

## RESEARCH ARTICLE

# Evaluation of Oxidative Stress as a Contributor of Anesthetic Agents Effects on Oocyte Quality and ICSI Outcome in Iraqi Patients

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## ABSTRACT

**Background:** Infertility is described as a couple's failure to conceive for at least a year, even when using unprotected, natural sex. Even though all anesthetic chemicals have been revealed in the follicular fluids, general anesthesia is still used in many IVF centers for patients who want to get pregnant. However, few or restricted studies support the adverse effects of these medicines on oocyte structure during ICSI, especially in relation to reactive oxygen species (ROS) measurements in plasma during the preoperative and postoperative periods, as well as their impacts on Oocyte Quality.

**Objective:** This paper provides an overview of data on the potential impacts of various anesthetic agents (particularly for Ketamine and Opioids) on Oocyte Quality in the ART cycle, focusing on the oxidative stress-free radical parameter.

**Material and Methods:** The existing comparative study was conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies at Al-Nahrain University Baghdad, Iraq. The study comprised 60 infertile women split into two groups at random. All of the patients were administered general anesthesia, with 30 of them receiving ketamine (0.5 mg/kg) and the other 30 receiving remifentanyl (0.5 mg/kg) for anesthesia induction. The research was conducted from December 2020 to June 2021. All participants signed a written informed consent form before being included in the study. Patients' records were kept. We set up an intravenous line and collect serum for testing (ROS) levels in all patients before initiating general anesthesia and afterward. Clinical evaluation (history, examination, and investigation), controlled ovarian stimulation, ovulation stimulation, egg retrieval under general anesthesia, and follicular fluid collection, egg stripping, egg maturity evaluation, and intra-egg sperm injection into mature cells will all be performed on all participants (MII).

**Results:** The participants in this study were 60 infertile women divided into two groups: 30 women who got remifentanyl during general anesthesia for oocyte retrieval and 30 women who received ketamine during general anesthesia for oocyte retrieval. The concentrations of reactive oxygen species in the remifentanyl and ketamine groups were compared. Before anesthesia, the median serum ROS concentrations did not change significantly between the remifentanyl and ketamine groups ( $p = 0.051$ ). After anesthesia, the median serum ROS concentrations did not change significantly between the remifentanyl and ketamine groups ( $p = 0.367$ ). Furthermore, no significant differences in median follicular fluid ROS concentrations were found between the remifentanyl and ketamine groups ( $p = 0.051$ ).

**Conclusion:** The oocyte and embryo features of remifentanyl and ketamine were not significantly different, indicating that none is preferable to the other in this regard. When remifentanyl or ketamine was given, there was no significant change in serum or follicular fluid ROS levels.

**Keywords:** General anaesthesia, Infertility, Ketamine, Oocyte quality, Reactive oxygen species, Remifentanyl.

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## INTRODUCTION

Infertility is defined as an inability to conceive after one year of unprotected sexual activity. Approximately 7 percent of the male population is affected, collectively explaining infertility in half of all couples affected.<sup>1</sup> According to a large-

scale study, female factors account for about half infertility cases, male factors account for 20% to 30%, and both factors account for 20% to 30% due to the shared causes of both genders. According to current meta-analysis research, male factors are found in Infertility affecting 20–70% of couples.<sup>2</sup>

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Some clinicians use the terms infertility and subfertility interchangeably.

On the other hand, formal definitions are essential for efficient reproductive illness treatment. Around 186 million people worldwide suffer from infertility, most of whom live in poorer countries. While the most powerful negative indicator of fertility is a woman's age before conception.<sup>3</sup> The microenvironments associated with hydrosalpingeal fluid, follicular fluid, and peritoneal fluid affect sperm–oocyte interaction, oocyte quality, and oocyte function mediated by sperm.<sup>4</sup> Anesthetic treatment for oocyte retrieval may impair the results and success rates of in vitro fertilization (IVF). The influence of two different anesthetic techniques for oocyte retrieval (general anaesthesia vs. sedation) on IVF results was examined in this study. We used a hypnotic dosage of remifentanyl (Ultiva™) for general anesthesia with either propofol or isoflurane. Depending on clinical needs, midazolam, diazepam, or propofol were used to achieve sedation.<sup>5</sup> Remifentanyl was first developed in the early 1990s and is a clinically fible opioid. It is administered intravenously to induce drowsiness and analgesia in patients enduring painful surgical procedures, with little effect on cognition.<sup>6</sup> Ketamine It was developed in the 1960s as a possible replacement for phencyclidine, a potent hallucinogenic drug. It's a synthetic dissociative anesthetic that's nonbarbiturate.<sup>7</sup>

## MATERIALS AND METHODS

This potential comparative study was done on sixty infertile females who were undergoing intracytoplasmic sperm injection (ICSI) at the infertility center of High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, Baghda, Iraq, during the period from July 2020 until December 2021 regardless to the presence or absence of previous Assisted Reproductive Technologies (ARTs) trials. Ethical approval of the current The report was published by the Hospital's Local Medical Ethical Committee High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University. The morphological assessment of the oocytes aspirated from the ovaries of infertile females and their resulting embryos was done in the ICSI laboratory of the High Institute of Infertility Diagnosis and Assisted Reproductive

Technologies. The measurement of reactive oxygen species (ROS) in the follicular fluid and serum by (ELISA) in a private laboratory in the serum and follicular fluid.

## RESULTS

The comparison of reactive oxygen species concentrations between remifentanyl and ketamine groups is shown in Table 1. There were no significant differences in median serum ROS concentrations before anesthesia between remifentanyl and ketamine groups ( $p = 0.051$ ). There was also no significant difference in median serum ROS concentrations after anesthesia between remifentanyl and ketamine groups ( $p = 0.367$ ). In addition, there were no significant difference in median follicular fluid reactive oxygen species (ROS) concentrations between remifentanyl and ketamine groups ( $p = 0.051$ ). The comparison of fertility parameters between remifentanyl and ketamine groups is shown in Table 2. There was no significant difference in median total number of oocytes between remifentanyl and ketamine groups ( $p = 0.711$ ). There was also no significant difference in median germinal vesicle (GV) oocyte count between remifentanyl and ketamine groups ( $p = 0.432$ ).

In addition, there was no significant difference in median immature metaphase I (MI) oocyte count between remifentanyl and ketamine groups ( $p = 0.057$ ). Moreover, there was no significant difference in median mature metaphase II (MII) oocyte count between remifentanyl and ketamine groups ( $p = 0.302$ ). Further, there was no significant difference in median abnormal oocyte count between remifentanyl and ketamine groups ( $p = 0.971$ ). Furthermore, there was no significant difference in median rupture oocyte count between remifentanyl and ketamine groups ( $p = 0.758$ ).

## DISCUSSION

This study showed no significant difference in median serum ROS concentrations before and after anesthesia and in mean follicular fluid oxygen species ROS concentrations between remifentanyl and ketamine groups. Therefore, either drug can be chosen for general anesthesia when performing oocyte retrieval without being afraid of significantly higher oxidative stress associated with one drug than the other. After a thorough

**Table 1:** Comparison of ROS concentrations between remifentanyl and ketamine groups

Characteristic	Remifentanyl <i>n</i> = 30	Ketamine <i>n</i> = 30	<i>P</i>
<i>ROS Before anesthesia U/I</i>			
Median (IQR)	1550.10 (2280.49)	661.17 (697.84)	0.051 M
Range	148.05–5160.42	153.12–975000.00	NS
<i>ROS After anesthesia U/I</i>			
Median (IQR)	1064.50 (1770.08)	783.54 (545.34)	0.367 M
Range	163.31–4092.15	176.76–2531.78	NS
<i>ROS In follicular fluid U/I</i>			
Median (IQR)	860.79 (2095.46)	864.64 (739.78)	0.848 M
Range	130.89–4571.99	239.20–2757.86	NS

*n*: number of cases; **IQR**: inter-quartile range; **M**: Mann Whitney U test; **NS**: not significant at  $p > 0.05$

**Table 2:** Comparison of fertility parameters between remifentanil and ketamine groups

Characteristic	Remifentanil n = 30	Ketamine n = 30	P
<i>Total number of oocytes</i>			
Median (IQR)	7.00 (8.00)	9.00 (6.00)	0.711 M
Range	3.00–23.00	2.00–24.00	NS
<i>Germinal vesicle (GV) oocyte</i>			
Median (IQR)	0.00 (1.00)	0.00 (2.00)	0.432 M
Range	0.00–3.00	0.00–5.00	NS
<i>Immature metaphase I (MI) oocyte</i>			
Median (IQR)	1.00 (2.00)	2.00 (3.00)	0.057 M
Range	0.00–9.00	0.00–10.00	NS
<i>Mature metaphase II (MII) oocyte</i>			
Median (IQR)	5.00 (6.00)	5.00 (5.00)	0.302 M
Range	1.00–19.00	0.00–13.00	NS
<i>Abnormal oocyte</i>			
Median (IQR)	0.00 (1.00)	0.00 (1.00)	0.971 M
Range	0.00–2.00	0.00–4.00	NS
<i>Ruptured oocyte</i>			
Median (IQR)	0.00 (0.00)	0.00 (0.00)	0.758 M
Range	0.00–4.00	0.00–2.00	NS

n: number of cases; IQR: interquartile range; M: Mann Whitney U test; NS: not significant at  $p > 0.05$

search in the available published articles, we failed to find a study similar to ours to compare our results with it. However, previous experimental studies have demonstrated that remifentanil is associated with ameliorating oxidative stress because it leads to lower MDA levels of MDA.<sup>8</sup> In another study, it has been that ketamine administration was associated with lowering MDA level.<sup>9</sup> Therefore, concerning oxidative stress, the use of drugs remifentanil and ketamine is safe.

In the current study, there was no significant difference in median total number of oocytes, median germinal vesicle (GV) oocyte count, median immature metaphase I (MI) oocyte count, median mature metaphase II (MII) oocyte count, median abnormal oocyte count, median rupture oocyte count, and median fertilized two pronuclei (2PN) oocyte count between remifentanil and ketamine groups. Therefore, ketamine and remifentanil can be used in general anesthesia for oocyte retrieval in preparation for ICSI procedure since neither drug significantly affected oocyte or embryo characteristics. Our results are comparable to that of Hameeda *et al.* in 2020 with respect to total oocyte count, metaphase II (MII) oocytes, metaphase I (MI) oocytes and ruptured oocytes; however, we disagree with Hameeda *et al.* in 2020 with respect to germinal vesicle (GV) oocyte and abnormal oocytes since in our study there was no significant difference between remifentanil and ketamine group; whereas, in the study of Hameeda *et al.*, germinal vesicle oocytes were less and abnormal oocytes were more in ketamine group. Previous reports have shown conflicting results, with some authors favoring better oocyte

count and quality using remifentanil.<sup>10,11</sup> others described a lack of significant difference.<sup>12-15</sup> Concerning ketamine, some authors described no significant adverse effects of oocyte quality.<sup>16</sup> Whereas others discourage ketamine use because of associated low-quality oocytes.<sup>17</sup>

## CONCLUSION

There was no significant difference in oocyte between remifentanil and ketamine, indicating that neither is superior to the other in this regard.

There was no significant difference in ROS levels in serum and follicular fluid when remifentanil and ketamine were used, indicating that none is superior to the other in this regard.

Remifentanil is superior to ketamine in terms of recovery time, although it is associated with much lower systolic blood pressure than ketamine.

According to a correlation study, oxidative stress substantially impacts oocyte quality. Hence using anti-oxidants regularly in ART may help to improve oocyte quality.

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