after discontinuation of anesthesia. If VAS ≥3, patients were received meperidine 0.5 mg/kg (EXIR, Iran) in the cases of HR < 100 beats/min or morphine 0.1 mg/kg (Darou pakhsh, Iran) in patients with HR > 100 beats/min. Postoperative BP, HR, nausea and vomiting and shivering were recorded. If patients complained of nausea and/or vomiting, ondansetron (4 mg, EXIR, Iran) was administrated intravenously. In case of shivering, $O_2$ with simple face mask (5–8 lit) and meperidine (25 mg) was administrated. A five point verbal scale was used for measuring level of patient satisfaction (1: poor, 2: fair, 3: good, 4: very good, 5: excellent).

Following denudation of cumulus-oocyte complexes, only metaphase II (MII) oocytes were fertilized using ICSI procedure. At approximately 16–18 h post sperm injection, presence of two polar bodies and distinct pronuclei confirmed fertilization. However, the number of transferred embryo were individualized for each patient based on their clinical situations, maximum of three embryos were transferred. Chemical pregnancy was confirmed by positive βhCG test, 14 days after embryo transfer. Clinical pregnancy was determined after ultrasound observation of fetal heart at 6 weeks of pregnancy.

Post-induction systolic and diastolic BP and HR and pregnancy rate was considered as primary endpoints. Statistical analysis was performed using statistical package for social science (SPSS, version 23, Inc. Chicago, IL, USA) for windows. Data were analyzed using one way analysis of variance (ANOVA) and repeated measures tests. Least significant difference (LSD) and Games–Howell tests were used as post-hoc tests. Chi square test was used for categorical variables. P value less than 0.05 was considered statistically significant.

## Results

In the present double-blinded clinical trial, 340 patients were assessed for eligibility and randomized for transvaginal oocyte retrieval following general anesthesia and 105 were lost to follow up (Fig. 1).

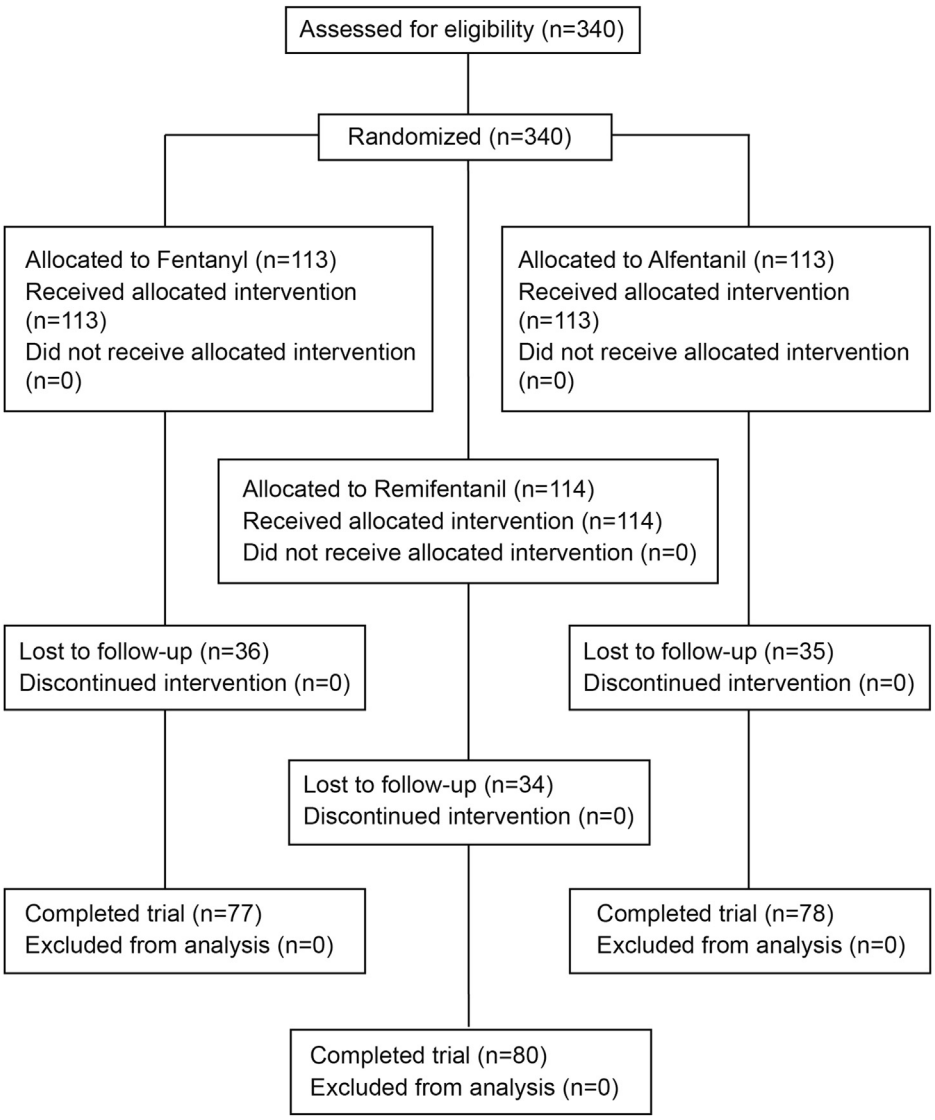


**Fig. 1.** CONSORT flow diagram of the study.

Basic characteristics of patients are summarized in Table 1. No statistically significant differences were noted among groups with regard to age, body mass index (BMI), basal LH, FSH and AMH level.

Mean procedure time for TUGOR was similar among groups (A: 7.26 ± 2.09 min, F: 7.08 ± 2.81 min, R: 6.74 ± 1.95 min, P = 0.275) but time to respond to verbal command was significantly different (A: 1.99 ± 1.64 min, F: 2.56 ± 1.72 min, R: 1.78 ± 1.34 min, P < 0.05).

**Table 1**
Baseline characteristic of patients.

| Variables | Alfentanil (n = 78) | Fentanyl (n = 77) | Remifentanil (n = 80) | P-value |
|---|---|---|---|---|
| Age (years) | 30.8 ± 4.72 | 30.74 ± 5.22 | 30 ± 4.37 | 0.516[a] |
| BMI (kg/m$^2$) | 25.33 ± 4.79 | 26.17 ± 4.82 | 26.73 ± 4.91 | 0.245[a] |
| LH (mIU/ml) | 3.89 ± 1.45 | 3.9 ± 1.67 | 4.47 ± 2.16 | 0.116[a] |
| FSH(mIU/ml) | 4.77 ± 1.5 | 5.05 ± 1.58 | 4.28 ± 1.71 | 0.315[a] |
| AMH(ng/ml) | 2.65 ± 1.28 | 2.36 ± 1.25 | 2.61 ± 1.32 | 0.359[a] |

[a] ANOVA test.

There were no significant differences among groups with respect to first and second postoperative pain intensity, patient satisfaction, pre and post-induction systolic and diastolic BP (Table 2). Terminal systolic (A: 101.61 ± 9.15 mmHg, F: 105.29 ± 12.61 mmHg, R: 102 ± 12.91 mmHg, P < 0.05) and diastolic (A: 59.97 ± 9 mmHg, F: 65.63 ± 9.13 mmHg, R: 63.69 ± 11.01 mmHg, P < 0.01) BP was significantly different among groups. No significant HR changes from pre-induction value were seen. The incidence of opioid-induced cough was significantly higher in remifentanil group (A: 21.8%, F: 11.7%, R: 31.3%, P < 0.05). The occurrence of vomiting and shivering was one in A group and one in R group respectively.

There were no statistical significant differences among groups with respect to progesterone and estradiol level on hCG day, endometrial thickness, total number of retrieved, MII oocytes and embryos transferred (Table 3). Fertilization rate was significantly different among groups (A: 51.6%, F: 54.4%, R: 62.2%, P < 0.05). Also, there were no statistical significant differences among groups with respect to the rate of implantation, biochemical and clinical pregnancy.

**Table 2**
Hemodynamic characteristics of patients.

| Variables | Alfentanil (n = 78) | Fentanyl (n = 77) | Remifentanil (n = 80) | P-value |
|---|---|---|---|---|
| Procedure time (min) | 7.26 ± 2.09 | 7.08 ± 2.81 | 6.74 ± 1.95 | 0.275[a] |
| Time to respond to verbal command (min) | 1.99 ± 1.64 | 2.56 ± 1.72 | 1.78 ± 1.34 | 0.014[a] |
| First postoperative pain intensity score (VAS (0–10)) | 0.18 ± 0.61 | 0.26 ± 0.57 | 0.39 ± 0.59 | 0.072[a] |
| Second postoperative pain intensity score (VAS (0–10)) | 0.054 ± 0.23 | 0.11 ± 0.42 | 0.051 ± 0.32 | 0.495[a] |
| Patient satisfaction score (1–5) | 4.09 ± 0.28 | 4.13 ± 0.47 | 4.09 ± 0.36 | 0.71[a] |
| Pre-induction systolic blood pressure (mmHg) | 128.5 ± 13.18 | 126.1 ± 17.66 | 126.08 ± 14.97 | 0.673[a] |
| Post-induction systolic blood pressure (mmHg) | 110.86 ± 14.43 | 108.93 ± 14.52 | 108.25 ± 14.38 | 0.478[a] |
| Terminal systolic blood pressure (mmHg) | 101.61 ± 9.15 | 105.29 ± 12.61 | 102 ± 12.91 | 0.01[a] |
| Pre-induction diastolic blood pressure (mmHg) | 79.64 ± 11.55 | 79.76 ± 13.29 | 79.76 ± 11.04 | 0.997[a] |
| Post-induction diastolic blood pressure (mmHg) | 65.81 ± 12.34 | 65.49 ± 10.32 | 64.27 ± 12.94 | 0.894[a] |
| Terminal diastolic blood pressure (mmHg) | 59.97 ± 9 | 65.63 ± 9.13 | 63.69 ± 11.01 | 0.003[a] |
| Pre-induction heart rate (beats/min) | 98.04 ± 15.15 | 93.81 ± 15.8 | 94.98 ± 16.73 | 0.26[a] |
| Post-induction heart rate (beats/min) | 82 ± 10.99 | 80.49 ± 13.7 | 78.27 ± 12.14 | 0.465[a] |
| Terminal heart rate (beats/min) | 75.14 ± 9.24 | 76.67 ± 10.13 | 75.61 ± 9.95 | 0.821[a] |
| Opioid induced cough (%) | 17 (21.8) | 9 (11.7) | 25 (31.3) | 0.012[b] |

[a] ANOVA test.
[b] Chi square test.

## Discussion

The results of present study revealed different hemodynamic parameters and fertilization rates, but similar pregnancy outcome in women undergoing TUGOR with alfentanil, fentanyl and remifentanil-based general anesthesia.

The diverse anesthetic techniques including locoregional anesthesia, monitored anesthesia care (MAC), sedation and general anesthesia have been used for TUGOR, but optimal technique should be consistent with high comfort level of patients based on ethnical, cultural, socioeconomic status and the least impact on ART outcome. General anesthesia is one of the most frequent techniques for ART procedure. There are conflicting results considering the effect of general anesthesia on ART outcome while some studies reflects the negative impacts [10], the others implicated similar outcome between patients undergoing general anesthesia and analgesia [11,12]. Based on studies that implicate the presence of anesthetics in FF [3], each chosen technique for TUGOR should be rapid onset and offset and have minimal impact on outcome.

One concern regarding the poor IVF outcome following general anesthesia is about the toxic effect of inhaled anesthetics. There are some reports that implicate the negative impact of $N_2O$ on fertilization and pregnancy rate in patients undergoing general anesthesia for TUGOR [13,14]. Hammadeh et al. [15] demonstrated higher number of collected oocytes and similar cleavage and pregnancy rate in patients undergoing remifentanil based general anesthesia without $N_2O$ versus sedation with midazolam, diazepam or propofol. In our study, maintenance of anesthesia was safely achieved with mixture of propofol, 50% oxygen-enriched air and opioids, which is contrary to studies that used $N_2O$ as maintenance anesthetics. Moreover, we did not use any halogenated agents during general anesthesia. It was reported that halogenated agents have deleterious effects on embryo quality and pregnancy rate [10,16].

In addition, our procedure time was shorter (7 ± 2.3 min) than other studies [14,17] that minimize the time of anesthetic exposure and the duration of postsurgical stay in operating room.

Opioids-based general anesthesia is widely used for oocyte retrieval procedures. Most frequently opioids involved in general anesthesia includes: alfentanil, fentanyl and remifentanil. To the best of our knowledge, no similar study was conducted to compare mentioned opioids outcome in patients undergoing TUGOR.

Time of respond to verbal commands was significantly shorter in remifentanil group than fentanyl group, but the difference between remifentanil and alfentanil groups and the differences between fentanyl and alfentanil groups were not statistically significant. Quick awakening from anesthesia reveals shorter time of recovery and hospital stay. In a study assessing the effect of bispectral index-guided total intravenous anesthesia, Saleh et al. [17] demonstrated a significant reduction in recovery time in patients undergoing general anesthesia for TUGOR with remifentanil-propofol versus fentanyl-propofol. A review study by Komatsu et al. [18] found that remifentanil is associated with faster postoperative recovery time and lower BP and HR. It is likely that rapid analgesic effects in onset and offset of remifentanil versus fentanyl may have contributed to shorter recovery time. In the present study, all

**Table 3**
Ovarian stimulation characteristics and pregnancy outcome.

| Variables | Alfentanil (n = 78) | Fentanyl (n = 77) | Remifentanil (n = 80) | P-value |
|---|---|---|---|---|
| Total gonadotropin dose (amp) | 38.47 ± 12.73 | 42.95 ± 16.81 | 40.68 ± 17.31 | 0.215[a] |
| Progesterone level on human chorionic gonadotropin day (ng/ml) | 0.77 ± 0.43 | 0.7 ± 0.42 | 0.76 ± 0.42 | 0.574[a] |
| Estradiol level on human chorionic gonadotropin day (pg/ml) | 1583.06 ± 550.58 | 1628.83 ± 536.12 | 1677.04 ± 640.45 | 0.637[a] |
| Endometrial thickness (mm) | 9.81 ± 1.55 | 9.42 ± 1.53 | 9.39 ± 1.3 | 0.147[a] |
| Total number of retrieved oocyte | 10.28 ± 5.32 | 10.84 ± 5.51 | 9.74 ± 4.59 | 0.409[a] |
| Metaphase II | 8.09 ± 5.34 | 8.67 ± 5.08 | 7.87 ± 4.1 | 0.575[a] |
| Two pronuclear/total number of retrieved oocyte (%) | 425/823 (51.6) | 453/833 (54.4) | 492/791 (62.2) | 0.018[a] |
| Total number of embryos transferred | 2.81 ± 0.77 | 2.88 ± 086 | 2.86 ± 0.71 | 0.577 |
| Implantation rate (%) | 48/219 (21.9) | 53/219 (24.2) | 49/229 (21.4) | 0.814[a] |
| Biochemical pregnancy (%) | 39 (50) | 40 (51.9) | 39 (48.8) | 0.922[b] |
| Clinical pregnancy (%) | 33 (42.3) | 35 (45.5) | 35 (43.8) | 0.925[b] |

[a] ANOVA test.
[b] Chi square test.

groups indicated significant difference in BP and HR compared to pre-induction values but no further intervention was required for hypotension. Fentanyl indicated milder hypotensive effect than others while HR changes were similar among groups. It seems that fentanyl maintains more hemodynamic stability.

The incidence of opioid-induced cough was significantly higher in remifentanil group than others. Similarly, a study by Kim et al. [19] reported incidence of remifentanil-induced cough in a higher percentage. Only one patient in alfentanil and one patient in remifentanil group were complaining of nausea-vomiting and shivering respectively. Fentanyl induced more hemodynamic stability and less post-operative complications. Following evaluation of patient's satisfaction revealed that fentanyl provides greater satisfaction.

In a study by Hammadeh et al. [15] general anesthesia with remifentanil was recommended for IVF. The superiority of remifentanil on anesthetic profile and ART outcome was also suggested in a clinical trial study by Jarahzadeh et al. [20], who examined patients undergoing MAC technique. Soussis et al. [3] indicated no significant differences in fertilization rate or pregnancy rate in three groups of patients undergoing sedation/analgesia using midazolam, fentanyl or alfentanil for TUGOR. In a study by Matsota et al. [21] for comparing of analgesia with remifentanil versus anesthesia with propofol and alfentanil, no significant differences were observed in anesthetic profile and IVF outcome. In the present study, no significant differences were reported between groups with regard to pregnancy outcomes. According to the results of present study, significant difference was seen in fertilization rate. Also, further analysis indicated that remifentanil group have significantly higher fertilization rate than alfentanil while the difference was not statistically significant between remifentanil and fentanyl groups. In a retrospective study, no increasing adverse effects of higher alfentanil doses on oocyte and embryo quality and pregnancy outcome were reported.

It seems that ultra-short half life and fast elimination of remifentanil from FF influences developmental potency of oocytes. Although, fertilization rate was higher in remifentanil than fentanyl group but the difference was not statistically significant. In addition, fentanyl induced more hemodynamic stability and less post-operative side effects. So it can be concluded that remifentanil and fentanyl are more efficient for TUGOR procedures. The results of present study demonstrated that all opioids have the same efficiency with regards to patient satisfaction and pregnancy outcome; however, alfentanil seems to be inferior for TUGOR due to higher negative effect on fertilization rate and less hemodynamic stability.

## Conflict of interest

We declare that we have no conflict of interest.

## Disclaimers

The views expressed in the present study are those of author and not an official position of the institution or funder.

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