Effect of drugs used in general anesthesia on oocyte and embryo quality in Iraqi infertile females undergoing intracytoplasmic sperm injection

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ABSTRACT

Various types of anesthetic techniques were described for oocyte recovery. Different anesthetic agents have been used with different effects on oocyte quality and embryonic development and studies on the potential toxicity of general anesthesia ended up with conflicting results. Many experiments as well as human studies documented the existence of anesthetic agents in the follicular fluid (FF) with possible adverse effects on the oocyte quality and subsequent embryo development. Ketamine and remifentanyl were used for the studied groups to compare oocytes and embryos characteristic of infertile women during oocytes retrieval under general anesthesia: one group receiving ketamine, midazolam, and propofol and the other group receiving remifentanyl, midazolam and propofol. 60 infertile females were undergoing intracytoplasmic sperm injection categorized in two groups, group I received midazolam, remifentanyl and propofol; whereas, group II received midazolam, ketamine and propofol. There was highly significant difference in mean abnormal oocyte between ketamine and remifentanyl groups. Grade III embryos were significantly limited to ketamine group. FF ketamine and remifentanyl were not significantly correlated to any of oocyte characteristics or embryo characteristics. Anesthetic agents, ketamine and remifentanyl, were detected in the FF of infertile women and within recommended doses. Ketamine resulted in adverse effects on oocyte and embryo quality in comparison with remifentanyl represented by greater percentage of abnormal oocytes and that bad quality embryos were limited to ketamine group.

Keywords: Ketamine; Remifentanyl; General anesthesia; Oocyte retrieval; Oocyte and embryo quality; ICSI.

1. Introduction

A significant proportion of couples worldwide are going to face the problem of infertility. For instance, about 10-15 % of couples worldwide had the experience of infertility (*Moridi, et al.* ^[1]). One of the highly advanced and recently introduced treatment approaches in infertility management is in vitro fertilization (IVF) (*Sharma, et al.* ^[2]). This technique involves the aspiration of mature oocytes from the infertile women's ovaries. In vitro fertilization of these oocytes is subsequently carried out and the developing embryo is eventually transferred to the infertile woman's uterus (*Vlahos, et al.* ^[3]). The harvesting of oocytes is one of the most important aspects of the IVF cycle, as oocyte quality affects fertilization, embryo quality, and implantation (*Tola, EN.* ^[4]). The process is very painful and stressful as the pain is caused by the passage of the needle through the vaginal wall and by the manipulation of the ovary mechanically (*Kwan, et al.* ^[5]; *Oliveira Júnior, et al.* ^[6];

Rolland, et al. ^[7]). Therefore, managing anxiety and pain when retrieving oocytes makes anesthesia an integral part of the IVF procedure (*Urfalioglu and Yaylali* ^[8]). Various types of anesthetic techniques described for oocyte recovery include neuraxial anesthesia (spinal or epidural), general anesthesia, regional block techniques (paracervical/preovarian block), conscious sedation, and electro-acupuncture or any combination of the above (*Rolland, et al.* ^[7]; *Urfalioglu and Yaylali* ^[8]; *Bümen, et al.* ^[9]; *Goutziomitrou, et al.* ^[10]; *Vasudevan, et al.* ^[11]). General anesthesia (GA), involving a depressing consciousness level, must be carried out and maintained by an anesthesia specialist in a hospital setting. Despite being used in the majority of fertility centers, agreement by clinicians about the type of aesthetic drugs used is still lacking (*Bümen, et al.* ^[9]; *Tola, EN.* ^[4]). Different anesthetic agents have been used with different effects on oocyte quality and embryonic development and studies on the potential toxicity of GA

ended up with conflicting results (*Vlahos, et al.* ^[3]; *Rolland, et al.* ^[7]; *Bümen, et al.* ^[9]; *Matsota, et al.* ^[12]; *Piroli, et al.* ^[13]; *Matsota, et al.* ^[14]). Several experimental, as well as human studies, documented the existence of anesthetic agents in the follicular fluid (FF) with possible adverse effects on the oocyte quality and subsequent embryo development (*Oliveira Júnior, et al.* ^[6]; *Urfalioglu and Yaylali* ^[8]; *Bümen, et al.* ^[9]; *Matsota, et al.* ^[12]; *Wilhelm, et al.* ^[15]; *Jarahzadeh, et al.* ^[16]); however, data about ketamine are lacking (*Matsota, et al.* ^[14]). The ideal agent used for the oocyte recovery technique should preserve hemodynamic and respiratory stability during the procedure, be free of toxic effects on oocytes, produce rapid onset and fast recovery at the end of the procedure, and be easy to administer (*Sarikaya, et al.* ^[17]). Remifentanyl is ultra-short acting and very potent synthetic opioid analgesic. It is 20 times more potent than alfentanil (*Beleña, et al.* ^[18]). It is characterized by fast onset (one minute) and a short-acting time (8 to 10 minutes)

with rapid elimination from systemic circulation (*Bümen, et al.* ^[9]). Ketamine is a perfect anesthetic agent as it offered all the components of anesthesia needed for surgery: loss of consciousness, satisfactory pain relief, and antegrade amnesia (*Gales and Maxwell* ^[19]). It is recommended for surgical interventions of a short time because of its short duration of action (10 to 15 minutes) and fast onset (45 to 50 seconds) (*Kolp, et al.* ^[20]). Both ketamine and remifentanyl are commonly used during aesthetic procedures required for oocyte retrieval (*Tola, EN.* ^[4]; *Bümen, et al.* ^[9]; *Jarahzadeh, et al.* ^[16]; *Lier, et al.* ^[21]). To the best of the knowledge, there is no available data comparing ketamine and remifentanyl in a single study during oocyte retrieval with respect to fertility outcome. Therefore, the current study aimed to compare oocytes and embryos characteristic obtained from two groups of infertile women during oocytes retrieval under general anesthesia: one group receiving ketamine, midazolam, and

propofol, and the other group receiving remifentanyl, midazolam, and propofol.

2. Materials and Methods

2.1 Study Design

This prospective comparative study was done on 60 infertile females who were undergoing intracytoplasmic sperm injection (ICSI) at the infertility center of the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Reproductive Physiology, Al Nahrain University, Baghdad, Iraq, during the period from July 2019 until April 2020. Ethical approval of the current study was issued by the Local Medical Ethical Committee of the Institute. Patients with poor ovarian reserve, hyperprolactinemia, chronic disease like diabetes, hypertension, chronic renal disease and those underwent oocyte retrieval with anesthesia method other than GA were excluded. All patients were subjected to full history taking, physical examination, and investigation. Controlled Ovarian Hyperstimulation with flexible Gonadotropin-Releasing Hormone

(GnRH) antagonist protocol was used for all patients. Final oocytes maturation was established by the administration of hCG or hCG and Triptorelin (dual triggering) when two to three leading follicles were observed at an average diameter of 18 mm.

2.2 General anesthesia protocol

An assessment of hemodynamic status was done for all participant females as well as the demographic data (age, height, weight, and American Society Anesthesiologist (ASA) status). Standard Monitoring (heart rate (HR), non-invasive blood pressure (NIBP), pulse oximetry (SpO₂), 3 lead ECG) applied to all patients on admission to the institute's operating room for oocyte recovery. Then patients were categorized into two groups randomly. Patients in Group I received 0.05 mg/kg IV midazolam and 0.5-1 mcg/kg IV remifentanyl with 2 mg/kg IV propofol. Group II received 0.05 mg/kg IV midazolam and 0.5 mg/kg IV ketamine with 2 mg/kg IV propofol. In either group, maintenance of anesthesia was done with

2% Sevoflurane and a 100% O₂ introduced by the facial mask.

2.3 IVF procedures and Follicular Fluid collection

Transvaginal oocyte retrieval was performed 34-36 hours after the injection of the trigger with ultrasound guidance. Then the FF was immediately brought to an embryology specialist in order to gather the retrieved cumulus-oocytes complexes (COC). Following the isolation of the oocyte, the remaining FF was centrifuged for 10 minutes at 3000 rpm for the separation of debris and cellular contents. The FF supernatant was then transferred into a sterile collecting tube, followed by storage at -20°C waiting for assay time. Assessment of each oocyte (after denudation) was carefully done, observing the existence, or lacking the first polar body or germinal vesicle. Ova that were morphologically intact and extruded the first polar body (metaphase II) were selected for microinjection. Fertilization was assessed for evidence of normality,

about 12 to 18 hours following the ICSI process, based on the existence of two pronuclei (2PN). The developed embryos were graded following the Istanbul consensus workshop (*Alpha scientists in reproductive medicine and ESHRE special interest of embryology* ^[22]) and classified into grades I, II, and III. Grade I embryo with less than 10% fragmentation, stage-specific cell size, no multinucleation. Grade II embryo with 10–25% fragmentation, stage-specific cell size for the majority of cells, no evidence of multinucleation. Grade III embryo with severe fragmentation (>25%), cell size did not stage-specific, evidence of multinucleation.

2.4 Determination of ketamine and remifentanyl in follicular fluid

Follicular fluid obtained on the day of oocyte retrieval was used for the estimation of ketamine and remifentanyl levels by Reversed-Phase High-performance Liquid Chromatography

(HPLC) technique. FF samples were analyzed in the Ministry of Science and Technology/ Department of Environment and Water by HPLC model (SYKAM) Germany. Pump model: S 2100 Quaternary Gradient Pump, Autosampler model: S 5200, Detector: UV (S 2340) and Column Oven model: S 4115. The mobile phase was (acetonitrile: phosphate buffer) (80:20 v/v), the column is C18-ODS (25 cm * 4.6 mm), and detector UV – 270 nm for Ketamine at a flow rate (1.1 ml/min) and 220 nm for Remifentanil at flow rate 0.8 ml/min. at 37°C. Anesthetic drugs concentration was measured by using the following equation (*Ewadh and Jawad [23]*)

$$\text{Sample Concentration} = (\text{Sample Area} / \text{Standard Area}) \times \text{Standard Concentration}$$

3. Statistical Analysis

Data were analyzed using a statistical package for social sciences (SPSS, IBM, Chicago, USA, version 23). Qualitative data were expressed as number and

percentage; whereas quantitative data were expressed as mean, and standard deviation. Independent sample t-test was used to compare the mean between two groups, whereas, the chi-square test was used to compare proportions between two groups. The degree of association between continuous variables was calculated by Pearson's correlation coefficient (r) and the level of significance was chosen at $p \leq 0.05$.

4. Results

The demographic characteristics of infertile women enrolled in this study were shown in *Table 1*. There was no significant difference in mean age, mean body mass index (BMI), mean duration of infertility, type of infertility, causes of infertility, and several previous IVF cycles, between ketamine and remifentanil, treated groups, ($p > 0.05$), *Table 1*. The oocyte characteristics of infertile women enrolled in the current study are shown in *Table 2*. There was no significant difference in mean total oocyte

Table (1): Demographic characteristics of infertile women enrolled in the current study

Characteristic	Ketamine group <i>n</i> = 30	Remifentanil group <i>n</i> = 30	<i>P</i>
<i>Age (years)</i>			
<i>Mean ±SD</i>	30.30 ±6.24	30.30 ±5.65	1.000 † NS
< 35, <i>n</i> (%)	21 (70.0 %)	25 (83.3 %)	0.222 ¥ NS
≥ 35, <i>n</i> (%)	9 (30.0 %)	5 (16.7 %)	
<i>BMI (kg/m²)</i>			
<i>Mean ±SD</i>	28.76 ±4.56	28.76 ±5.42	0.996 † NS
<i>Underweight, n</i> (%)	0 (0.0 %)	1 (3.3 %)	---
<i>Normal, n</i> (%)	8 (26.7 %)	6 (20.0 %)	
<i>Overweight, n</i> (%)	12 (40.0 %)	12 (40.0 %)	
<i>Obese Class I, n</i> (%)	6 (20.0 %)	7 (23.3 %)	
<i>Obese Class II, n</i> (%)	3 (10.0 %)	3 (10.0 %)	
<i>Obese Class III, n</i> (%)	1 (3.3 %)	1 (3.3 %)	
<i>Duration of infertility (years)</i>			
<i>Mean ±SD</i>	6.87 ±3.73	6.85 ±3.31	0.985 † NS
< 5, <i>n</i> (%)	7 (23.3 %)	7 (23.3 %)	---
5-10, <i>n</i> (%)	18 (60.0 %)	18 (60.0 %)	
> 10, <i>n</i> (%)	5 (16.7 %)	5 (16.7 %)	
<i>Type of infertility</i>			
<i>Primary, n</i> (%)	18 (60.0 %)	17 (56.7 %)	0.793 ¥ NS
<i>Secondary, n</i> (%)	12 (40.0 %)	13 (43.3 %)	
<i>Causes of infertility</i>			
<i>Male factor, n</i> (%)	17 (56.7 %)	16 (53.3 %)	0.488 ¥ NS
<i>Female factor, n</i> (%)	6 (20.0 %)	4 (13.3 %)	
<i>Combined, n</i> (%)	1 (3.3 %)	0 (0.0 %)	
<i>Unexplained, n</i> (%)	6 (20.0 %)	10 (33.3 %)	
<i>Number of previous IVF</i>			
0, <i>n</i> (%)	22 (73.3 %)	27 (90.0 %)	0.095 ¥ NS
1, <i>n</i> (%)	4 (13.3 %)	3 (10.0 %)	
2, <i>n</i> (%)	4 (13.3 %)	0 (0.0 %)	

n: number of cases; SD: standard deviation; BMI: body mass index; †: Independent samples t-test; ¥: Chi-square test; NS: Not significant at *P*> 0.05

Table (2): Oocyte characteristics of infertile women enrolled in the current study

Characteristic	Ketamine group <i>n</i> = 30	Remifentanil group <i>n</i> = 30	<i>P</i> †
Total oocyte number			
<i>Mean±SD</i>	11.97±3.73	10.7±2.65	0.135 † NS
Metaphase II (MII) %			
<i>Mean±SD</i>	65.17±19.59	69.37±11.71	0.318 † NS
Metaphase I (MI) %			
<i>Mean±SD</i>	13.22±13.44	11.26±10.41	0.529 † NS
Germinal vesicle (GV) %			
<i>Mean±SD</i>	3.32±7.69	7.26±8.27	0.061 † NS
Abnormal %			
<i>Mean±SD</i>	14.31±11.26	6.00±7.66	0.001 † HS

Table (3): Embryo characteristics of infertile women enrolled in the current study

Characteristic	Ketamine group <i>n</i> = 30	Remifentanil group <i>n</i> = 30	<i>P</i>
Grade I Embryo %			
<i>Mean±SD</i>	58.75 ± 33.71	73.01 ± 26.25	0.072 † NS
Grade II Embryo %			
<i>Mean±SD</i>	23.17 ± 24.89	23.45 ± 23.52	0.952 † NS
Grade III Embryo %			
<i>Mean±SD</i>	8.75 ± 18.84	0.00 ± 0.00	0.014 † S

n: number of cases; SD: standard deviation; †: Independent samples t-test; NS: Not significant at $P > 0.05$; S: significant at $P \leq 0.05$; HS: Highly significant at $P \leq 0.01$

Table (4): Correlations of follicular fluid concentration of anesthetic agents to oocyte and embryo characteristics

Characteristic	Ketamine		Remifentanil	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
<i>Total oocyte number</i>	-0.022	0.910 NS	-0.252	0.179 NS
<i>Metaphase II (MII) oocyte</i>	0.167	0.379 NS	0.04	0.835 NS
<i>Metaphase I (MI) oocyte</i>	-0.206	0.275 NS	0.195	0.302 NS
<i>Germinal vesicle (GV) oocyte</i>	-0.191	0.313 NS	-0.202	0.285 NS
<i>Abnormal oocyte</i>	-0.047	0.803 NS	0.057	0.764 NS
<i>Grade I embryo number</i>	-0.178	0.347 NS	0.074	0.697 NS
<i>Grade II embryo number</i>	0.175	0.354 NS	-0.033	0.864 NS
<i>Grade III embryo number</i>	0.062	0.745 NS	----	----

r: Pearson's correlation coefficient; NS: not significant at $P > 0.05$

number, mean metaphase II(MII)%, mean metaphase I (MI)%, and mean germinal vesical (GV) oocyte % between ketamine and remifentanil treated groups ($p > 0.05$), as shown in **Table 2**. However, there was a highly significant difference in mean abnormal oocyte % between ketamine and remifentanil groups, 14.31 ± 11.26 versus 6.00 ± 7.66 , respectively ($p = 0.001$); being higher in the ketamine group, **Table 2**. The embryo characteristics of infertile women enrolled in the current study are shown in

Table 3. There was no significant difference in grade I and grade II embryos between the ketamine group and remifentanil groups ($p > 0.05$); however, grade III embryos were significantly limited to the ketamine group ($p = 0.014$), **Table 3**. FF concentration of ketamine and remifentanil were not significantly correlated to any of oocyte characteristics or embryo characteristics ($p > 0.05$), **Table 4**.

5. Discussion

In this study, to compare the outcome of intracytoplasmic sperm injection (ICSI) cycle, namely oocyte characteristics and embryo characteristics, 60 infertile women were chosen randomly and classified into two groups, 30 receiving ketamine and 30 receiving remifentanyl during general anesthesia for oocyte retrieval. The results showed that there are no significant differences in demographic characteristics, namely age, BMI, duration of infertility, type of infertility, causes of infertility, and the number of previous IVF cycles between the remifentanyl group and ketamine group ($p>0.05$). The lack of significant difference can lead to avoidance of any bias in fertility outcome related to a younger age, shorter duration of infertility, optimum BMI, or variation in causes of infertility which will limit the explanation of any possible difference in fertility outcome to variation in the type of anesthetic drug used namely remifentanyl and ketamine. There was no significant difference in mean total oocyte number,

mean MII oocyte %, mean MI oocyte %, and mean germinal vesical (GV) oocyte % between ketamine and remifentanyl treated groups ($p>0.05$). However, there was a highly significant difference in mean abnormal oocyte% between ketamine and remifentanyl groups ($p=0.001$); being higher in the ketamine group. It has been found that remifentanyl has no adverse effect on the quality of retrieved oocytes when compare the anesthetic techniques using propofol and fentanyl versus midazolam and remifentanyl associated with the paracervical block with lidocaine or comparing GA (atropine, remifentanyl, and propofol) versus paracervical block or analgesia with remifentanyl versus anesthesia with propofol and alfentanil (*Oliveira Júnior, et al.* ^[6]; *Bümen, et al.* ^[9]; *Matsota, et al.* ^[12]). Also, remifentanyl has the advantage of significantly higher total oocyte number when it was given in continuous intravenous infusion and compare with local anesthesia (*Milanini, et al.* ^[24]) or given in GA (remifentanyl

with either propofol or isoflurane) and compare with sedation (midazolam, diazepam, or propofol) (*Hammadeh, et al.* ^[25]). Nevertheless, no significant difference in the total number of oocytes has been found by other studies (*Bümen, et al.* ^[9]; *Matsota, et al.* ^[12]; *Lier, et al.* ^[21]). Regarding ketamine, some authors found no significant negative effect subjected by ketamine on oocyte quality when comparing the effect of ketamine, thiopental, and propofol for sedation during oocyte retrieval (*Nossair and Maaty* ^[26]); however, a negative drawback on oocyte quality linked to ketamine had been shown by (*Tola, EN.* ^[4]) when compared to propofol or propofol/ketamine. Other studies concluded no significant negative impact related to ketamine regarding oocyte quality and number when compared to propofol or fentanyl/propofol/isoflurane (*Urfalioglu and Yaylali* ^[8]; *Ben-Shlomo, et al.* ^[27]). So far, two points can be inferred from the above discussion, the first one is the lack of a previous study

comparing ketamine to remifentanyl. The second point is that the effect of either drug on oocyte quality and the number is still controversial and needs further research work; however, current results favor remifentanyl in this regard. The acting time of remifentanyl is shorter than ketamine. Thus, a longer-acting time of ketamine could probably cause damage in the oocyte (as abnormal oocytes were highly significant with the ketamine group) due to longer exposure of ketamine on oocytes. There was no significant difference in grade I and grade II embryos between the ketamine and remifentanyl treated group ($p>0.05$); however, grade III embryos were significantly limited to the ketamine treated group ($p=0.014$), as none of the women within remifentanyl treated group had grade III embryos. Hence, obtaining good quality embryos was comparable in both groups while bad quality embryos were limited to the ketamine treated group. Some studies showed no significant difference in embryo quality when remifentanyl

compared to alfentanil/propofol, local anesthesia, pethidine/midazolam (*Matsota, et al.* ^[12]; *Lier, et al.* ^[21]; *Milanini, et al.* ^[24]; *Barut, et al.* ^[28]). However, other studies showed that remifentanil is superior to fentanyl with respect to embryo score (*Jarahzadeh, et al.* ^[16]). In a previous study, ketamine was found not to adversely affect embryo quality when compared to propofol (*Tola, EN.* ^[4]). However, (*Nossair and Maaty* ^[26]) stated a negative impact subjected by ketamine on embryo quality, embryo development, cleavage rate, fertilization rate, pregnancy, and implantation rate, with more abortion rate when compared to propofol for sedation during oocyte retrieval. Therefore, there is no previous study comparing the effect of ketamine and remifentanil on embryo quality in women undergoing oocyte retrieval for IVF/ICSI program. Whereas, the current study to the best of our knowledge, is the first one to make a comparison between remifentanil and ketamine on embryo quality and it has shown that remifentanil

is superior to ketamine as bad quality embryos were limited to ketamine treated group. This may be explained by that remifentanil has a short duration of action with rapid elimination from systemic circulation without drug accumulation (*Bümen, et al.* ^[9]; *Lier, et al.* ^[21]). This may lead to less exposure to anesthesia with less determinate effect on oocyte and after the embryo. The rapid elimination and clearance of remifentanil are due to its rapid and predictable metabolism by tissue and plasma non-specific esterase, mainly to a carboxylic acid (non-active byproduct) (*Beleña, et al.* ^[18]; *Ziesenitz, et al.* ^[29]). However, the metabolism of ketamine is mainly hepatic (80%) producing nor-ketamine which is a weak analgesic with 20 to 30 % ketamine potency. Nor-ketamine is then hydroxylated via glucuronoconjugation and excreted in urine and bile (*Mion and Villeveille* ^[30]). In the current study, the FF concentration of both ketamine and remifentanil were not significantly correlated to oocyte characteristics and

embryo characteristics ($p>0.05$). Previously, a little number of researchers measured the FF concentration of anesthetic agents and some of them use a little number of participants thus, further investigation should be carried out to achieve a safe conclusion (*Matsota, et al. [14]*). Some studies (*Endler, et al. [31]*; *Imoedemhe, et al. [32]*; *Wikland, et al. [33]*; *Soussis, et al. [34]*; *Ben-Shlomo, et al. [35]*) measured the concentration of a variety of anesthetic agents (thiopental, thiamylal, lidocaine, midazolam, fentanyl, alfentanil, and propofol) in FF however, data about ketamine are lacking. (*Imoedemhe, et al. [32]*; *Ben-Shlomo, et al. [35]*) found that the FF concentration of propofol was not significantly correlated to oocytes characteristics during IVF/ICSI cycles. It is worth to mention that the current study was the first one to include FF assessment for ketamine. In addition to there is no previous study comparing the impact of the FF concentration of both ketamine and remifentanil on oocyte and embryo

characteristics in women undergoing oocyte retrieval for IVF/ICSI program.

6. Conclusions

In conclusion, both anesthetic agents, ketamine, and remifentanil were detected in the follicular fluid of infertile women and within recommended doses, ketamine resulted in significant adverse effects on oocyte and embryo quality in comparison with remifentanil represented by a significantly greater percentage of abnormal oocytes and that bad quality embryo were limited to ketamine group.

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Author Contribution

Mohsin, HAH performed the study, examined and reviewed results, and manuscript writing with the help and supervision of Jwad MA, and Reshan, RG.

Conflict of Interest

The author declares no conflict of interest.

Ethical Clearance

The study was approved by the Ethical Approval Committee.

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