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Comparison between Effects of Ketamine and Remifentanil Used During Oocyte Retrieval on ICSI Outcome

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ABSTRACT

Background: A number of experimental as well as human studies documented the existence of anesthetic agents in the follicular fluid with possible adverse effects on the oocyte quality and subsequent fertilization and implantation; however, data about ketamine are lacking. Controversial data has emerged with some favors the existence of variation in fertility parameters and others deny such an association.

Objective: Is to compare the effect of drugs used for general anesthesia during oocyte retrieval (ketamine vs remifentanil) on ICSI outcome

Patients and methods: The current prospective comparative study has been carried out at the infertility center of "High Institute of Infertility Diagnosis and Assisted Reproductive Technologies /Reproductive Physiology/Al- Nahrain University/ Baghdad/ Iraq" form July 2019 through April 2020. The study included 60 infertile women undergoing intracytoplasmic sperm injection (ICSI) with a variety of causes of infertility with an age range of 19 to 44. Those patients were categorized into two groups according to anesthetic regimen introduced during general anesthesia for oocyte retrieval. The first group received ketamine, midazolam and propofol while the second group received remifentanil, midazolam and propofol.

Results: the results of present study showed that remifentanil resulted in higher fertilization rate than ketamine in a highly significant manner ($P < 0.01$); however, cleavage rate was comparable in both groups. There was significant difference ($p<0.05$) in rate of positive pregnancy test between ketamine group and remifentanil group, 20.0 % versus 46.7 %, respectively ($P = 0.028$); being higher in remifentanil group. Recovery time was shorter in remifentanil group in comparison to ketamine group in a highly significant manner ($P < 0.01$); nevertheless, procedure time was comparable in both groups ($P > 0.05$). A cutoff value of recovery time of ≤ 10 minutes resulted in a 80 % sensitivity and 65 % specificity in predicting positive pregnancy outcome.

Conclusion: Remifentanil is superior to ketamine in routine general anesthesia procedures for ova pickup in IVF/ICSI procedures because of significantly higher fertilization rate, pregnancy rate and shorter recovery time.

Key words: ICSI, general anesthesia, oocyte retrieval, ketamine, remifentanil

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INTRODUCTION

The success of *In vitro* fertilization (IVF) is determined by positive yield in a sequence of IVF stages, including "controlled ovarian stimulation (COS), oocyte pick-up (OPU), fertilization, embryo transfer, and implantation". The process of OPU is essential, because the quality of oocyte affects fertilization, embryo quality, and implantation (Tola, 2019). The OPU process is painful and needs sedation, anesthesia or analgesia alone, despite it is a minimally invasive technique (Goutziomitrou *et al.,* 2015). For OPU, General anesthesia (GA) is used in most of IVF clinics. However, there is no consensus on type of anesthetic agents use among clinician performing OPU (Bumen *et al*., 2011).

The use of different methods of anesthesia and their associated medication have been extensively evaluated in terms of impact on fertility parameters such as oocyte characteristics and embryo quality and the main outcome was of course the achievement of clinical pregnancy outcome (Sharma *et al*., 2015). A number of experimental as well as human studies documented the existence of anesthetic agents in the follicular fluid with possible adverse effects on the oocyte quality and subsequent fertilization and implantation (Wilhelm et al., 2002; Bumen *et al*., 2011; Jarahzadeh *et al*., 2011; Matsota *et al*., 2012; Urfalıoğlu and Yaylalı, 2016; Oliveira *et al*., 2016); however, data about ketamine are lacking (Matsota *et al*., 2015).

Controversial data has emerged from such literatures with some favors the existence of variation in fertility parameters and others deny such and association. Remifentanil is a rapid and ultra-short acting opioid analgesic has been encouraged by a number of authors because of short duration of action (8-10 minutes) and better fertility outcome in association with ova pick up (Bumen *et al*., 2011; Jarahzadeh *et al*., 2011; Lier *et al*., 2015; Oliveira *et al*., 2016). On the other hand, Ketamine is one of common medication in use during aesthetic procedures required for oocyte retrieval because of little risk of cardiac instability, minimal respiratory depressive effects, and good analgesic and anesthetic properties (Vlahos *et al*., 2009; Tola, 2019); however its use has been discouraged by some authors because of the development some maternal adverse effects (Peltoniemi *et al*., 2016). To the best of our knowledge, there is no available data comparing ketamine and remifentanil in a single study during oocyte retrieval with respect to fertility outcome. Therefore, the aim of the current study was to compare ICSI outcome 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 remifentanil, midazolam and propofol.

PATIENTS AND METHODS

The current prospective comparative study has been carried out at the infertility center of "High Institute of Infertility Diagnosis and Assisted Reproductive Technologies/ Al-Nahrain University/ Baghdad/ Iraq" form July 2019 through April 2020. The study included 60 infertile women undergoing intracytoplasmic sperm injection (ICSI) with a

variety of causes of infertility with an age range of 19 to 44. Those patients were categorized into two groups according to anesthetic regimen introduced during general anesthesia for oocyte retrieval. The first group received ketamine, midazolam and propofol while the second group received remifentanil, midazolam and propofol.

All participants passed through the routine ICSI procedure including clinical evaluation (history, examination and investigation), controlled ovarian stimulation, triggering of ovulation, oocyte retrieval under general anesthesia, follicular fluid collection for later assessment of the concentration of anesthetic drugs (remifentanil and ketamine), oocyte denudation, oocyte maturation evaluation, intracytoplasmic sperm injection of mature (MII) oocytes, evaluation of fertilization and cleavage and embryo grading, embryo selection and embryo transfer, luteal phase support, beta hCG determination (to document biochemical pregnancy).

Sperm processing has been carried after oocyte denudation. Oocyte and embryo quality were assessed depending on microscopical morphological criteria. Measurement of follicular fluid concentration of ketamine and remifentanil was based on high performance liquid chromatography (HPLC).

RESULTS

The demographic characteristics, serum hormone concentrations and ovarian stimulation characteristics of infertile women enrolled in this study were shown in tables 1, 2 and 3, respectively. There was no significant difference in any of these characteristics, between ketamine and remifentanil treated groups, ($P > 0.05$). The mean Fertilization rate and mean cleavage rate in ketamine and remifentanil groups are shown in figure 1. There was highly significant difference in mean fertilization rate between ketamine groups and remifentanil group, 66.51 ±16.25 % versus 79.20 ±16.27 %, respectively ($P = 0.004$); being higher in remifentanil group, figure 1. However, there was no significant difference in mean cleavage rate between ketamine groups and remifentanil group, 87.77 ±18.72 % versus 94.58 ±14.81 %, respectively ($P = 0.124$), figure 1. The pregnancy rate in infertile women enrolled in the current study is shown in table 4. There was significant difference in rate of positive pregnancy test between ketamine group and remifentanil group, 20.0 % versus 46.7 %, respectively ($P = 0.028$); being higher in remifentanil group, table 4. The procedure time and recovery time of infertile women enrolled in the current study are shown in figure 2. There was no significant difference in mean procedure time between ketamine and remifentanil groups, 11.17 ±4.32 minutes versus 10.87 ±4.31 minutes, respectively ($P = 0.789$), figure 2. However, there was highly significant difference in mean recovery time between ketamine and remifentanil groups, 15.93 ±4.25 minutes versus 7.73 ±3.10 minutes, respectively ($P < 0.001$); being less in remifentanil group, figure 2.

In order to find the optimum recovery time cutoff value that can predict positive pregnancy outcome with acceptable accuracy, receiver operator characteristic curve analysis was carried out and the results are shown in figure 3, table 5 and table 6. Accordingly, the cutoff value was ≤ 10 minutes with a sensitivity of 80 %, a specificity of 65 %, a positive predictive value of 53.3 %, a negative predictive value of 86.7 % and an accuracy level of 70 %. The area under curve (AUC) was 0.749 and the level of significance was high ($P < 0.001$), indicating that the ROC curve is valid. The rate of true positive results, false positive results, true negative results and false negative results are shown in table 6.

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

Characteristic	Ketamine group *n* = 30	Remifentanil group *n* = 30	*P*
Age (years)			
Mean ±SD	30.30 ±6.24	30.30 ±5.65	1.000 † NS
Range	19 -40	19 -44	
< 35, *n* (%)	21 (70.0 %)	25 (83.3 %)	0.222 ¥ NS
≥ 35, *n* (%)	9 (30.0 %)	5 (16.7 %)	
BMI (kg/m2)			
Mean ±SD	28.76 ±4.56	28.76 ±5.42	0.996 † NS
Range	21.35 -41.5	16.87 -41.7	
Underweight, *n* (%)	0 (0.0 %)	1 (3.3 %)	---
Normal, *n* (%)	8 (26.7 %)	6 (20.0 %)	
Overweight, *n* (%)	12 (40.0 %)	12 (40.0 %)	
Obese Class I, *n* (%)	6 (20.0 %)	7 (23.3 %)	
Obese Class II, *n* (%)	3 (10.0 %)	3 (10.0 %)	
Obese Class III, *n* (%)	1 (3.3 %)	1 (3.3 %)	
Duration of infertility (years)			
Mean ±SD	6.87 ±3.73	6.85 ±3.31	0.985 † NS
Range	1.5 -17	1.5 -13	

< 5, *n* (%)	7 (23.3 %)	7 (23.3 %)	---
5-10, *n* (%)	18 (60.0 %)	18 (60.0 %)	
> 10, *n* (%)	5 (16.7 %)	5 (16.7 %)	
Type of infertility			
Primary, *n* (%)	18 (60.0 %)	17 (56.7 %)	0.793 ¥ NS
Secondary, *n* (%)	12 (40.0 %)	13 (43.3 %)	
Causes of infertility			
Male factor, *n* (%)	17 (56.7 %)	16 (53.3 %)	0.488 ¥ NS
Female factor, *n* (%)	6 (20.0 %)	4 (13.3 %)	
Combined, *n* (%)	1 (3.3 %)	0 (0.0 %)	
Unexplained, *n* (%)	6 (20.0 %)	10 (33.3 %)	
Number of previous IVF			
0, *n* (%)	22 (73.3 %)	27 (90.0 %)	0.095 ¥ NS
1, *n* (%)	4 (13.3 %)	3 (10.0 %)	
2, *n* (%)	4 (13.3 %)	0 (0.0 %)	

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

Table 2: Serum hormonal levels of infertile women participating in the current study

Hormone	Ketamine group *n* = 30	Remifentanil group *n* = 30	*P* †
D_2FSH (IU/ml)			
Mean ±SD	6.66 ±1.28	6.94 ±1.77	0.478 NS
Range	3.7 -9	3.8 -9.5	
D_2 LH (IU/ml)			
Mean ±SD	4.54 ±1.66	5.06 ±2.10	0.298 NS
Range	1.6 -8.96	2.1 -10	
D_2 E_2(pg./ml)			
Mean ±SD	31.93 ±8.15	33.50 ±8.44	0.466 NS
Range	11.9 -48.8	14.9 -50	
D_2PRL(ng/ml)			
Mean ±SD	14.70 ±5.08	13.66 ±7.11	0.517 NS
Range	1 -22.6	1 -28.6	
D_2TSH (m IU/ml)			
Mean ±SD	1.69 ±0.55	1.42 ±0.48	0.052 NS
Range	0.8 -3.3	0.3 -2.5	
E_2 at trigger(pg./ml)			
Mean ±SD	1121.00 ±547.40	1081.80 ±656.18	0.802 † NS
Range	209.6 -2109	128.92 -2292	

n: number of cases; SD: standard deviation; D_2:cycle day two; FSH: follicle stimulating hormone; LH: Luteinizing hormone; E_2: Estradiol; PRL: Prolactin; TSH: Thyroid stimulating hormone; †: Independent samples t-test; NS: Not significant at $P > 0.05$

Table 3: Ovarian Stimulation characteristics of women enrolled in the current study according to group

Characteristic	Statistical index	Ketamine group *n* = 30	Remifentanil group *n* = 30	*P*
Total gonadotropin ampoules	Mean ±SD	22.55 ±9.67	21.68 ±11.55	0.754 † NS
	Range	9 -51	14 -60	
rFSH ampoules	Mean ±SD	19.08 ±5.64	17.68 ±7.38	0.412 † NS
	Range	9 -32	0 -45	
hMG ampoules	Mean ±SD	3.47 ±5.45	4.00 ±11.73	0.157 † NS
	Range	0 -20	0 -60	

Type of trigger				
hCG	*n* (%)	18 (60.0 %)	25 (83.3 %)	0.090 ¥ NS
Triptorelin	*n* (%)	2 (6.7 %)	0 (0.0 %)	
hCG and Triptorelin	*n* (%)	10 (33.3 %)	5 (16.7 %)	

n: number of cases; SD: standard deviation; rFSH: recombinant follicular stimulating hormone; hMG: human menopausal gonadotropin; ; hCG: human chorionic gonadotropin; †: Independent samples t-test; ¥: Chi-square test; NS: Not significant at $P > 0.05$

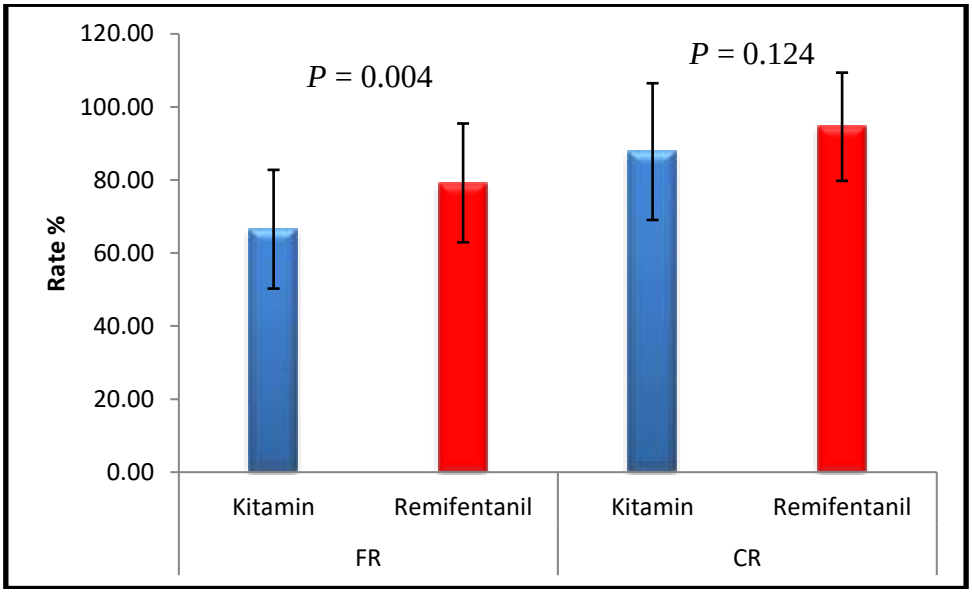

Figure 1: Bar chart showing comparison of fertilization rate (FR) and cleavage rate (CR) between ketamine and Remifentanil groups

Table 4: Pregnancy rate in infertile women enrolled in the current study

Pregnancy test	Total *n* = 60		Ketamine *n* = 30		Remifentanil *n* = 30		*P*
	n	%	*n*	%	*n*	%	
Positive	20	33.3	6	20.0	14	46.7	0.028 ¥ S
Negative	37	61.7	22	73.3	15	50.0	
Cryo-preserved	2	3.3	1	3.3	1	3.3	
No embryo	1	1.7	1	3.3	0	0.0	

n: number of cases; ¥: Chi-square test; S: significant at $P \leq 0.05$

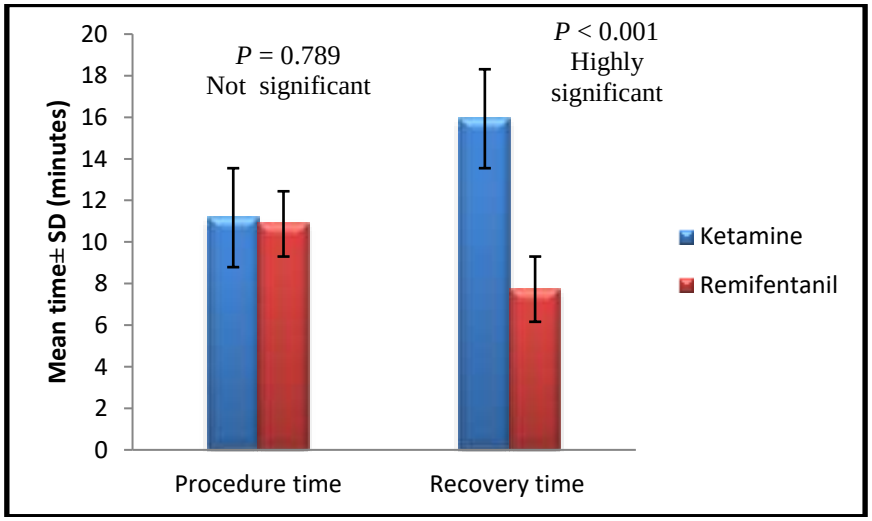

Figure 2: Bar chart showing the procedure time and recovery time of infertile women enrolled in the current study

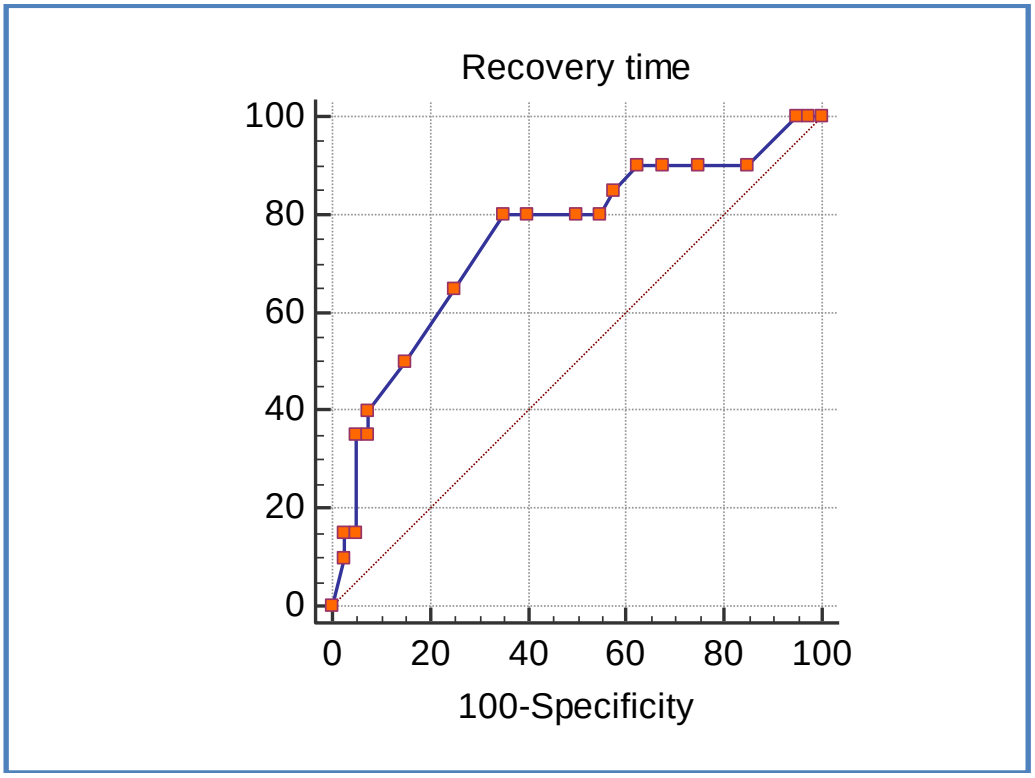

Figure 3: Receiver operator characteristic (ROC) curve to find the optimum recovery time cutoff value that can predict positive pregnancy outcome with acceptable accuracy

Table 5: Characteristics of the ROC curve

Characteristic	Result
Cutoff (minutes)	≤ 10
AUC	0.749
95 % CI	0.621 to 0.852
P	< 0.001 HS
Sensitivity %	80 %
Specificity %	65 %
PPV %	53.3 %
NPV %	86.7 %
Accuracy %	70.0 %

AUC: area under the curve; CI: confidence interval; HS: highly significant at $P \leq 0.01$

Table 6: Comparison of results of pregnancy test and the predictive power of recovery time cutoff value

Recovery time (minutes)	Positive pregnancy *n* = 20	Negative pregnancy *n* = 40
≤ 10 (*n* = 30)	16 (80.0 %) "TP"	14 (35.0 %) "FP"
> 10 (*n* = 30)	4 (20.0 %) "FN"	26 (65.0 %) "TN"

n: number of cases; TP: true positive; FP: false positive; FN: false negative; TN: true negative

DISCUSSION

In this study, in order to compare the outcome of intracytoplasmic sperm injection (ICSI) cycle, namely positive pregnancy test, fertilization rate and cleavage rate, 60 infertile women were chosen and classified into two groups, 30 receiving ketamine and 30 receiving remifentanil during general anesthesia for oocyte retrieval.

In this study, there was highly significant difference in mean fertilization rate between ketamine and remifentanil treated groups; being higher in remifentanil treated group. However, there was no significant difference in mean cleavage rate between ketamine and remifentanil treated groups.

Regarding opioids, some authors compared the effects of GA (remifentanil with either propofol or isoflurane) and sedation (midazolam, diazepam or propofol) used for oocyte retrieval. They found no significant differences in

cleavage rate between these two groups (Hammadeh *et al*., 1999).

In a randomized clinical trial held by Matsota *et al*., in 2012, remifentanil was contrasted to propofol-alfentanil for transvaginal oocyte retrieval, but not ketamine, and no significant difference was found with respect to fertilization and cleavage rate (Matsota *et al*., in 2012). It has been also stated that remifentanil has no significant adverse effect on fertilization rate when compared to propofol/alfentanil/ nitrous oxide, fentanyl, and local anesthesia (Wilhelm *et al*., 2002; Barut *et al*., 2008; Bumen *et al*., 2011; Jarahzadeh *et al*., 2011; Oliveira *et al*., 2016).

On the other hand, a number of authors have demonstrated significantly lower fertilization rate in women receiving ketamine in comparison with women receiving other agents, thiopental and propofol (Nossair and Maaty, 2017; Tola, 2019); however, a study done in Turkey has shown no significant difference in fertilization rate between ketamine anesthetized group and other groups anesthetized by propofol and ketamine (Urfalıoğlu and Yaylalı , 2016).

So far, no previous study compared remifentanil to ketamine in oocyte retrieval and the difference in fertilization and cleavage rates and hence this study is the first one to do so with results favoring the use of remifentanil to ketamine as fertilization rate was significantly higher in women receiving remifentanil than women receiving ketamine. The duration of action of ketamine is longer than that of remifentanil, 10-15 minutes versus 8-10 minutes, respectively, (Valhos, 2009; Bumen *et al*., 2011). thus, the longer duration of action of ketamine may explain the less fertilization rate because of longer oocyte exposure to ketamine in comparison with remifentanil.

In the current study, there was significant difference in rate of pregnancy between ketamine group and remifentanil group, 20.0 % versus 46.7 %; being higher in remifentanil group. Indeed, the ideal anesthetic technique for IVF should provide good surgical anesthesia with minimal side effects, a short recovery time, high rate of successful pregnancy, and shortest required duration of exposure (Sharma *et al*., 2015).

It has been shown that remifentanil resulted in a higher pregnancy rate when compared to other anesthetic agents like fentanyl/propfol/nitrous oxide and fentanil (Wilhelm *et al*., 2002; Jarahzadeh *et al*., 2011).

Added to that, several authors have described no negative drawback of remifentanil in comparison to midazolam/propofol, local anesthesia, propofol/alfentanyl, propofol/ fentanyl, and pethidin/ midazolam, regarding positive pregnancy outcome (Hammadeh *et al*., 1999; Barut *et al*., 2008; Bumen *et al*., 2011; Matsota *et al*., 2012; Lier *et al*., 2015; Oliveira *et al*., 2016) and ketamine was not used in all these studies.

Regarding ketamine several authors have found insignificant negative impact for ketamine with respect to pregnancy outcome when compared to fentanyl/ propfol/ isoflurne, propofol in infertile women undergoing oocyte retrieval (Ben-Shlomo 1999; Urfalıoğlu and Yaylalı, 2016; Tola, 2019); however, Nossair and Maaty in 2017 have found significantly less pregnancy rate in association with the use of ketamine in comparison to thiopental and propofol and they did not included remifentanil in their study.

So far, no previous study compared remifentanil to ketamine in oocyte retrieval and the difference in pregnancy rate and hence this study is the first one to do so with results favoring the use of remifentanil to ketamine as pregnancy rate was significantly higher in women receiving remifentanil than women receiving ketamine. Remifentanil has short duration of action with rapid elimination from systemic circulation without drug accumulation (Bümen *et al*., 2011; Lier *et al*., 2014). This may lead to less exposure to anesthesia with less determinate effect on oocyte and subsequent to embryo or even endometrium which may explain more pregnancy rate in remifentanil in comparison with ketamine.

In the current study, there was no significant difference in mean procedure time between ketamine and remifentanil treated groups; however, there was highly significant difference in mean recovery time between ketamine and remifentanil groups; being less in remifentanil group. It has been found that using ketamine or propofol in general anesthesia for oocyte retrieval would not produce significant variation in procedure time (Urfalıoğlu and Yaylalı, 2016; Tola, 2019). On the other hand, it has been found that the use of remifentanil in comparison to other anesthetic agent like local anesthesia, propofol/alfentanil, and pethidine/midazolam, produced no significant variation in procedure time (Bumen *et al*., 2011; Matsota *et al*., 2012; Lier *et al*., 2015). Whereas, other authors, found that remifentanil resulted in a shorter procedure time when compared to propofol/alfentanil/nitrous oxide (Wilhelm *et al*., 2002). All these studies did not include comparison between ketamine and remifentanil in respect procedure time.

Regarding recovery time Casaki *et al*., in 1999, Jarahzadeh *et al*., in 2011 and Oliveira *et al*., in 2016 have observed significantly shorter recovery time by infertile women receiving remifentanil in comparison to infertile women receiving fentanyl/propofol or fentanil. Whereas, Urfalıoğlu and Yaylalı in 2016 and Nossair and Maaty in 2017 have found longer recovery time attributed to ketamine when compared to propofol and thiopental, while Tola, 2019 has reported no significant difference in recovery time when comparing ketamine to propofol. The fast elimination of remifentanil from systemic circulation and high clearance without drug accumulation permits rapid recovery from anesthesia with fast consciousness return (Lier *et al*., 2014; Santonocito *et al*., 2018). The rapid elimination and clearance of remifentanil is due to its rapid and predictable metabolism by tissue and plasma non-specific esterase, mainly to carboxylic acid (non-active byproduct) (Beleña *et al*., 2016; Ziesenitz *et al*., 2018). However, 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 primarily hydroxylised via glucurono conjugation and excreted in urine and bile (Mion and Villevieille, 2013).

In the current study we were able to address a cutoff value for recovery time of less than or equal 10 minutes to be an acceptable predictor for pregnancy outcome. Unfortunately, no previous report is available about the best predictive minimal recovery time; therefore, this paper may be the first one to raise this issue.

However, thorough search in the available published articles failed to reveal a study comparing procedure time and recovery time between ketamine and remifentanil. Therefore, the current study can be regarded as the first study to evaluate the difference in procedure time and recovery time between remifentanil and ketamine and the first study to address shorter recovery time in association with remifentanil in comparison with ketamine.

CONCLUSION

The application of remifentanil is superior to ketamine in general anesthesia for ova pickup procedures because of its significant correlation with certain IVF parameters and shorter recovery time.

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