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Evaluation of the Effect of Submucosal Vaginal Administration of Ketamine on Postoperative Pain in IVF Candidates

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Abstract

Introduction: *acute post-operative pain is still a medical issue and unwelcome adverse effects in any procedure even in oocyte retrieval for IVF, that consider a less invasive procedure.* ***Aim:*** *This study aims to evaluate the analgesic effect of ketamine when injected at the sub-mucosa of the genital tract for women scheduled for oocyte retrieval for IVF.* ***Method and Materials:*** *46 women participated in this randomize control study. Aged between 18-45 years old, scheduled for oocyte retrieval for IVF. Participants were divided into 2 groups (A&B), with 23 participants in each one. The interventional group(A) received 0.5mg of ketamine submucosal in the vagina and the control group(B) received 0.5mg of normal saline in the submucosa of the Vagina, both before ovarian puncturing. The pain intensity was evaluated after recovery, after 2 hours, and after 6 hours of the procedure.* ***Results:*** *The mean age in the case group and the placebo group was (38.00±5.117) and (34.48± 7.780) years, respectively (P>0.05). Significant differences were noticed in the VAS score of pain postoperatively, in addition to, a decrease in supplement analgesic dose requirements (P<0.05).* ***Conclusion:*** *women who received ketamine at the sub-mucosa of the vagina had lower pain intensity in comparison to the other women, and also, expressed a high level of satisfaction regarding their pain level.*

Keywords: *Ketamine, Oocyte Retrieval, Visual Analog Score, Conscious Anesthesia, Post-Operative Pain*

INTRODUCTION

Postoperative pain is still a major medical issue, over 20% of patients reported significant pain (1, 2). An essential component of in vitro fertilization (IVF) treatment is the transvaginal retrieval of eggs from the ovary. Although a less invasive method, is nonetheless stressful and requires analgesics and conscious sedation (3). The aspirating needle causes pain during oocyte retrieval (OR) when it punctures the vaginal skin and ovarian capsule (4). Postsurgical pain is an unwelcome sensation and Patients experience functional limits, and the surgical team feels humiliated as a result (5). Various methods are available in order to relieve pain after surgical intervention. Such as "multimodal", NSAIDs. However, there is a persistent risk of gastrointestinal issues. The majority of studies show

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a reduction in postoperative opioid needs and pain that is most noticeable in the first 24 hours when using ketamine (5, 6). Ketamine significantly relieves pain. The most significant phenomenon in the transmission of pain is spinal cord sensitization of N-methyl-dimethyl-aspartate receptors (NMDA), and Ketamine, is a non-competitive NMDA antagonist, prevents nociceptors from becoming centrally sensitized by blocking peripheral afferent noxious stimulation (7, 8). The clinical uses for ketamine now are very diverse since it has withstood the harsh storms of time (9). Ketamine is a "unique drug" because Ketamine's unique properties (potent analgesia with minimal respiratory depression) make it a very valuable alternative in certain situations. More recently it has become popular as an adjunct administered at sub-analgesic doses to limit or reverse opioid tolerance and in the therapy of serious depression. Also, Ketamine can be given in several routes, (8, 10, and 11). The Submucosal injection of ketamine is a new attractive method of utilizing ketamine that is being used in a wide variety of clinical doses for procedures, such as Rhinoplasty and dental work (9, 12). A study was done by Majidinejad. S. et.al, entitled, "The Effects of Different Doses of Submucosal vs. Intravenous Ketamine for Conscious-sedation in Children Candidates for Diagnostic-Therapeutic Procedures in Emergency Department" to examine the effects of ketamine submucosal injections at various doses with intravenous injections on children. It's been shown that submucosal ketamine is suitable alternative to IV ketamine and the duration of the impact was the longest with submucosal ketamine. Other desirable effects such as Surgeon satisfaction scores were determined to be very good (13). Numerous statistical techniques are used for pain analysis (14). The Visual Analogue Scale (VAS) is a common method for estimating pain. The pain VAS is a continuous scale made up of two verbal descriptors, one for each symptom extreme, that are anchored by a line that is either horizontal (HVAS) or vertical (VVAS), typically 10 centimeters (100 mm) in length. In terms of pain intensity, the scale is typically anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 10 [100-mm scale]) (14, 15).

The aim of this study is to evaluate the analgesic power of ketamine when administered at the sub-mucosa of the vagina for Oocyte retrieval for IVF candidates.

METHOD AND MATERIALS

This study was conducted at Imam Khomeini Hospital in Tehran, Iran, in the Vali-Asr operation theaters of assistant reproductive technique from April 2023 until May 2023. All samples were women candidates undergoing oocyte retrieval for IVF aged 18-45 years old with infertility history. In this randomize clinical trial, 46 women candidates for oocyte retrieval for IVF were enrolled. All women were classified with ASA (I, II), and they were monitored with the standard of care. Patients in both groups received pre-medication with 0,02mg/kg Midazolam and 1mcg/kg Fentanyl. General anesthesia with the oxygen mask was instituted with propofol in a bolus dose of 1mg/kg and 90mcg/kg/min infusion dose as maintenance for anesthesia till the end of the procedure. Ventilation was spontaneous with an oxygen supplement via a simple face mask. The group randomization is done by computer-generated numbers. The information about pain scores is obtained from the patient after recovery. Patients in the intervention group received 0.5mg of ketamine in the upper third of the vaginal mucosa by the gynecology surgeon. On the other hand, the control group received the same volume of physiological normal saline with the same method. Systemic blood pressure (SBP) and heart rate (HR) were recorded before induction of general anesthesia and after arrival in the post-anesthesia care unit (PACU). Postoperatively, in the PACU, the pain score was assessed by a visual analog scale for pain (VAS) [straight line with one end meaning no pain and the other end meaning the worst pain imaginable. A patient marks a point on the line that matches the amount of pain she feels]. After recovering from anesthesia, at PACU, the patient was asked if she can give the level for pain she is feeling from 0-10. Pain score assessed after recovery, two hours, and six hours after the

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procedure. Any type of hallucination or nausea and vomiting was recorded during the first hour after the procedure. In this study, we tried to collect representative data from a representative sample size. Hence, our inclusion, and exclusion criteria will be not considered as difficult to reduce the probability of selection bias and increase the sample size of patients (power of the study). The participants of this study were women who had conscious sedation and analgesia for IVF candidates. Patients with emergency operations, Lack of medical documents, seizure history, and age (over 45 years and less than 18 years) were excluded. All participants undergoing controlled ovarian hyper stimulation have been monitored by TVUS [transvaginal ultrasound] and measurement of the hormone estradiol level in their blood. Ovulation is triggered by giving an injection of recombinant hCG then oocytes are retrieved between the 35th and the 40th hour after triggering.

RESULTS

The demographic variables of age, height, weight, and BMI are described in Table (4.1). Its shows that there are no differences between the interventional group (A) and placebo group (B) regarding demographic characteristics including gender, mean age (38.00±5.117) years in the case group, (34.48± 7.780) years for placebo. (P-value =0.078), mean height (160.04±4.237), (157.52±5.265). (P-value =0.080), and weight (P-value =0.094), and also mean body mass index (BMI), (P-value = 0.205).

The P-value in all the above parameters was >0.05. The main goal of this study results, the mean pain intensity of using ketamine submucosally was (0.78±1.47) at PACU, (0.52±1.238) after 2 hours, and (0.22±0.671) after 6 hours of the intervention in group A.

according to the results of this study, it shows that the VAS score was significantly lower in the interventional (A) group in three times period intervals including post-anesthesia care unit (PACU), 2hours after intervention, and six hours after intervention. (p- value<0.05). Table (2), figure (1). The evaluation of side effects and patient satisfaction. The first group received fewer analgesic drugs with a percentage of 0% in comparison to the second group, however, the level of satisfaction was higher with group(A) in comparison to (B) group who received diclofenac as supplement analgesics with a percentage of 100%. Moreover, the percentage of the main side effects of ketamine usage in terms of (hallucination/PONV) was (1 (4.3%)), (0 (0.0%)) in both groups sequentially. although the frequency percentage is lower in the placebo (B) group, the p-value was insignificant (p-value >0.05). The same thing applies to other side effects in terms of dizziness, even though, the percentage was higher in the interventional group equal to 1 patient out of 23 in group A and 0 patients out of 23 in group B, the p-value was insignificant (Table 3, figure 1, 2). Systolic and diastolic blood pressure were recorded in 2-time intervals after induction of anesthesia and after intervention with a mean of (127.30 ±13.485) in group A. and a mean of (106.52 ±12.217) in group B for systolic blood pressure after induction of anesthesia. The mean of systolic blood pressure after the intervention was (117.74±10.763) in group A. and the mean of (118.87±10.550) in group B. The mean of diastolic blood pressure after induction of anesthesia was (81.91±7.621) in group A. and (66.09 ±8.979) in group B. while the mean of diastolic blood pressure was described as (73.22 ±9.395) in group A. and (70.74 ±7.694) in group B. Although, initial systolic and diastolic blood pressure shows to be lower in group A, however, no significant changes occur after intervention in the two groups. (P-value = 0.721) for systole. (P-value = 0.333) for diastole in two of the groups. The mean heart rate after the intervention was (74.30±8.22) in group A, and (84.09±9.25) in group B. It is shown significant between the two groups after intervention (P-value<0.05). Even though it was lower in group A before the intervention. No significant changes occur in respiratory rate and oxygen saturation before and after the intervention. The mean respiratory rate before intervention (9.74 ±2.094) in the interventional group, and the placebo group (9.83 ±1.992), and after the intervention the mean was

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(12.17 ±0.778) in group A, and in group, B was (12.35±0.832). After the intervention the mean O2 saturation was (99.8261±0.49103) in group A, and (99.9130 ±0.41703) in group B. (P-value >0.05) (Table 4).

Table 1: Demographic Changes

variable	Group	Mean	Std. Deviation	T-Test	df	P-Value
age	A	38.00	5.117	1.814	44	0.078
	B	34.48	7.780			
height	A	160.04	4.237	1.790	44	0.080
	B	157.52	5.265			
weight	A	65.96	8.931	1.712	44	0.094
	B	60.83	11.264			
BMI	A	25.6865	2.73231	1.287	44	0.205
	B	24.4201	3.84770			

Std deviation= stander deviation, BMI= body mass index.

Table 2: VAS Score of Pain

variable	Group	Mean	Std. Deviation	T-Test	df	P-Value
VAS.PACU	A	0.78	1.476	8.576	44	0.001
	B	5.65	2.288			
VAS.2H	A	0.52	1.238	9.864	44	0.001
	B	4.70	1.608			
VAS.6H	A	0.22	0.671	6.463	44	0.001
	B	2.43	1.502			

VAS= visual analog score of pain. PACU= post-anesthesia care unit.

Table 3: Other Outcomes

variable		Group A	Group B	T-Test	df	P-Value
Hallucination		1 (4.3%)	0 (0.0%)	1.022	1	0.999
PONV		1 (4.3%)	0 (0.0%)	1.022	1	0.999
Dizziness		1 (4.3%)	0 (0.0%)	1.022	1	0.999
Diclofenac use		0 (0.0%)	23 (100%)	46	1	0.001
Level of satisfaction	Completely satisfied	19(82.6%)	5 (21.7%)	19.652	4	0.001
	Partially satisfied	2 (8.7%)	3 (13.0%)			
	No opinion	2 (8.7%)	5 (21.7%)			
	Partially dissatisfied	0 (0.0%)	4 (17.4%)			
	Completely dissatisfied	0 (0.0%)	6 (26.1%)			

PONV = postoperative nausea and vomiting.

Table 4: Hemodynamics Changes

variable	Group	Mean	Std. Deviation	T-Test	df	P-Value
SBPi	A	127.30	13.485	5.477	44	0.001
	B	106.52	12.217			
SBPa	A	117.74	10.763	0.360	44	0.721
	B	118.87	10.550			
DBPi	A	81.91	7.621	6.444	44	0.001
	B	66.09	8.979			
DBPa	A	73.22	9.395	0.979	44	0.333
	B	70.74	7.694			
Hri	A	79.65	9.726	0.976	44	0.334
	B	77.00	8.671			
Hra	A	74.30	8.22	3.790	44	0.001

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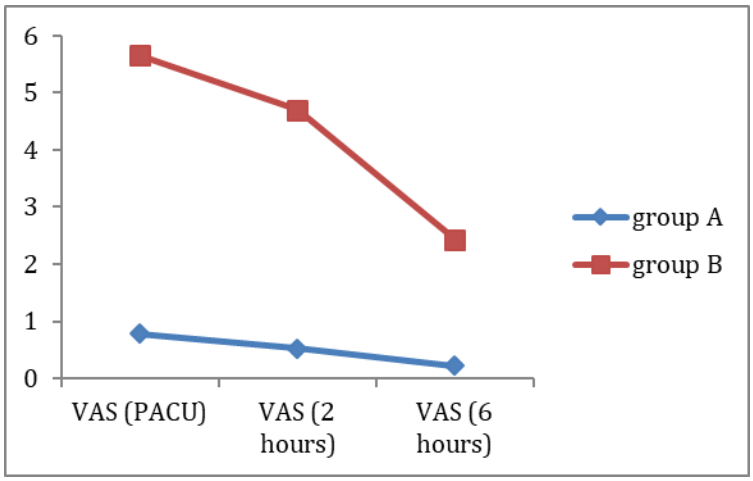
	B	84.09	9.25			
Rri	A	9.74	2.094	0.144	44	0.886
	B	9.83	1.992			
Rra	A	12.17	.778	0.733	44	468
	B	12.35	.832			
O2i	A	93.00	4.056	3.200	44	0.002
	B	96.61	3.394			
O2a	A	99.8261	.49103	0.647	44	0.521
	B	99.9130	.41703			

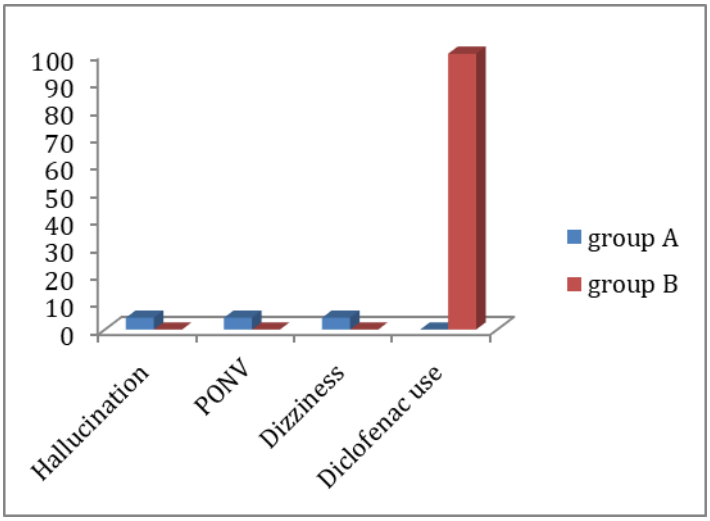
SBPi = systolic blood pressure after induction, SBPa = systolic blood pressure after the intervention, DBPi = diastolic blood pressure after induction, DBPa = diastolic blood pressure after the intervention, Hri = heart rate after induction, Hra= heart rate after the intervention, Rri= respiratory rate after induction, Rra= respiratory rate after the intervention, O2i= oxygen, O2a= oxygen saturation after intervention.

Figure 1: Changes in VAS score of pain.



VAS = visual analog score.

Figure 2: Other outcomes



PONV = postoperative nausea and vomiting.

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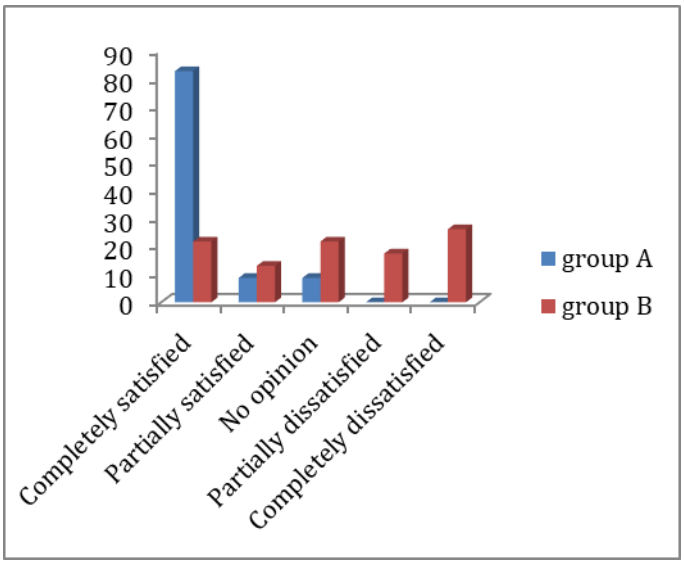
Figure 3: Patient's level of satisfaction



DISCUSSION

This study was conducted to determine the sub-mucosal analgesic effect of ketamine in women candidates for oocyte retrieval for IVF. 46 patients were included in this randomized control trial, classified into two groups. Group (A), the interventional group, and group (B), the placebo group. Ketamine was administered submucosally in 23 patients, while the rest 23 patients received normal saline.

According to Table (1), no significant variation was found in the baseline characters of the participants in age, weight, height, and body mass index. Although there is a variation in mean/stander deviation that is considered to be high in the term age and weight, but the P-value is higher than 0.05. We might have significance if we increase the number of samplings. Regarding other demographic findings in terms of height (P-value = 0.080), and BMI (0.205), shows no significant differences between the two groups. (p-value > 0.05). In our study, we assume to have significance in some demographic findings if we increase the number of samples gathered.

Statically-significant differences were noticed in terms of the visual analog score of pain (VAS). Table (2) and Figure (1), represented a highly significant lower VAS score of pain at 3 points of time (PACU, 2 hours, and 6 hours after intervention) in the interventional group in comparison to the control group. (P-value = 0.001). Represents that ketamine reduces the pain intensity too much extent after vaginally sub-mucosal administration in women scheduled for oocyte retrieval for IVF procedures.

In our study we inject the NMDA receptor antagonist in a different method than what is known about routine administration of ketamine, we inject it peripherally rather than intravenously, however, our study results show that we can have the analgesic effect of ketamine even when we change the way of administration, and we have the analgesic effect too. Since peripheral nociceptors have NMDA receptors, local and topical application of ketamine seems like a reasonable strategy that could enable the attainment of greater local tissue concentrations to prevent adverse CNS effects (8). The ability of ketamine to block NMDA receptor-mediated pain facilitation and modulates receptors via allosteric means, reducing the activity of brain regions that react to painful stimuli may account for its analgesic effectiveness, which correlates well with these effects (16, 17).

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Gursoytrak.et.al, (2021). Reported that ketamine is recommended use as it is lower the pain score throughout the first 12 hours after the submucosal administration (18). But, in contrast to our study, the author used 0.3 mg/kg plus local anesthetics for the first group and 0.3 mcg/kg dexmedetomidine plus local anesthetics for the second group. While in our study we compare the effect of 0.5mg ketamine to the placebo group. Therefore, there might no need to use any additives with ketamine when we want to use it locally for pain relief after surgery, as this is proved by the results of our study. the other outcomes described by Hallucination, PONV, and dizziness with a frequency percentage of (4.3%), one patient for each term of side effect in group A, and a frequency percentage of (0.0%) in group B. in Table (3), even though the frequency percentage was lower in the group (B), yet no significant differences can be shown in both groups, as it can be seen in figure (2). Indicates that ketamine's side effect is approximately non-exist when administer with this route of injection. (P-value =0.999). Our study indicates that we can reduce the adverse effect after vaginally sub-mucosal administration of the NMDA receptors antagonist.

Postoperative nausea and vomiting induce because many of reasons, including pain, dehydration, female gender, smokers, and the injection of ketamine. Ketamine can make you feel nauseous, probably by preventing serotonin from being absorbed in synaptic terminals (19). Since our patients were not in pain because our study results express significantly low pain intensity, non-smokers, irrigate sufficiently during the procedures, in addition, we inject ketamine at the sub-mucosa of the genital tract for the case group, and the control group did not receive ketamine. All that together could be the reason behind we do not notice significant nausea and vomiting postoperatively as our study results show.

Safavi, et.al. (2011), According to their study when they infiltrate ketamine at the surgical incision, there were no significant variations between groups in terms of hallucinations, PONV, or dizziness (7). But in contrast to our study, ketamine was administered subcutaneously.

However, the study of W. Song, et.al. (2013). Reported that ketamine made nausea worse and made feeling drowsy more frequent (19). But this study did not use ketamine submucosally, nor anywhere locally, on the contrary, they used it intravenously.

Our study results showed that injection of ketamine at submucosa not just decreased the postoperative pain but successfully reduce the need for opioid consumption for six hours. supplement use of analgesic and level of satisfaction of the patients in Figure (2&3), shows all patients in group (B) received diclofenac as a supplement analgesic dose with a frequent percentage of 100%, however, the level of satisfaction regarding analgesia was significantly higher in the interventional group who received ketamine, with the percentage of (82.6%) complete satisfaction. (P-value =0.001). Table (3) showed that clearly.

Since there are NMDA nociceptors peripherally (8). We assumed that ketamine inhibits those receptors when injected locally (at sub-mucosa). Furthermore, this might be related to that Ketamine's analgesic effects extend beyond NMDA receptors. There is evidence that it communicates with opioid receptors. Some of the opioid's analgesic effects on the central nervous system may be due to an opioid receptor present in the brain and spinal cord (17, 20).

ŞANLI, et.al. (2016), discovered that the group that took ketamine submucosally scored much higher on patient satisfaction than any of the other groups after the procedure (12). Moreover, pain killers use was not required until 30 minutes after surgery, and even then, it was less than what was seen in the control group.

But, contrary to our study, they added 1mg/kg lidocaine to 0.5mg/kg of ketamine, whereas, our study used 0.5mg ketamine solely independent of the weight, all participants received the same dose of

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ketamine, and we monitored the pain score not just at the first hour after recovery, but to six hours after the procedure.

Systolic and diastolic blood pressure were recorded in 2-time intervals after induction of anesthesia and after the intervention. the present study shows that, Although, initial systolic and diastolic blood pressure shows to be lower in group A, however, no significant changes occur after intervention in the two groups. (P-value = 0.721) for systole. (P-value = 0.333) for diastole in two of the groups. Table (4). Indicates ketamine has a lower negative effect on hemodynamic changes when administered submucosally. Even though, that there are differences revealed before intervention, these might be related to the other anesthetic drugs that we used in our study to induce anesthesia such as fentanyl and propofol.

Propofol's most noticeable side effect is a drop in arterial blood pressure during anesthesia induction. An induction dose of 2 to 2.5 mg/kg results in a drop in systolic blood pressure of 25% to 40% regardless of the existence of cardiovascular disease. Midazolam results in a greater drop in arterial blood pressure (8, 21).

Safavi, et.al. (2011), found that Systolic and diastolic blood pressure did not substantially differ across the groups at any point during surgery or in the postoperative time when infiltrating ketamine to reduce pain after surgery (7).

However, in our study, they used 1-2mg/kg of ketamine subcutaneously.

Heart rate is shown to be a bit higher in the placebo group and lower in the interventional group after the intervention, significance can be seen between the two groups. (P-value <0.05). Although, no significance is seen before the intervention. (P-value= 0.333). As we mentioned before in this study, ketamine character by an increase in heart rate when injected intravenously, but our study results proved that cardiac activation is not achieved with submucosal injection and so no significant increase in heart rate after recovery, Particularly, might be because we administered the drug in little doses also, because our participants were not feeling pain as our study results showed, therefore, heart rate does not elevate by the pain stimulation. Table (4).

Furthermore, no significant changes occur in terms of the respiratory rate before and after intervention. (P-value >0.05). This study results demonstrated that no changes can occur in ketamine's pharmacology on breathing function when administer in another route otherwise than intravenously. This means ketamine administration with this route of injection (sub-mucosa), has no negative impact on respiratory parameters. Table (4).

Moreover, Oxygen saturation shows no differences in both groups after intervention (P-value =0.521). Table (4). Even though, it is shown to be lower in group A. but these changes especially after induction of anesthesia are normal and it comes from the respiratory derive inhibition of the other intravenous anesthetic drugs such as propofol, fentanyl, and midazolam that we used to induce a state of anesthesia during the procedure as we mentioned previously in this study. But all studies showed that ketamine has no character to produce an inhibition in breathing derive even with intravenous injection, besides we use supplemental oxygen delivered to the women throughout the surgery and during the recovery. As evidenced by an unaffected reaction to carbon dioxide, ketamine has little impact on the central respiratory derive, But, a brief (1 to 3 minute) decrease in minute breathing may take place after the bolus injection of an induction intravenous dosage of ketamine (2 mg/kg) (21). Moreover, the drug that we used to perform anesthesia, propofol characterizes by a short-term apnea after a bolus dose, a transient apnea may occur after an intravenous injection of midazolam, particularly when opioid premedication, also diminishes the ventilatory reaction to carbon dioxide (8). The combination of these medications could be the cause of facing a transient

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reduction in oxygen saturation especially since we did not use invasive devices for airway instrumentation and the ventilation was spontaneous in this study.

Majidinejad. et.al, (2020), in their study, indicated significant changes occur in terms of respiratory rate in all groups after the injection of ketamine, (13). In contrast to our study which shows no significant variation after the intervention, also, in contrast to our study, in their study they compare submucosal ketamine with intravenous ketamine in children's participants. While in our study we compare submucosal ketamine with placebo in adult women candidates. On the other hand, according to Safavi et al.'s study (2011), O2 saturation, HR, systolic, diastolic, and mean arterial pressure were not substantially different among the groups at any point during surgery and in the postoperative period (7). Whereas, our study demonstrates differences before intervention and no significant variation after intervention. Our study is the first study that compares vaginally sub-mucosal administration of ketamine with a placebo in oocyte retrieval procedures. And the results demonstrated that injection of ketamine at the sub-mucosa of the genital tract for women undergoing oocyte retrieval procedures for IVF under conscious sedation anesthesia is providing powerful analgesia postoperatively and successfully decreases the opioid and other analgesics consumption to much extent. In addition to a decrease in post-ketamine injection sides effects such as hallucination, PONV, and others, and finally, hemodynamic changes were shown to be stable after the intervention. These results were followed by a high level of satisfaction in patients who received ketamine in comparison to those who did not receive it. In conclusion, we highly recommend the use of ketamine in this route of administration, due to its effects in relieving pain after the surgery, in addition to the ability to reduce the impact of side effects. Furthermore, we recommend increasing the number of sample selections to reveal more about the changes and to have higher power for the study, also extend the time of monitoring pain score to 48 hours and the effect on IVF outcomes.

Ethical approval

The study's ethical permission was granted by the ethical committee at Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1401.244).

Conflicting interests

The authors say they have no competing interests.

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