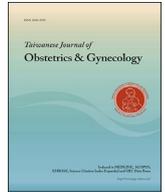




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Original Article

The effect of anesthetic agents for oocyte pick-up on in vitro fertilization outcome: A retrospective study in a tertiary center

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ABSTRACT

Objective: General anesthesia is used in most in vitro fertilization (IVF) clinics for oocyte pick-up (OPU), however, there is no consensus on type of anesthetic agent use among clinicians performing OPU. Therefore, we aimed to evaluate the effects of propofol, ketamine, or combination of propofol and ketamine (P + K) for OPU on IVF outcome.

Material and methods: Three hundred and thirty three women (n = 333) undergoing IVF treatment were retrospectively included and were evaluated in three groups depending on whether they received propofol (n = 217), or ketamine (n = 60), or P + K (n = 56) for anesthesia during OPU.

Results: Baseline characteristics and duration of anesthesia of each group were comparable except lower motile sperm percentage in the ketamine group compared to the propofol group (p = 0.002). Fertilization rate (FR) was decreased with ketamine compared to propofol (p = 0.013) and P + K (p = 0.008). After adjustment for sperm motility, this negative effect of ketamine on FR persisted. Implantation, clinical pregnancy, take-home baby rates, and oocyte retrieval parameters (number of total retrieved oocyte, metaphase II oocytes, embryo and methaphase II rate, and embryo quality) did not differ between the groups. Extended anesthesia duration (>30 min) was associated with low implantation (p = 0.04) and clinical pregnancy rates (p = 0.02).

Conclusion: Ketamine use during OPU can affect FR compared to propofol and P + K. Long durations of anesthesia also seem to decrease implantation and clinical pregnancy rates.

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Introduction

In vitro fertilization (IVF) success depends on positive outcomes in a number of IVF stages, including controlled ovarian stimulation (COS), oocyte pick-up (OPU), fertilization, embryo transfer, and implantation. The OPU process is important, as oocyte quality influences fertilization, embryo quality, and implantation. The process involves aspiration of follicles containing follicular fluid and cumulus-oocyte complexes [1]. Although the OPU process is a minimally invasive procedure, it is painful. Therefore, it is usually performed under anesthesia [1].

For OPU, general anesthesia is used in most IVF clinics [2]. However, there is no consensus on type of anesthetic agent use among clinicians performing OPU. The most commonly used anesthetic agent during OPU is intravenous propofol, with pre-medication involving an anxiolytic/analgesic combination of

midazolam or fentanyl, respectively [3]. Propofol is a short-acting anesthetic agent with short induction and recovery times [4] as well as good alertness and minimal nausea in the postoperative phase [5]. Propofol was thought to be a safe drug for use in IVF, because a minimum dosage is adequate to achieve anesthesia [6]. However some murine studies have revealed propofol to be associated with reduced fertilization rates (FR) [7,8] and inhibition of the development of blastocysts in one-cell embryos [8].

Ketamine is also commonly administered for general anesthesia and analgesia during OPU [9]. Ketamine offers a number of advantages, including little risk of cardiac instability, minimal respiratory depressive effects, and good analgesic properties [10]. Disadvantages are frequent nausea, vomiting, psychomimetic effects, tachycardia, and a long recovery time [11].

A combination of ketamine and propofol (P + K) is considered suitable for short procedural sedation and analgesia [12], because it enables rapid recovery and earlier discharge times [11]. Low incidence of adverse effects [11,13], less hemodynamic instability, and reduced respiratory depression have been reported with P + K

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compared to ketamine [14]. In addition, neither ketamine nor P + K was associated with a significant decrease in blood pressure or pulse rate as compared with that of propofol [11].

The effects of different anesthetic agents on IVF outcomes, such as fertilization and embryo development remain unclear. To our knowledge, there are no studies in the English literature on the effects of propofol, ketamine, and P + K anesthesia during OPU on IVF outcomes. Therefore, the aim of the present study was to evaluate the effects of these three medications for the anesthesia of OPU on IVF outcomes.

Material and method

The present study includes retrospective data, evaluating a 4-year period from September 2014 through September 2017. Hospital files of patients undergoing OPU under general anesthesia were used for the study. The IVF Unit, where the study was performed is structured within the Department of Obstetrics and Gynecology at Suleyman Demirel University Hospital, a main tertiary center in southwestern Turkey covering about a 1-million population with approximately 400 infertility treatments provided annually. The study was approved by the local ethics committee with the protocol number 72867572.050.01–157922.

The participants were primary infertile women undergoing IVF treatment under general anesthesia. Availability of anesthesia data was the priority of inclusion criteria. All participants had a minimum of one-year infertility duration.

Demographic data including age, body mass index (BMI) (kg/m^2), smoking, alcohol use, and basal hormone levels were obtained from patient files, in addition to information on the etiology and duration of infertility.

The exclusion criteria were the presence of hypersensitivity to ketamine or propofol, chronic diseases (such as diabetes, hypertension, liver, or kidney disease), bronchoconstrictive diseases, endocrinopathies, cancer, infectious diseases, and autoimmune diseases in addition to use of cocaine, opiates, or glucocorticoids.

COS and oocyte retrieval parameters

All the patients' records were retrospectively evaluated. The stimulation protocol (agonist/antagonist), gonadotropin type (recombinant follicle stimulating hormone [r-FSH] and/or urinary FSH [u-FSH]), starting dose of gonadotrophin used for COS, human chorionic gonadotropin (hCG) type (urinary or recombinant), and presence of ovarian hyperstimulation syndrome (OHSS) were recorded.

The following embryologic data were acquired: total number of oocytes retrieved, oocyte stage (germinal vesicle [GV], metaphase I [MI] or MII), oocytes with anomalies or degeneration, oocytes with empty zona (EZ), fertilization, embryo number, and embryo quality. On the same day of oocyte retrieval, intra cytoplasmic sperm injection (ICSI) of the oocytes was performed and fertilization was evaluated 16–18 h later. Oocytes were considered successfully fertilized when two pronuclei were observed by inverted microscopy. The formula was used to calculate the FR was as follows ($\text{Fertilized oocytes}/\text{MII oocytes} \times 100$) [15–17]. Fresh single embryo with the highest quality was transferred by a Wallace catheter when the embryos had reached at least 8 cell stage on day 3. Vaginal progesterone (Crinone gel 8% vaginal gel, Merc Serono, Istanbul, Turkey) intravaginal 90 mg per day was initiated on oocyte retrieval day for luteal support until the pregnancy test. If the pregnancy test results was positive, vaginal progesterone was continued for 12 weeks.

We divided patients into those with a poor ovarian response (total oocytes retrieved: < 5) or normal ovarian response (total

oocytes retrieved: ≥ 5). The MII rate was defined as the number of MII oocytes divided by the total number of oocytes retrieved.

Embryo quality was evaluated under an inverted microscope at $\times 400$ magnification in our IVF clinic. The quality of embryos was graded from 1 to 3. Embryos were graded as grade 1 (good quality), grade 2 (moderate quality), or grade 3 (poor quality). Embryos with even-sized blastomeres and those with $< 5\%$ fragments were classified as grade 1. Those with blastomeres with slight-to-moderate size differences and 5–50% fragments were classified as grade 2. Grade 3 embryos were classified as those with markedly different-sized blastomeres and $> 50\%$ fragments. The following parameters were evaluated and recorded. The clinical embryo implantation rate was defined as the number of gestational sacs observed at sonographic screening at 6 weeks of pregnancy divided by the number of embryos transferred. Clinical pregnancy was confirmed if a visible fetal heart beat was visualized in an intrauterine gestational sac by transvaginal ultrasound. Take home baby rate was defined as having a liveborn infant.

General anesthesia protocol

In our IVF unit, all women are referred for preanesthesia evaluation by an anesthetist for clinical assessment. A resident anesthesiologist also accompanies all OPU procedures.

The following data were obtained from the patients' anesthetic files: duration of anesthesia (min), premedications used for anesthesia, dosage of anesthetic used (mg), peripheral capillary oxygen saturation (SpO_2), the difference of heart rate (HR) and mean arterial pressure (MAP) between the value 5 min after the induction of anesthesia and the baseline value before induction of anesthesia.

All the patients fasted for 12 h before the OPU procedure in accordance with the general anesthesia protocol of our unit. All the patients underwent noninvasive arterial pressure, continuous electrocardiogram, pulse oximetry monitoring, and oxygen was administered via a facial mask. A peripheral venous 22-gauge catheter was placed for administration of serum physiologic and anesthetic agents. Anxiolysis was induced by midazolam (0.03–0.07 mg/kg) administered intravenously, and analgesia was induced by remifentanyl (2 $\mu\text{g}/\text{kg}$) administered intravenously. For the induction and maintenance of anesthesia, the patients received propofol only (1–2 mg/kg), ketamine only (dose of 25 mg up to 100 mg), or P + K. The choice of anesthesia medication protocol depended on the anesthesiologist's preference at the beginning of the OPU procedure.

Outcome measures

The primary outcome measure was clinical success of IVF which is defined as FR, implantation, clinical pregnancy, and take home baby rates. Secondary outcome measures were oocyte retrieval parameters including the total number of retrieved oocytes, developmental stage of the oocytes (GV, MI, and MII), abnormal oocytes (EZ, anomalies, or degeneration), MII rate-, embryo number, and embryo quality on embryo transfer day.

Statistical analysis

The Statistical Package for Social Sciences for Windows (SPSS 20, Chicago, IL, USA) was used. A p value less than < 0.05 was considered statistically significant. The distributions of continuous data were evaluated by Kolmogorov Smirnov test. The variables were compared with one-way ANOVA and k-independent sample test depending on normal or abnormal distribution, respectively. Pairwise comparisons of the groups were performed with post hoc Bonferroni correction. Continuous variables were presented as mean \pm standard deviations (SD). Categorical variables such as

etiology of infertility, smoking, alcohol use, type of gonadotropins used, embryo quality, and IVF outcome parameters were compared by descriptive statistics including χ^2 -test or Fischer's exact test on the basis of sample size and were presented as percentages. Pearson or Spearman correlation analyses were used to evaluate correlations between continuous variables. Logistic regression analyses were used to determine associations across dependent and independent variables.

Results

Of the 433 hospital IVF files that initially met inclusion criteria, 100 were excluded due to incomplete data with remaining 333 women included into the study (76.9%), consisting of the propofol group ($n = 217$, 65.16%), the ketamine group ($n = 60$, 18%), and the P + K group ($n = 56$, 16.81%).

Demographic features of the groups

The mean age of the propofol, ketamine, and P + K groups were 31.94 ± 5.91 , 31.73 ± 4.81 , and 30.58 ± 5.19 years, respectively. Age, partner's age, BMI, duration of infertility, previous IVF cycle (if performed), and basal hormone levels were distributed homogeneously between the groups. The total sperm counts were also similar between the three groups. However the percentage of motile sperms, especially the percentage of fast progressive motile sperms (A) was significantly different between the groups ($p = 0.002$). The percentage of motile sperm was lower in the ketamine group ($33.08 \pm 24.21\%$) compared with that in the propofol group ($45.88 \pm 25.13\%$, $p = 0.002$). p values for comparisons of propofol and P + K groups ($p = 1.0$) and also ketamine and P + K groups ($p = 0.052$) did not reach statistical significance. Etiologic factors associated with infertility and smoking and alcohol use were similar among the groups (Table 1).

Ovarian stimulation characteristics and anesthesia-related parameters

The gonadotropin-releasing hormone antagonist protocol for down-regulation of the pituitary gland and recombinant hCG were used in all women. Most women were stimulated using both r-FSH and u-FSH ($n = 239/333$ [71.8%]). None of the stimulation parameters, including the type of gonadotropins, starting dose of r-FSH, or starting dose of u-FSH differed significantly between the groups. Poor ovarian response and the presence of OHSS were similar between three groups. The duration of anesthesia was 27.28 ± 12.15 min in the propofol group, 24.16 ± 8.49 min in the ketamine group, and 28.83 ± 12.32 min in the P + K group with no significance for comparisons ($p = 0.8$). The mean dose of propofol used per patient in the propofol group was 156.08 ± 47.37 mg and the mean dose of ketamine used per patient was 88.03 ± 28.34 mg in the ketamine group. In the P + K group, the mean dose of propofol was 139.28 ± 50.37 mg, and the mean dose of ketamine was 44.55 ± 18.93 mg. As expected, the mean doses of propofol and ketamine in the P + K group were lower than those in the propofol group and ketamine group. SpO₂, the difference of MAP and HR between the value 5 min after the induction of anesthesia and the baseline value before induction of anesthesia were comparable between three groups ($p = 0.6$, $p = 0.07$, and $p = 0.06$, respectively). Duration of recovery was 40 min in the propofol group, 45 min in the ketamine group and 42 min in the P + K group ($p = 0.7$) (Table 2).

The effect of anesthetic agents on oocyte retrieval parameters and embryo

A median of 8.62 oocytes, 9.8 oocytes, and 8.83 oocytes were retrieved in the propofol, the ketamine and the P + K groups, respectively. There were no significant between-group differences

Table 1
Baseline demographic features of the groups.

	Propofol group n = 217	Ketamine group n = 60	P + K group n = 56	p value
Age (years)	31.94 ± 5.91	31.73 ± 4.81	30.58 ± 5.19	0.2
Partner's age (years)	34.96 ± 6.1	34.51 ± 5.41	33.33 ± 4.88	0.1
BMI (kg/m ²)	25.8 ± 4.79	25.12 ± 4.5	25.61 ± 4.7	0.6
Duration of infertility (years)	6.46 ± 4.58	7.13 ± 3.65	5.9 ± 3.93	0.3
Previous IVF cycle	1.47 ± 0.85	1.76 ± 0.88	1.62 ± 1.18	0.1
Basal hormone levels				
FSH (mIU/ml)	8.99 ± 6.3	7.52 ± 2.38	8.57 ± 4.51	0.1
LH (mIU/ml)	5.98 ± 4.08	5.20 ± 3.04	6.43 ± 8.83	0.4
E2 (pg/ml)	58.43 ± 65.88	56.86 ± 43.54	60.79 ± 86.43	0.9
PG (ng/ml)	1.01 ± 1.37	0.85 ± 0.90	0.81 ± 0.38	0.4
Sperm parameters				
Total count (million)	60.52 ± 60.81	65.87 ± 88.23	66.03 ± 69.78	0.7
Motility (%)	45.88 ± 25.13	33.08 ± 24.21	44.26 ± 26.14	0.002^a
A (%)	12.98 ± 13.74	7.71 ± 10.55	11.89 ± 14.06	0.026^b
Etiology of infertility				
PCOS	34/217 (15.7%)	6/60 (10%)	8/56 (14.3%)	
Unexplained	60/217 (27.6%)	17/60 (28.3%)	14/56 (25%)	
DOR	50/217 (23%)	10/60 (16.7%)	14/56 (25%)	0.16
Tubal	19/217 (8.8%)	0/60 (0%)	2/56 (3.6%)	
Endometriosis	3/217 (1.4%)	1/60 (1.7%)	1/56 (1.8%)	
Male	51/217 (23.5%)	26/60 (43.3%)	17/56 (30.4%)	
Maternal habits				
Smoking use (%)	16/217 (7.4%)	5/60 (8.3%)	8/56 (14.3%)	0.2
Alcohol use (%)	1/217 (0.5%)	0/60 (0%)	0/56 (0%)	0.7

P + K: Combination of propofol and ketamine; BMI: Body mass index; IVF: In vitro fertilization; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; PG: Progesterone; A: Percentage of fast progressive motile sperm; PCOS: Polycystic ovary syndrome; DOR: Diminished ovarian reserve.

^a p value is significant between propofol and ketamine group ($p = 0.002$) by Bonferroni. p value is not significant between propofol and P + K group ($p = 1$) and also ketamine and P + K group (0.052) by post hoc Bonferroni.

^b p value is significant between propofol and ketamine group ($p = 0.02$) by Bonferroni. p value is not significant between propofol and P + K group ($p = 1.0$) and also ketamine and P + K group ($p = 0.2$) by post hoc Bonferroni.

Table 2
Ovarian stimulation characteristics and anesthesia-related parameters.

	Propofol group n = 217	Ketamine group n = 60	P + K group n = 56	p value
Type of gonadotrophins				
r-FSH (%)	64/217 (29.5%)	15/60 (25%)	15/56 (26.8%)	0.7
u-FSH + r-FSH	153/217 (70.5%)	45/60 (75%)	41/56 (73.2%)	
Starting dose of r-FSH	249.02 ± 62.40	232.91 ± 64.35	238.39 ± 55.58	0.1
Starting dose of u-FSH	132.18 ± 42.46	140.55 ± 39.27	143.75 ± 26.4	0.1
Poor ovarian response (n%)	72/217 (33.3%)	18/60 (30.5%)	17/56 (30.4%)	0.3
Presence of OHSS (n%)	9/217 (4.1%)	2/60 (3.3%)	2/56 (3.6%)	0.9
Duration of anesthesia (min)	27.28 ± 12.15	24.16 ± 8.49	28.83 ± 12.32	0.8
Median dose of anesthetic drugs (mg)	156.08 ± 47.37	88.03 ± 28.34	P = 139.28 ± 50.37 K = 44.55 ± 18.93	<0.0001
SpO ₂ %	99.5	98	99	0.6
MAP difference ^a	15	10	12	0.07
HR difference ^a	10	6	8	0.06
Duration of recovery (min)	40	45	42	0.7

P + K: Combination of propofol and ketamine; r-FSH: Recombinant follicle stimulating hormone; u-FSH: Urinary follicle stimulating hormone; OHSS: Ovarian hyperstimulation syndrome; SpO₂ = peripheral capillary oxygen saturation; HR = Heart rate; MAP = Mean arterial pressure.

^a The difference between the value 5 min after the induction of anesthesia and the baseline value before induction of anesthesia.

in the total number of oocytes retrieved, GV stages, MII stages, oocytes with anomalies or degeneration, and oocytes with EZ. However, the number of MI-stage oocytes was significantly higher in the ketamine group (1.94 ± 2.3) as compared with that in the propofol group (1.21 ± 1.5 , $p = 0.009$). There was no difference in the number of MI-stage oocytes in the propofol group versus that in the P + K group and no difference in the ketamine group as compared with that in the P + K group. The MII rate, embryo number, and embryo quality were also comparable between the groups (Table 3).

The effect of anesthetic drugs on the success of IVF

ICSI was performed in only 293 of the 333 patients for the following reasons: In 7 patients testicular sperm extraction was unsuccessful; in 24 patients, no oocytes were retrieved during OPU; and in 9 patients, only immature oocytes were retrieved during OPU. The FR was significantly lower in the ketamine group ($40.49 \pm 32.89\%$) as compared with that in the propofol group ($54.65 \pm 32.73\%$, $p = 0.013$) and P + K group ($59.62 \pm 29.82\%$, $p = 0.008$). However, there was no significant difference in FRs between the propofol and P + K groups ($p = 1.0$). Embryo transfer

was performed in 241 of the 293 women in whom ICSI was performed, as fertilization did not occur in 52 patients. Single embryo transfer was undertaken according to Turkish laws on reproduction. About 56% of all the embryo transfers were on day 3, 22% on day 4, and 22% on day 5. However, the embryo transfer day was not significantly different between the propofol, ketamine, and P + K groups ($p = 0.1$). Implantation rate was lower in the ketamine group (4/40, 10%) as compared with that in the propofol (36/158, 22.8%) and P + K (10/43, 23.3%) groups with no significant differences ($p = 0.1$). Clinical pregnancy (17.1% in the propofol group, 10% in the ketamine group, and 22.5% in the P + K group) and take-home baby rates (15.8% in the propofol group, 7.5% in the ketamine group, and 14% in the P + K group) were not significantly different between the groups. Data related to the effects of the different anesthetic agents on IVF outcomes are shown in Table 4.

We evaluated the predictive effect of the type of agent used to induce anesthesia on FR, which was classified as normal (FR > 60%) or low (FR < 60%). When age, BMI, etiology of infertility, percentage of sperm motility, fast progressive sperm motility (grade A percentage), and duration of anesthesia were taken as covariates, ketamine administration had a negative predictive effect on normal FRs ($p = 0.01$, $\beta = -1.08$, OR [95% CI] = 0.33 [0.14–0.77]). The

Table 3
The effect of anesthesia agents on oocyte retrieval parameters and embryo.

	Propofol group n = 217	Ketamine group n = 60	P + K group n = 56	p value
Oocyte number (n)				
Total oocyte count	8.62 ± 6.7	9.8 ± 7.57	8.83 ± 6.93	0.4
MI	5.86 ± 4.66	6.55 ± 4.97	5.89 ± 4.49	0.6
MI	1.21 ± 1.5	1.94 ± 2.3	1.26 ± 1.51	0.011 ^a
GV	0.98 ± 1.69	1 ± 1.58	1.19 ± 2.7	0.7
Oocyte with anomalies	0.19 ± 0.76	0.1 ± 0.48	0.14 ± 0.48	0.6
Oocyte with degeneration	0.16 ± 0.57	0.15 ± 0.63	0.1 ± 0.56	0.7
Oocyte with EZ	0.21 ± 0.66	0.05 ± 0.22	0.12 ± 0.33	0.1
MI rate (%)	68.71 ± 24.40	70.98 ± 20.47	70.54 ± 22.94	0.7
Embryo count (n)	3.56 ± 3.03	3.1 ± 3.34	3.92 ± 2.82	0.3
Embryo quality				
Grade 1 (n, %)	141/161 (87.6%)	37/41 (90.2%)	42/44 (95.5%)	
Grade 2 (n, %)	17/161 (10.5%)	3/41 (7.3%)	1/44 (2.3%)	0.6
Grade 3 (n, %)	3/161 (1.9%)	1/41 (2.4%)	1/44 (2.3%)	
Embryo transfer day				
Day 3	81/158 (51.3%)	23/39 (59%)	30/43 (69.8%)	
Day 4	35/158 (22.2%)	11/39 (28.2%)	7/43 (16.3%)	0.1
Day 5	42/158 (26.6%)	5/39 (12.8%)	6/43 (14%)	

P + K: Combination of propofol and ketamine; MI: Metaphase I; MII: Metaphase II; GV: Germinal vesicle; EZ: Empty zona.

^a The p value is significant for comparison between propofol and ketamine groups ($p = 0.009$) by post hoc Bonferroni. The p value is not significant for comparisons between propofol and P + K groups ($p = 1.0$) and also ketamine and P + K ($p = 0.09$) by post hoc Bonferroni.

Table 4

The effects of anesthetic drugs on the success of IVF.

	Propofol group n = 217	Ketamine group n = 60	P + K group n = 56	p
FR (%)	54.65 ± 32.73	40.49 ± 32.89	59.62 ± 29.82	0.005^a
Implantation (n%)	36/158 (22.8%)	4/40 (10%)	10/43 (23.3%)	0.1
Clinical pregnancy (n%)	27/158 (17.1%)	4/40 (10%)	9/43 (22.5%)	0.3
Take home baby (n%)	25/158 (15.8%)	3/40 (7.5%)	6/43 (14%)	0.4

P + K: Combination of propofol and ketamine; IVF: In vitro fertilization; FR: Fertilization rate.

^a P value is significant between propofol and ketamine groups (p = 0.013) and ketamine and P + K groups (p = 0.008) by post hoc Bonferroni. P value is not significant between propofol and P + K group (p = 1) by post hoc Bonferroni.

presence of endometriosis was also a negative predictive factor of FRs ($p = 0.028$). Table 5 shows the predictive effects of the anesthetic agents on FRs.

After adjustment for covariates, the type of anesthetic agent was not predictive of implantation, clinical pregnancy, and take-home baby rates. Only age had a negative predictive effect on implantation ($p = 0.004$, $\beta = -0.08$, OR [95% CI] = 0.91 [0.86–0.97]), clinical pregnancy ($p = 0.045$, $\beta = -0.06$, OR [95% CI] = 0.93 [0.88–0.99]), and take-home baby rates ($p = 0.044$, $\beta = -0.07$, OR [95% CI] = 0.93 [0.87–0.99]) (data not shown).

Association between the duration of anesthesia and IVF outcomes

The duration of anesthesia and oocyte retrieval parameters were not correlated with FRs (data not shown). A long duration of anesthesia was considered longer than 30 min under anesthesia. A long duration of anesthesia was not associated with embryo quality ($p = 0.43$), normal FR ($p = 0.98$), or take-home baby rates ($p = 0.056$). However, implantation ($p = 0.04$) and clinical pregnancy ($p = 0.02$) rates in women with a long duration of anesthesia were lower than those without a long duration. There was no association between long duration of anesthesia and oocyte retrieval parameters, FRs, and embryo number. Data on the duration of anesthesia and IVF outcomes are presented in Table 6.

Discussion

Here, we aimed to evaluate the effect of different anesthetic agents used in general anesthesia on IVF outcomes including oocyte retrieval parameters and clinical success of IVF defined as FR, implantation, clinical pregnancy, and take home baby rates. Our study indicated that the use of ketamine as an anesthetic agent during OPU was associated with a lower FR as compared with that of IVF patients given propofol or P + K.

Previous studies of the effect of propofol on FRs reported discordant results [8,18–20]. The present study detected no association between propofol and low FRs, consistent with that of a study by Alsalili et al. [18]. In contrast to the present study, dose-

and time-dependent toxic effects of propofol on FRs was reported in mice [7,8]. However, no detrimental effects of propofol on fertilization and quality of embryos was detected in humans by Ben-Shlomo et al. [19]. In another study, the use of propofol and thiopental appeared to be associated with lower FRs as compared with those recorded using lidocaine and prilocaine or sevoflurane [20]. Similar IVF outcomes following administration of ketamine, thiopental, and no anesthesia protocols [21] and similar FRs in propofol and thiopental groups were reported [1,22]. In our study, the percentage of sperm motility, especially the percentage of fast progressive motile sperm (A%) was significantly decreased in the ketamine group as compared with that in the propofol group but not the P + K group. The reduced FR could be associated with a lower motile sperm count. However, the negative effect of ketamine on FR persisted after adjustment for sperm motility and a fast progressive sperm count. The acting time of propofol (3–10 min) is shorter than ketamine (10–15 min) [11,23]. Longer acting time could be one of the reasons of the negative effect of ketamine on FR due to the longer exposure of ketamine on oocytes. Propofol and ketamine administered together provide rapid recovery compared to ketamine alone, and therefore exposure of the oocytes to anesthetic agents is shortened [11].

In the present study, the duration of anesthesia and oocyte retrieval parameters were not correlated with FRs. We also found no association between longer durations of anesthesia (>30 min) and oocyte retrieval parameters, embryo quality, normal FR, and take-home baby rates. However, implantation and clinical pregnancy rates following extended anesthesia time were lower than those with shorter durations. In line with our findings, the duration of anesthesia and total dose of propofol administered were not associated with fertilization and embryo quality in humans [19]. However Janssenswillen et al. [3] reported that exposure to propofol for 30 min was deleterious to subsequent embryo cleavage and development up to the blastocyst state in mice. In our study, the mean duration of anesthesia did not exceed 30 min in any of the patient groups. The latter could explain why the duration of anesthesia was not associated with FRs. In previous studies, increased propofol levels in the follicular fluid of humans was shown to be

Table 5

Predictive effect of anesthetic agents on fertilization rate.

	β	p value	OR	95% CI for OR	
				Lower	Upper
Endometriosis	Not applicable	0.028	Not applicable	Not applicable	Not applicable
PCOS	0.11	0.91	1.12	0.14	8.72
Unexplain	0.19	0.85	1.21	0.16	9.07
DOR	0.67	0.52	1.96	0.25	15.35
Tubal	0.67	0.54	1.962	0.22	17.22
Male	-0.54	0.59	0.58	0.07	4.4
P + K	Not applicable	0.5	Not applicable	Not applicable	Not applicable
Propofol	-0.35	0.28	0.7	0.36	1.34
Ketamine	-1.08	0.01	0.33	0.14	0.77

Covariates: Age, BMI, etiology of infertility, the percentage of sperm motility, the percentage of fast progressive sperm motility (A%), duration of anesthesia. PCOS: Polycystic ovary syndrome; DOR: Diminished ovarian reserve; P + K: Combination of propofol and ketamine.

Table 6
Association of the duration of anesthesia and IVF outcome.

	Duration of anesthesia (<30 min, n = 276)	Duration of anesthesia (≥30 min, n = 55)	p value
Embryo quality			
Grade 1	182/203 (89.7%)	38/43 (88.4%)	
Grade 2	16/203 (7.9%)	5/43 (11.6%)	0.43
Grade 3	57/203 (2.5%)	0/43 (0%)	
Normal FR (%) (>60%)	126/243 (51.9%)	26/50 (52%)	0.98
Positive implantation	46/199 (23.1%)	4/42 (9.5%)	0.04
Presence of clinical pregnancy	38/199 (19.1%)	2/42 (4.8%)	0.02
Presence of take home baby	32/199 (16.1%)	2/42 (4.8%)	0.056
Oocyte retrieval parameters			
Total oocyte number	8.74 ± 6.85	9.56 ± 7.16	0.42
MII number	5.94 ± 4.75	6.21 ± 4.32	0.69
MI number	1.33 ± 1.71	1.45 ± 1.58	0.62
GV number	0.96 ± 1.6	1.32 ± 2.74	0.19
Oocyte with anomalies	0.17 ± 0.67	0.18 ± 0.72	0.9
Oocyte with degeneration	0.15 ± 0.59	0.12 ± 0.51	0.71
EZ	0.14 ± 0.47	0.27 ± 0.89	0.13
MII rate (%)	69.68 ± 23.25	68.28 ± 24.42	0.69
FR (%)	52.26 ± 33.25	55.39 ± 30.6	0.53
Embryo number	3.52 ± 3.15	3.58 ± 2.58	0.91

IVF: In vitro fertilization; FR: Fertilization rate; MII: Metaphase II; MI: Metaphase I; GV: Germinal vesicle; EZ: Oocyte with empty zona.

directly correlated with the total dose of propofol administered [3,24,25]. Therefore, it has been suggested that the OPU procedure should be kept as short as possible due to the accumulation of anesthetic agents in follicular fluid and their possible roles on quality and fertilization ability of oocytes [24]. The negative impact of long anesthesia duration on implantation and clinical pregnancy rates could be due to the adverse effects of dose and time dependent anesthetic agents as proven in previous studies [8].

In the present study, ovarian stimulation characteristics and oocyte retrieval parameters including the occurrence of OHSS, ovarian response, and total number of oocytes retrieved were similar between the groups. Only the number of MI oocytes was elevated in the ketamine group as compared with that in the propofol group. In contrast to these findings, total number of oocytes retrieved was reported to be similar in propofol and thiopental patient groups [1]. We found similar embryo numbers and grades between the groups. We also found similar implantation, clinical pregnancy, and take-home baby rates between the groups, even after adjustment for age, BMI, the percentage of sperm motility, the percentage of fast progressive sperm motility (A%), duration of anesthesia, and the etiology of infertility. Only age was a negative predictive factor for implantation, clinical pregnancy, and take-home baby rates, as expected. It has been reported that similar live birth rates, as well as embryo quality, in propofol-versus thiopental-treated groups in previous studies [1,22,26]. Researchers also failed to identify adverse effects of propofol on embryo quality assessed using in vitro studies [8,19]. In contrast, some studies demonstrated toxic effects of propofol, nitrous oxide, and midazolam on gametes and embryos in vitro [27–29]. Propofol has been suggested to have a detrimental effect on FRs but not on the developmental competence of mouse embryos [7]. Similar biochemical, clinical pregnancy, and live birth rates per oocyte retrieved were reported for propofol and thiopental, albeit implantation rates were lower following thiopental as compared to propofol administration [1]. Exposure to propofol was found to be associated with adverse effects on fertilization and further development [3]. Sterzik et al. [21] reported similar IVF outcomes in ketamine-versus thiopental-treated groups and suggested that ketamine-induced anesthesia was more suitable than thiopental-induced anesthesia for the OPU process due to elevated prolactin and β -endorphin levels following thiopental. Therefore, they suggested that general intubation anesthesia with thiopental should be avoided. Sterzik et al. also found no differences considering

estradiol and progesterone levels; however, prolactin and β -endorphin levels following ketamine were higher compared to controls that received no anesthesia [21].

The exact mechanisms of anesthetic agents and prolonged exposure to anesthetic agents on IVF outcome are not clear. Although long durations of anesthesia seemed to be related to lower implantation and clinical pregnancy rates but not poor embryo quality in our current study. Anesthetic agents and extended durations of anesthesia (longer than 30 min) could probably cause damage in oocytes and subsequently embryos that cannot be detected by our morphological evaluation of the embryos. Damage in DNA integrity of oocytes and embryos that cannot be determined by standard evaluation methods could be one of the reasons. Because the embryos and oocytes are graded on the basis of their morphological criteria, the morphology is not directly related to the genetic condition. The nuclear and cytoplasmic maturity of an oocyte is important for the development of pronuclei and the subsequent completion of fertilization. The genetic maturity of an embryo is also important for cleavage and development up to blastocyst stage as well as implantation to endometrium. Furthermore, anesthetic agents can affect endometrial cells, as their doubling time is shorter [30]. Alterations in endometrial cells can also interfere with implantation. Alterations in prolactin and β -endorphin levels or steroid hormone levels that haven't been investigated in our study design can also influence IVF outcomes [21].

The main limitation of the present study was its retrospective design and small sample size. The lack of determination of complications during anesthesia and adverse effects of the agents studied were other limitations. The lack of power calculations should also be considered, when assessing statistically significant differences in our results. During induction of general anesthesia, drugs other than propofol and ketamine (e.g., midazolam and remifentanyl) were administered as premedications. However, these co-interventions were identical between the groups. Nevertheless, a specific pharmacologic interaction of either propofol or ketamine with remifentanyl cannot be excluded, and this should be noted when interpreting the results.

Conclusion

In conclusion, the use of ketamine as an anesthetic agent during OPU could affect FRs. However, 3 distinctive anesthetic protocols do not appear to be related to differences in implantation, clinical

pregnancy, and take-home baby rates. Duration of anesthesia should be kept less than 30 min due to an association between long duration of anesthesia and lower implantation and clinical pregnancy rates. Further large sample-sized and prospective randomized controlled trials should be performed to evaluate the effect of anesthesia agents on IVF outcome.

Conflict of interest

The author declares that they have no conflict of interest.

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