Original Article

A comparison of ondansetron in preventing postoperative nausea and vomiting for patients with or without preoperative anxiety with painless egg retrieval: a prospective, randomized, controlled trial

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Background: Patients undergoing painless egg retrieval are prone to preoperative anxiety, and whether preoperative anxiety induces postoperative nausea and vomiting (PONV) is debated. The primary objective of this prospective, randomized, controlled study was to compare the clinical effect of ondansetron in preventing PONV for patients with and without preoperative anxiety. The secondary objective was to investigate whether preoperative anxiety was associated with PONV.

Methods: The self-rating anxiety scale (SAS) was used to assess the anxiety patients undergoing painless egg retrieval. Patients with a SAS standard score of 50–60 were selected to the anxiety group (n=105); and patients with a SAS standard score of 25–35 were assigned to the non-anxiety group (n=104). Venous blood samples of both groups of patients were obtained during admission and 1 hour after surgery, and all serotonin (5-HT) levels were tested using an enzyme-linked immunosorbent assay. The anxiety group was then randomly assigned into two subgroups: ondansetron (AO group, n=53) and placebo saline (AS group, n=52). Similarly, patients in the non-anxiety group were also randomly assigned to one of two subgroups: ondansetron (NO group, n=51) and placebo saline (NS group, n=53). The AO and NO groups received 8 mg (4 mL) of intravenous ondansetron 15 minutes before surgery, while the AS and NS groups received an equivalent volume (4 mL) of normal saline. We then analyzed the vital signs, risk factors for nausea and vomiting, intraoperative anesthetic doses, incidences of nausea and vomiting in 24 hours after surgery, serum 5-HT level before and after surgery, other adverse responses, pain scores, and satisfaction.

Results: A total of 200 patients eventually completed this study. The serum 5-HT values in the anxiety group were higher before and after surgery than in the non-anxiety group ($P<0.05$), but there was no significant difference in serum 5-HT before and after surgery in the same group ($P>0.05$). The incidence of PONV was more significant in the AS group than in the NS group ($P<0.05$). The incidence of PONV was also higher in the AS group than in the AO group ($P<0.05$). Still, there was no statistically significant difference between the NO and NS groups ($P>0.05$). There were no significant differences between the

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four groups in vital signs, risk factors for nausea and vomiting, intraoperative anesthetic doses, other adverse responses and pain scores (P>0.05). Patients in the AS group had lower satisfaction scores than those in the other three groups (P<0.05).

Conclusions: Patients experiencing preoperative anxiety have a greater risk of PONV following painless egg retrieval compared to those without preoperative anxiety. Ondansetron can reduce the occurrence of PONV in patients with preoperative anxiety, but it has no discernible preventative effect in non-anxious patients.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400079504.

Keywords: Ondansetron; painless egg retrieval; preoperative anxiety; serotonin (5-HT); postoperative nausea and vomiting (PONV)

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Introduction

Preoperative anxiety is a prevalent psychological issue in patients undergoing painless egg retrieval (1). Currently, the global incidence of infertility is progressively rising (2). In vitro fertilization (IVF)-embryo transfer is widely utilized worldwide, and one of the most essential procedures is ultrasound-guided transvaginal puncture egg retrieval (3). Infertile women are afraid of the pain caused by the puncture operation. Moreover, they are concerned about the unknown outcome of the procedure before egg retrieval, which can cause a variety of physiological, and social problems, such as sensitivity, anxiety, lack of self-worth, and social identity (4-6). Excessive, persistent anxiety can lead to a variety of perioperative problems (7,8) and can even endanger the patient's life (9).

Postoperative nausea and vomiting (PONV) is the most common postoperative complication (10). Female gender, a history of motion sickness, non-smoking status, previous experiences of PONV, and age under 50 years represent significant risk factors for PONV, with female gender emerging as the most influential predictor (11). It is evident that PONV significantly impairs patient recovery, particularly among young women.

It revealed that serotonin (5-HT) controls and regulates many physiological and psychological processes, including mood, learning, memory, circadian rhythm, locomotion, socialization, aggression, etc. (12-14). Furthermore, research has demonstrated a close relationship between 5-HT receptors and nausea and vomiting (15,16). Ondansetron is a highly potent 5-HT_3 receptor antagonist with central and peripheral anti-emetic effects (17). As a result, we discovered that preoperative anxiety and PONV are both related to 5-HT receptors, and whether there is an association between the two is not commonly reported in the literature.

Patients undergoing IVF-embryo transfer are almost exclusively young women, with higher rates of preoperative anxiety and PONV. Some studies have suggested that preoperative anxiety predicts PONV (18,19), but some

Highlight box

Key findings

- Patients with preoperative anxiousness have a higher incidence of postoperative nausea and vomiting (PONV) after painless egg retrieval than non-anxious patients. Ondansetron can minimize the occurrence of PONV in patients with preoperative anxiety, but it has no discernible preventative effect in non-anxious patients.

What is known and what is new?

- Patients undergoing painless egg retrieval are prone to preoperative anxiety. Preoperative anxiety has a high link with serotonin (5-HT) and associated receptors, and whether preoperative anxiety induces PONV is debated. Ondansetron is a highly potent 5-HT receptor antagonist with central and peripheral anti-emetic effects.
- This trial investigated the clinical effects of preoperative use of ondansetron for the prevention of PONV in anxious and non-anxious patients undergoing painless egg retrieval and explored the potential relationship between preoperative anxiety and PONV by detecting pre- and post-surgical levels of 5-HT in anxious and non-anxious patients.

What is the implication, and what should change now?

- This study may ultimately save medical costs, prevent unwanted pharmacological side effects that raise the risk during treatment, and reduce the incidence of PONV by lowering the patient's anxiety.

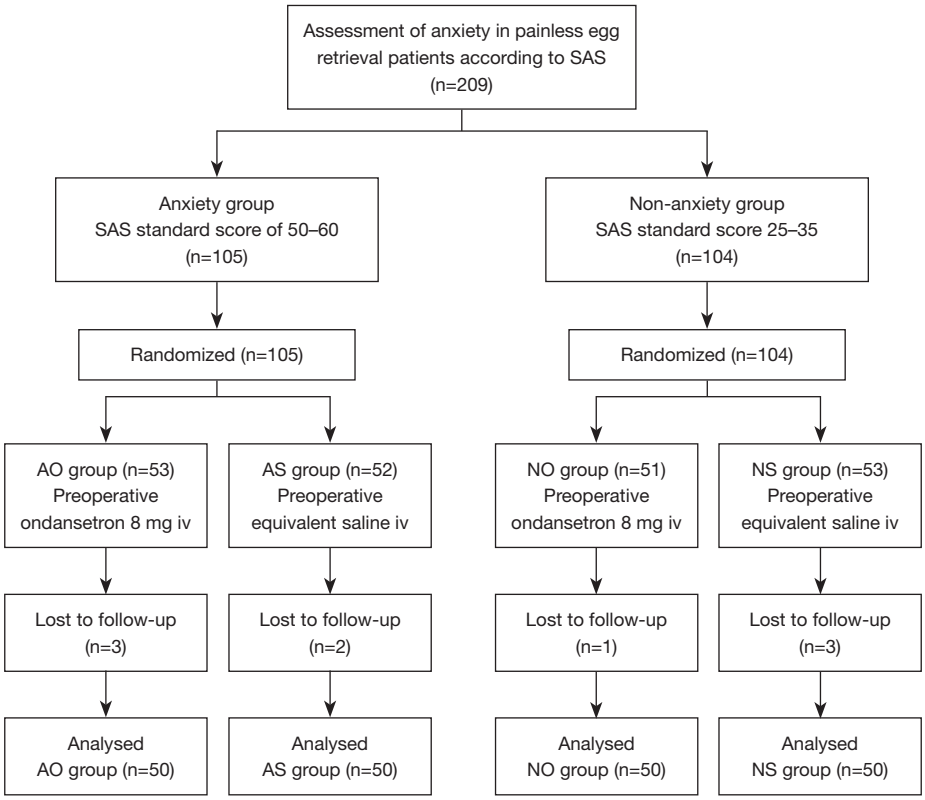

Figure 1 Flowchart of the trial design. SAS, anxiety self-rating scale; AO, patients in the anxiety group received intravenous ondansetron before surgery; AS, patients in the anxiety group received intravenous saline before surgery; NO, patients in the non-anxiety group received intravenous ondansetron before surgery; NS, patients in the non-anxiety group received intravenous saline before surgery.

have concluded that preoperative anxiety is not significantly associated with PONV (20). This trial aimed to investigate the clinical effects of preoperative use of ondansetron for the prevention of PONV in anxious and non-anxious patients undergoing painless egg retrieval and to explore the potential relationship between preoperative anxiety and PONV by detecting pre- and post-surgical levels of 5-HT in anxious and non-anxious patients. We present this article in accordance with the CONSORT reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-175/rc).

Methods

Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of The First People's Hospital of Yunnan Province (No. KHLL2023-KY026) approved this prospective, randomized, controlled trial, and patients or their families signed an informed consent form. Patients who underwent painless egg retrieval at The First People's Hospital of Yunnan Province's Department of Reproductive Medicine from March 2023 to May 2023 were screened for eligibility.

The clinical research design is shown in *Figure 1*.

Sample size calculation

Sample size calculations were based on a previous study on PONV (21). PASS 15.0 software was used for sample size estimation, setting the degree of certainty $1-\beta=0.80$ and the test level $\alpha=0.05$ (bilateral), then 42 cases of samples were needed in each group. Considering that 10% of the subjects dropped out, a total of 209 research subjects were enrolled in this study, and finally 50 cases were analyzed in each group respectively, which ensured the accuracy and scientificity of the results of the study.

Inclusion criteria

(I) Patients with an American Society of Anesthesiologists Standard (ASA) classification of I–II, New York Heart Association (NYHA) classification I–II;
(II) Age 25–45 years old;
(III) Body mass index (BMI) 18.5–24 kg/m^2;
(IV) The standard score of the anxiety self-rating scale was 50–60 points, and the standard score of the SAS of the non-anxiety group was 25–35 points;
(V) The operation time less than 30 minutes.

Exclusion criteria

(I) A history of chemoradiotherapy within one week, antiemetic with 5-HT receptor blockers;
(II) Patients with mental disorders or limited intellectual ability;
(III) Patients with gastrointestinal, craniocerebral and otogenic diseases that can cause nausea and vomiting;
(IV) Liver and kidney function impairment;
(V) History of malignancy or severe systemic disease;
(VI) Use of neurotrophic factor-related drugs within three months;
(VII) Patients who are allergic to ondansetron;
(VIII) Patients who do not agree to enroll in this clinical trial study.

Randomization

We used SPSS software to generate random numbers at a 1:1 ratio for the anxiety and non-anxiety groups and separated each group into two subgroups. The grouping results were sealed in envelopes and stored from the start till the end of the investigation. The randomized findings of the recruited individuals were distributed to study participants. Anesthesia was delivered by a professional anesthesiologist for each enrolled patient, and researchers collected intraoperative data. Postoperative monitoring was carried out by investigators who were not involved in anesthesia care. During the data-collecting period, there was no communication between the anesthesiologist and the researcher.

Anesthesia methods

Preoperative management and anesthesia monitoring setup

All patients fasted for 8 hours and abstained from drinking for 2 hours before surgery. After the patient entered the operating room, peripheral venous access was obtained and 2 mL of venous blood sample was drawn. The self-rating anxiety scale (SAS) was used to assess patients' preoperative anxiety half an hour before surgery in the pre-anesthesia care unit, and patients with an SAS standard score of 50–60 points were classified as anxious, while patients with an SAS standard score of 25–35 points were classified as non-anxious. Patients in the anxiety group were randomly allocated in two subgroups: the ondansetron subgroup (AO group) and the placebo subgroup (AS group), while patients in the non-anxiety group were also randomly divided into two subgroups: ondansetron subgroup (NO group) and saline subgroup (NS group). The AO and NO groups received 8 mg (4 mL) of intravenous ondansetron 15 minutes before surgery, while the AS and NS groups received an equivalent volume (4 mL) of normal saline.

The operating position was the lithotomy position, and the mask administered oxygen at a rate of 3–5 L/min. Before anesthesia was administered, the Monitor (Philips IntelliVue MX, USA) monitored the electrocardiogram (ECG), heart rate (HR), pulse, respiratory rate (RR), pulse oxygen saturation (SpO_2), and blood pressure (BP). Before vaginal disinfection, patients were injected 1–2 μg/kg intravenous fentanyl (Human Well Healthcare, 10A11081, China), followed by 1.5–2.0 mg/kg propofol (Corden Pharma S.P.A, RX356, Italy) 2 minutes later. After the patient's eyelash reflex and consciousness disappeared, the operation was started. The surgeon retrieved eggs through vaginal puncture under ultrasound guidance, penetrated the follicles through the vaginal vault with a single-lumen egg retrieval needle, and suctioned bilateral follicles with a negative pressure of 110 kPa. The anesthesiologist added propofol 0.5 mg/kg/bolus according to the operation time or when the patient has physical movement and moaning. In this study, anesthesia procedures were performed by the same experienced anesthesiologist, and surgical procedures were performed by the same experienced reproductive medicine specialist.

Intraoperative management

When the pulse oximetry reading fell below 90%, mask-positive pressure-assisted ventilation was performed. We employed atropine (Henan Runhong Pharmaceutical Co., Ltd., 2108082, China) to keep the HR between 50–100 beats per minute, and ephedrine (Northeast Pharmaceutical Group CO., Ltd., 230202, China) to keep BP changes within 20% of baseline.

Postoperative management

After the operation, the patients were transferred to the post-anesthesia care unit to continue monitoring their vital signs for 1 hour, 2 mL blood sample is then drawn and they were allowed to return home after their consciousness and orientation returned to normal, and if their vital signs were stable and no adverse reactions were observed.

Blood sample

Blood collector collected 2 mL of venous blood at the time of patients' admission and 1 hour after the surgery, and the specimens were left at room temperature for 10 minutes and then placed in a centrifuge (Eppendorf AG, Centrifuge 5804R, Leipzig, Germany) for natural coagulation. Samples were centrifuged at 3,000 rpm/separation for 10 minutes, and the supernatant was aspirated with a pipette gun and uniformly placed in a –80 ℃ refrigerator for freezing. Samples were taken out from the refrigerator in advance to equilibrate at room temperature for 1 hour. The kit (FANKEWEI, Cat. # F0755-A, Jiangsu, China) was balanced for 30 minutes. The standard empty and sample wells were then designed on the enzyme label coating plate, and 50 μL of different concentrations of standard were added to the typical wells in turn. In the sample well, 40 μL of sample diluent was added, followed by 10 μL of the sample to be measured. The mixture was gently shaken, and then 100 μL of microplate reagent was added per well. The plate was sealed with a plating film and incubated at 37 ℃ for 60 minutes. After the incubation period, the enzyme label coating plate was taken out and the plate film was uncovered, and the liquid was discarded. The diluted washing solution was left to stand for 30 seconds, discarded, and then spun dry. Subsequently, the absorbance of each well was measured successively at 450 nm using a microplate reader (BIO-TEK, Elx800, Vermont, USA) within 15 minutes.

Indicator recording

First, the patient's general condition is recorded, including age, height, weight, BMI value, ASA classification, preoperative fasting time, operation time, and risk factors for PONV: past smoking, previous PONV, and history of motion sickness. Second, the patient's vital signs were recorded at the time of admission (T_1), 3 minutes after anesthesia induction (T_2), and at discharge (T_3), including mean arterial pressure (MAP), HR, SpO_2, and RR, as well as the total amount of fentanyl and propofol during the surgical process. Third, the occurrence of PONV, pain scores and adverse responses (dizziness, drowsiness, and fatigue) within 1 hour was monitored. Finally, their satisfaction and delayed PONV were followed-up by telephone.

SAS

The 20-item SAS employed in this experiment has strong reliability and validity. This assessment, which takes about 10 minutes, captures the patient's emotional response to stress, and has previously been frequently used to assess preoperative anxiety (22).

PONV

Patients were evaluated according to the World Health Organization (WHO) grading criteria within 24 hours after surgery. Grade 0: no nausea and vomiting; Grade I: nausea, does not affect eating and daily life, 1–2 times a day; Grade II: temporary vomiting can be controlled, 3–5 times a day; Grade III: vomiting requires treatment, 6–10 times a day; Grade IV: uncontrollable vomiting more than 10 times a day.

Analgesia assessment

Postoperative pain was scored via the visual analog scale (VAS) 1 hour after surgery, ranging from 0 (no pain) to 10 (maximum pain). Scores of 1–3 denoted mild pain, 4–6 denoted moderate pain, and 7–10 represented severe pain.

Patient satisfaction

Satisfaction ratings range from 0 (very dissatisfied) to 10 (very satisfied), with higher scores representing greater satisfaction.

Statistical analysis

Subjects who completed the study according to the study protocol were analyzed. Patients with missing values were excluded from the trial. The primary analysis will be by per-protocol (PP). Statistical analysis was performed using SPSS 26.0 (IBM SPSS Inc., Armonk, USA) software. Normally distributed continuous data were described by mean ± standard deviation (SD), analysis of variance (ANOVA) was used for between-group comparison, and paired *t*-test was used for paired samples for intra-group comparison. Nonnormal quantitative data were expressed as medians [interquartile range (IQR)] and calculated using rank sum or nonparametric tests. The chi-square test was used for

Table 1 Baseline clinical characteristics of patients

Characteristics	AO group (n=50)	AS group (n=50)	NO group (n=50)	NS group (n=50)	P value
Age (years)	32 [28, 34]	29 [27, 34]	31 [28, 33]	31 [29, 35]	0.08
BMI (kg/m^2)	23 [18, 29]	22 [19, 25]	23 [19, 27]	22 [19, 25]	0.48
ASA classification					0.67
I	47 (94%)	46 (92%)	48 (96%)	45 (90%)	
II	3 (6%)	4 (8%)	2 (4%)	5 (10%)	
Fasting time (h)	13 [8, 17]	12 [9, 16]	13 [10, 16]	13 [10, 16]	0.77
Operation time (min)	7 [5, 9]	8 [6, 10]	8 [6, 10]	8 [6, 11]	0.26
Smoking	0	0	2 (4%)	0	0.25
History of PONV	8 (16%)	10 (20%)	9 (18%)	8 (16%)	0.96
History of motion sickness	29 (58%)	29 (58%)	22 (44%)	23 (46%)	0.36

Data are presented as median [interquartile ranges] or n (%). AO group, anxious ondansetron group; AS group, anxiety saline group; NO group, non-anxious ondansetron group; NS group, non-anxiety saline group; BMI, body mass index; ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting.

comparison of counts, which was represented by n (%). The rank sum test was used for grade data. P value <0.05 was considered statistically significant. All P values are two sided.

Results

From March 2023 to May 2023, 209 female patients who underwent painless egg retrieval in the outpatient clinic of The First People's Hospital of Yunnan Province were included. 9 patients failed to follow up after surgery and 200 patients were ultimately enrolled in the study (*Figure 1*).

Patient's baseline clinical characteristics and risk factors for PONV

The baseline clinical characteristics, including age, BMI, ASA classification, fasting time, and operation time did not show significant differences among the four groups. Similar results were obtained for risk factors for PONV between the groups (*Table 1*).

Perioperative vital signs of the patients

The P values of MAP, HR, SpO_2 and RR at T_1 (time of admission), T_2 (3 minutes after anesthesia induction), and T_3 (time of discharge) moments were higher than 0.05 in all four groups (*Table 2*).

Comparison of the incidence of PONV

None of the patients in all four groups developed grade III or IV nausea and vomiting. The incidence of grade II nausea and vomiting in the AS group was higher than that in the NS group and AO group (P<0.05), The incidence of PONV was also higher in the AS group than in the AO group (P<0.05). The four groups did not show significant differences in the incidence of grade I nausea and vomiting (P>0.05) (*Table 3*, *Figure 2*).

Preoperative and postoperative serum 5-HT value in patients in the anxiety group and non-anxiety group

The serum 5-HT values before and after surgery in the anxiety group were higher than those in the non-anxiety group (P<0.001) (*Table 4*, *Figure 3*).

Comparison of 5-HT values before and after surgery in the same group

The comparison of serum 5-HT before and after surgery between the same groups did not show significant changes (all P>0.05) (*Table 5*, *Figure 4*).

Table 2 Perioperative vital signs of the patients

Indicator	Time	AO group (n=50)	AS group (n=50)	NO group (n=50)	NS group (n=50)	P value
MAP (mmHg)	T_1	89 [67, 111]	96 [84, 108]	92 [81, 103]	92 [81, 103]	0.09
	T_2	81 [63, 100]	80 [69, 92]	78 [66, 90]	78 [68, 88]	0.40
	T_3	86 [72, 100]	88 [74, 102]	85 [73, 97]	86 [74, 99]	0.58
HR (times/min)	T_1	84 [61, 107]	85 [67, 103]	84 [68, 100]	82 [71, 94]	0.57
	T_2	74 [53, 97]	77 [63, 90]	74 [60, 88]	76 [65, 87]	0.54
	T_3	72 [66, 79]	71 [54, 88]	71 [58, 85]	75 [63, 87]	0.84
SpO_2 (%)	T_1	97.7±1.51	97.4±1.01	97.6±0.85	97.4±1.98	0.72
	T_2	99.7±0.66	99.8±0.66	99.7±0.61	99.6±0.97	0.74
	T_3	99.4±1.05	99.5±1.09	99.5±0.93	99.3±1.17	0.95
RR (times/min)	T_1	14.96±2.08	15.02±2.45	15.00±2.18	14.88±1.90	0.98
	T_2	10.28±1.51	10.20±1.37	10.04±1.37	10.76±1.45	0.07
	T_3	13.10±0.93	13.18±0.80	12.88±0.80	12.94±0.89	0.27

Data are presented as median [interquartile ranges] or mean ± standard deviation. AO group, anxious ondansetron group; AS group, anxiety saline group; NO group, non-anxious ondansetron group; NS group, non-anxiety saline group; MAP, mean arterial pressure; HR, heart rate; SpO_2, pulse oxygen saturation; RR, respiratory rate; T_1, time of admission; T_2, 3 minutes after anesthesia induction; T_3, time of discharge.

Table 3 Postoperative nausea and vomiting in four groups

Group	Grade I PONV	Grade II PONV	Grade III PONV	Grade IV PONV
AO group	7 (14%)	4 (8%)[a]	0	0
AS group	7 (14%)	17 (34%)	0	0
NO group	5 (10%)	8 (16%)	0	0
NS group	6 (12%)	8 (16%)[a]	0	0
P value		0.04		

Data are presented as n (%). [a], P<0.05, AO group compared the incidence of grade II PONV to the AS group and NS group compared the incidence of grade II PONV to the AS group. AO group, anxious ondansetron group; AS group, anxiety saline group; NO group, non-anxious ondansetron group; NS group, non-anxiety saline group; PONV, postoperative nausea and vomiting.

Intraoperative anesthetic dosage

The P values for total intraoperative propofol and fentanyl administration were higher than 0.05 in all four groups (P=0.83) and (P=0.45), respectively (*Table 6*).

Postoperative adverse effects

Differences between the four groups of patients regarding postoperative adverse effects including dizziness, drowsiness, and fatigue showed no significant differences, with (P=0.91, 0.83, 0.57) respectively (*Table 7*).

Pain scores and satisfaction scores

The four groups of patients had similar postoperative pain scores (P=0.051). Patients in the AS group had lower satisfaction scores than those in the other three groups (P<0.001) (*Table 8*).

Discussion

Preoperative anxiety is a nervous or tense state of mind caused by a patient's concerns about disease, operation, anesthesia, and treatment outcomes. Preoperative anxiety

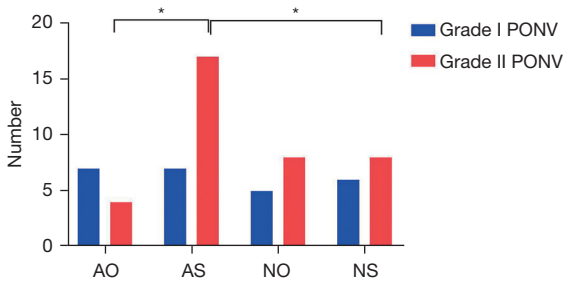

Figure 2 Postoperative nausea and vomiting in the four groups. *, P<0.05, AO group compared the incidence of grade II PONV to the AS group and NS group compared the incidence of grade II PONV to the AS group. The absence of grade III and IV PONV may be related to the good general condition of the egg retrieval patient and the low amount of anesthetic used during the operation. AO group, anxious ondansetron group; AS group, anxiety saline group; NO group, non-anxious ondansetron group; NS group, non-anxiety saline group; PONV, postoperative nausea and vomiting.

Table 4 Preoperative and postoperative serum 5-HT value in patients in the anxiety group and non-anxiety groups

Group	Preoperative 5-HT (ng/mL)	Postoperative 5-HT (ng/mL)
Anxiety group	694.05±46.86	693.99±54.97
Non-anxiety group	629.51±47.35	638.72±55.27
P value	<0.001	<0.001

Data are presented as mean ± standard deviation. 5-HT, serotonin.

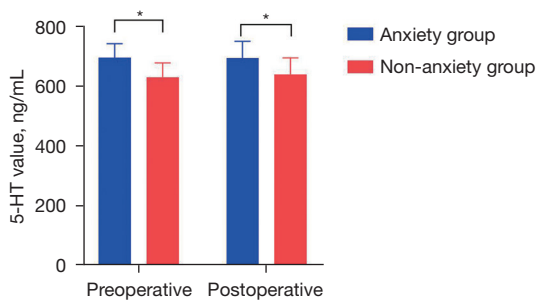

Figure 3 5-HT values (39–361 ng/mL) before and after surgery in the anxiety group and non-anxiety group. *, P<0.05, the non-anxiety group compared to the anxiety group. 5-HT, serotonin.

has been shown in numerous studies to have a deleterious impact on both intraoperative and postoperative progression (23-25). Gender, age, sleep disturbance, high BMI, preoperative discomfort, and prognosis are all associated with the prevalence of preoperative anxiety (26).

Our study's results demonstrated that the anxiety group's serum 5-HT values before and after surgery were higher than those of the non-anxiety group (P<0.05) and that there was no significant difference in the same group's serum 5-HT before and after surgery (P>0.05). Anxiety and depression have been found to be strongly associated with serum brain-derived neurotrophic factor (BNDF), neurotrophin-3 (NT-3) and 5-HT levels (27), with 5-HT being widely distributed in the central nervous system as an indolamine. It is released by the diaphragm, hippocampus, amygdala, thalamus, and hypothalamus, which is critical in the onset and progression of anxiety and depression (28-30). Many mouse studies have indicated that 5-HTTA$_1$ and 5-HT$_3$ receptors are related to anxiety behavior. The modulation of the number of 5-HT auto-receptors on middle suture nuclear neurons can modify adult mice's anxiety behavior (31,32). Regulation of both 5-HTA$_1$ and 5-HT$_3$ receptors has also been proven in studies to diminish anxiety states in adults (33). Furthermore, anxiety states can impact the intestinal microecology and immune cells via the brain-intestinal axis to change the patient's 5-HT level (34). Our findings are consistent with the above studies.

Although there was no difference in patient baseline clinical characteristics, PONV risk factors, intraoperative condition, or intraoperative medication, the incidence of grade II PONV in patients with preoperative anxiety was significantly higher than that in patients without anxiety (P<0.05). PONV is caused by a complex process involving the vomiting center and the peripheral chemoreceptor trigger area (CRTZ). The former found in the brainstem's lateral reticular structure, while the latter is situated at the bottom of the fourth ventricle. The blood-brain barrier does not protect CRTZ, which hosts a variety of receptors, including histamine receptors, 5-HT receptors, cholinergic receptors, neurokinin-1 receptors, dopamine receptors, and others. These receptors can directly sense signals from various neurotransmitters, drugs, and metabolites in the blood and cerebrospinal fluid. There are seven subtypes of 5-HT receptors, of which 5-HT$_3$ receptors are ligand-gated

Table 5 Comparison of 5-HT values before and after surgery in the same group

Group	Preoperative 5-HT (ng/mL)	Postoperative 5-HT (ng/mL)	P value
AO group	697.31±45.02	697.99±56.49	0.88
AS group	690.79±48.87	689.98±53.67	0.87
NO group	630.26±49.09	637.46±58.80	0.11
NS group	628.76±46.04	633.83±56.18	0.31

Data are presented as mean ± standard deviation. AO group, anxious ondansetron group; AS group, anxiety saline group; NO group, non-anxious ondansetron group; NS group, non-anxiety saline group; 5-HT, serotonin.

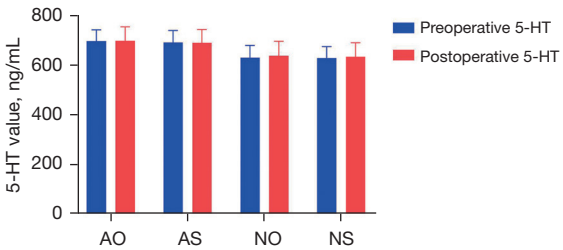

Figure 4 5-HT values before and after surgery in the same group. AO group, anxious ondansetron group; AS group, anxiety saline group; NO group, non-anxious ondansetron group; NS group, non-anxiety saline group; 5-HT, serotonin.

Table 6 Intraoperative anesthetic dosage group

Group	Propofol (mg)	Fentanyl (μg)
AO group	110 [90, 130]	95 [91, 99]
AS group	105 [85, 125]	100 [95, 105]
NO group	110 [90, 130]	100 [94, 106]
NS group	100 [80, 120]	95 [93, 97]
P value	0.83	0.45

Data are presented as median [interquartile ranges]. AO group, anxious ondansetron group; AS group, anxiety saline group; NO group, non-anxious ondansetron group; NS group, non-anxiety saline group.

Table 7 Postoperative adverse effects

Group	Dizziness	Drowsiness	Fatigue
AO group	6 (12%)	4 (8%)	1 (2%)
AS group	5 (10%)	6 (12%)	1 (2%)
NO group	5 (10%)	4 (8%)	0
NS group	7 (14%)	6 (12%)	0
P value	0.91	0.83	0.57

Data are presented as n (%). AO group, anxious ondansetron group; AS group, anxiety saline group; NO group, non-anxious ondansetron group; NS group, non-anxiety saline group.

Table 8 Patients' pain scores and satisfaction

Group	VAS score	Satisfaction score
AO group	4 [2, 6]	9 [8, 10][a]
AS group	3 [3, 6]	8 [7, 9]
NO group	3 [2, 4]	9 [9, 10][a]
NS group	3 [2, 4]	9 [8, 10][a]
P value	0.051	<0.001

Data are presented as median [interquartile ranges]. [a], P<0.05, compared the satisfaction score to the AS group. AO group, anxious ondansetron group; AS group, anxiety saline group; NO group, non-anxious ondansetron group; NS group, non-anxiety saline group; VAS, visual analogue scale.

ion channels most closely associated with vomiting (35). Some have shown that two neurotransmitters play a central role in mediating the emetic response: 5-HT, which acts on the 5-HT_3 receptor, and substance P, which targets the NK_1 receptor (36,37). We discovered that preoperative anxiety and PONV share a receptor and patients who develop PONV have higher preoperative anxiety scores (38). As a result, we conclude that preoperative anxiety is a significant cause of PONV and anxiety susceptibility predicts the development of PONV (39). The absence of grade III and IV PONV may be related to the good general condition of the egg retrieval patient and the anesthetic propofol is known as an antiemetic (40). Such an outcome was not predicted at the beginning of our trial, and the specific reasons need to be further investigated.

Ondansetron is a 5-HT_3 receptor antagonist that is

commonly used in chemotherapy and PONV (41), and its usual adverse effects include migraines, dizziness, constipation, and other symptoms (42). A meta-analysis revealed that oral or intravenous ondansetron is related to QT interval prolongation, especially in participants over 18 years old (43), confirming the prevalence and severity of its side effects. Ondansetron is entirely and promptly absorbed from the gastrointestinal tract and does not accumulate with repeated oral treatment. Nevertheless, due to first-pass hepatic metabolism, the bioavailability of oral ondansetron is only 60% that of intravenous injection (44). Ondansetron 8 mg IV had a high elimination half-life of 0.26 hours (45), with an average elimination half-life of 3.8±1 hours (46). In addition, during laparoscopic cholecystectomy, there is no difference in the incidence of PONV between ondansetron given one hour before anesthesia induction and ondansetron administered 30 minutes before the completion of operation (47). As ultrasound-guided transvaginal puncture egg retrieval surgery is rather brief, we chose a prophylactic intravenous injection of ondansetron 15 minutes before surgery to provide an anti-emetic effect while also facilitating the detection of PONV. This study discovered that preoperative ondansetron dramatically reduced the incidence of PONV in patients with preoperative anxiety, but there was no significant statistical difference in non-anxious patients. It is thought that preoperative 5-HT levels may be elevated in anxious patients and that the treatment of ondansetron blocks 5-HT receptors, avoiding nausea and vomiting in anxious people. Therefore, we recommend prophylactic ondansetron for PONV in patients with preoperative anxiety but not in non-anxious patients. This approach saves medical costs and prevents unwanted pharmacological side effects, thereby reducing the risk during treatment and decreasing the incidence of PONV by lowering the patient's anxiety and improving sleep quality (48).

In this study, we chose individuals who underwent painless egg retrieval on an outpatient basis. This operation is quite brief, and the anesthesia medicine is limited to propofol, which is thought to have anti-emetic properties. One study found that all-in-vein anesthesia with propofol reduced the risk of PONV by approximately 25% when compared to inhalation anesthesia (49). In addition, we used very small amounts of ephedrine to maintain BP during surgery because most of the included individuals were healthy young women. Some researchers have suggested that intramuscular injection of 0.5 mg/kg of ephedrine also has a preventive and therapeutic effect on PONV, and may exert its antiemetic effect by minimizing hypotension (50). During our anesthesia, we used a single intravenous dose of 0.1 mg/kg, with a maximum dose of 0.3 mg/kg, but the antiemetic effect of its intravenous route of administration has been rarely reported and more studies are needed. Taking into account the influence of some anesthetic and surgical factors on PONV, the incidence of postoperative PONV in patients in this trial remained as high as 31%. According to the literature, around 17% of patients suffered nausea, and 8% experienced vomiting following outpatient surgery (41), which is lower than the experimental results of our investigation and may be related to the type of operation. This may be due to the fact that infertility exposes married women to family and social pressures, and due to the long treatment period and traditional beliefs of IVF embryo transfer, they tend to be more anxious before surgery than other outpatient patients.

Furthermore, the study conducted a patient satisfaction survey on all four groups of patients and demonstrated that PONV might cause varying degrees of poor medical experience and diminish patient satisfaction. Most studies indicate that preoperative anxiety increases postoperative pain (51). Still, there was no significant difference in pain scores between the anxious and non-anxious groups in this study, possibly due to the relatively small surgical stimulation and mild pain associated with painless egg retrieval compared to major surgery.

Some limitations of our study should be mentioned. First, this study focused on female surgical patients, but the efficacy of ondansetron in combining preoperative anxiety in men or other surgical types of patients with PONV is not clear. Second, the preoperative anxiety of most of the patients included in this study was mild, and patients with moderate or severe anxiety were not included, so the correlation between 5-HT levels and the degree of anxiety has not been studied. Third, the specific mechanism of ondansetron in combating PONV in patients with preoperative anxiety is not clear. These need to be explored in further clinical and basic studies.

Conclusions

The results of this trial showed that individuals with preoperative anxiety had a higher incidence of PONV after painless egg retrieval than those with no anxiety. Ondansetron can minimize the occurrence of PONV in patients with preoperative anxiety but has no discernible

preventative effect in non-anxious patients.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-175/rc

Trial Protocol: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-175/tp

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-175/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-175/coif). A.K. has received honoraria for lecturing from CSL Behring GmbH (Switzerland) and advisory honoraria from Astrazeneca (Switzerland) and Pharmacosmos (Switzerland). The other authors have no conflicts of interest to declare.

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References

1. Maroufizadeh S, Navid B, Omani-Samani R, et al. The effects of depression, anxiety and stress symptoms on the clinical pregnancy rate in women undergoing IVF treatment. BMC Res Notes 2019;12:256.
2. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum Reprod Update 2015;21:411-26.
3. Sönmezer M, Gülümser Ç, Sönmezer M, et al. Transabdominal ultrasound guided oocyte retrieval using vaginal ultrasound probe: Definition of the technique. J Obstet Gynaecol Res 2021;47:800-6.
4. Klonoff-Cohen H, Chu E, Natarajan L, et al. A prospective study of stress among women undergoing fertilization or gamete intrafallopian transfer. Fertil Steril 2001;76:675-87.
5. Li H, Lei J, Xu F, et al. A study of sociocultural factors on depression in Chinese infertile women from Hunan Province. J Psychosom Obstet Gynaecol 2017;38:12-20.
6. Maroufizadeh S, Ghaheri A, Omani Samani R. Factors associated with poor quality of life among Iranian infertile women undergoing IVF. Psychol Health Med 2017;22:145-51.
7. Ludwig AK, Glawatz M, Griesinger G, et al. Perioperative and post-operative complications of transvaginal ultrasound-guided oocyte retrieval: prospective study of >1000 oocyte retrievals. Hum Reprod 2006;21:3235-40.
8. Vilos AG, Feyles V, Vilos GA, et al. Ureteric injury during transvaginal ultrasound guided oocyte retrieval. J Obstet Gynaecol Can 2015;37:52-5.
9. Stojnic J, Bila J, Tulic L, et al. Severe Hemoperitoneum due to Ovarian Bleeding after Transvaginal Oocyte Retrieval with Surgical Management: A Retrospective Analysis and Comprehensive Review of the Literature.

Medicina (Kaunas) 2023;59:307.
10. Shaikh SI, Nagarekha D, Hegade G, et al. Postoperative nausea and vomiting: A simple yet complex problem. Anesth Essays Res 2016;10:388-96.
11. Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. Br J Anaesth 2012;109:742-53.
12. Miyazaki K, Miyazaki KW, Doya K. The role of serotonin in the regulation of patience and impulsivity. Mol Neurobiol 2012;45:213-24.
13. Tortora F, Hadipour AL, Battaglia S, et al. The Role of Serotonin in Fear Learning and Memory: A Systematic Review of Human Studies. Brain Sci 2023;13:1197.
14. Bacqué-Cazenave J, Bharatiya R, Barrière G, et al. Serotonin in Animal Cognition and Behavior. Int J Mol Sci 2020;21:1649.
15. Kunitomi Y, Nakashima M, Seki T, et al. Intergenerational comparison of 5-HT(3)RA in the prevention of chemotherapy-induced nausea and vomiting in gastric cancer patients receiving cisplatin-based chemotherapy: an observational study using a Japanese administrative claims database. Support Care Cancer 2021;29:3951-9.
16. Chow R, Warr DG, Navari RM, et al. Should palonosetron be a preferred 5-HT(3) receptor antagonist for chemotherapy-induced nausea and vomiting? An updated systematic review and meta-analysis. Support Care Cancer 2018;26:2519-49.
17. Ito H, Akuzawa S, Tsutsumi R, et al. Comparative study of the affinities of the 5-HT3 receptor antagonists, YM060, YM114 (KAE-393), granisetron and ondansetron in rat vagus nerve and cerebral cortex. Neuropharmacology 1995;34:631-7.
18. Van den Bosch JE, Moons KG, Bonsel GJ, et al. Does measurement of preoperative anxiety have added value for predicting postoperative nausea and vomiting? Anesth Analg 2005;100:1525-32.
19. Atanasova M, Hinev S. Preoperative anxiety and its influence over the postoperative nausea and vomiting. Khirurgiia (Sofiia) 2009;(6):40-3.
20. Friedrich S, Reis S, Meybohm P, et al. Preoperative anxiety. Curr Opin Anaesthesiol 2022;35:674-8.
21. Balyan R, Kumar S, Lalitha K, et al. A Randomised Study To Compare Palonosetron With Ondansetron for Prophylaxis of Postoperative Nausea and Vomiting (PONV) Following Laparoscopic Gynecological Surgeries. Cureus 2022;14:e23615.
22. Dunstan DA, Scott N. Norms for Zung's Self-rating Anxiety Scale. BMC Psychiatry 2020;20:90.
23. Ki M, Kim DC, You SW, et al. Appropriateness of the anxiety subscale of the Hospital Anxiety and Depression Scale for Koreans to measure preoperative anxiety and the effect of preoperative anxiety on postoperative quality of recovery. Anesth Pain Med (Seoul) 2023;18:260-9.
24. Gu X, Zhang Y, Wei W, et al. Effects of Preoperative Anxiety on Postoperative Outcomes and Sleep Quality in Patients Undergoing Laparoscopic Gynecological Surgery. J Clin Med 2023;12:1835.
25. Stamenkovic DM, Rancic NK, Latas MB, et al. Preoperative anxiety and implications on postoperative recovery: what can we do to change our history. Minerva Anestesiol 2018;84:1307-17.
26. Costelloe C, Burns S, Yong RJ, et al. An Analysis of Predictors of Persistent Postoperative Pain in Spine Surgery. Curr Pain Headache Rep 2020;24:11.
27. Peng X, Feng S, Zhang P, et al. Analysis of influencing factors of anxiety and depression in maintenance hemodialysis patients and its correlation with BDNF, NT-3 and 5-HT levels. PeerJ 2023;11:e16068.
28. Samuels BA, Anacker C, Hu A, et al. 5-HT1A receptors on mature dentate gyrus granule cells are critical for the antidepressant response. Nat Neurosci 2015;18:1606-16.
29. Tanaka KF, Samuels BA, Hen R. Serotonin receptor expression along the dorsal-ventral axis of mouse hippocampus. Philos Trans R Soc Lond B Biol Sci 2012;367:2395-401.
30. Yohn CN, Gergues MM, Samuels BA. The role of 5-HT receptors in depression. Mol Brain 2017;10:28.
31. Richardson-Jones JW, Craige CP, Guiard BP, et al. 5-HT1A autoreceptor levels determine vulnerability to stress and response to antidepressants. Neuron 2010;65:40-52.
32. Richardson-Jones JW, Craige CP, Nguyen TH, et al. Serotonin-1A autoreceptors are necessary and sufficient for the normal formation of circuits underlying innate anxiety. J Neurosci 2011;31:6008-18.
33. de Kort AR, Joosten EA, Patijn J, et al. Selective Targeting of Serotonin 5-HT1a and 5-HT3 Receptors Attenuates Acute and Long-Term Hypersensitivity Associated With Neonatal Procedural Pain. Front Pain Res (Lausanne) 2022;3:872587.
34. Reigstad CS, Salmonson CE, Rainey JF 3rd, et al. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. FASEB J 2015;29:1395-403.
35. Rojas C, Raje M, Tsukamoto T, et al. Molecular mechanisms of 5-HT(3) and NK(1) receptor antagonists

in prevention of emesis. Eur J Pharmacol 2014;722:26-37.
36. Rojas C, Slusher BS. Pharmacological mechanisms of 5-HT$_3$ and tachykinin NK$_1$ receptor antagonism to prevent chemotherapy-induced nausea and vomiting. Eur J Pharmacol 2012;684:1-7.
37. Darmani NA, Chebolu S, Amos B, et al. Synergistic antiemetic interactions between serotonergic 5-HT3 and tachykininergic NK1-receptor antagonists in the least shrew (Cryptotis parva). Pharmacol Biochem Behav 2011;99:573-9.
38. Roh YH, Gong HS, Kim JH, et al. Factors associated with postoperative nausea and vomiting in patients undergoing an ambulatory hand surgery. Clin Orthop Surg 2014;6:273-8.
39. Laufenberg-Feldmann R, Müller M, Ferner M, et al. Is 'anxiety sensitivity' predictive of postoperative nausea and vomiting?: A prospective observational study. Eur J Anaesthesiol 2019;36:369-74.
40. Borgeat A, Ekatodramis G, Schenker CA. Postoperative nausea and vomiting in regional anesthesia: a review. Anesthesiology 2003;98:530-47.
41. Gan TJ, Belani KG, Bergese S, et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. Anesth Analg 2020;131:411-48.
42. Khan RB. Migraine-type headaches in children receiving chemotherapy and ondansetron. J Child Neurol 2002;17:857-8.
43. Singh K, Jain A, Panchal I, et al. Ondansetron-induced QT prolongation among various age groups: a systematic review and meta-analysis. Egypt Heart J 2023;75:56.
44. Koland M, Sandeep V, Charyulu N. Fast Dissolving Sublingual Films of Ondansetron Hydrochloride: Effect of Additives on in vitro Drug Release and Mucosal Permeation. J Young Pharm 2010;2:216-22.
45. Colthup PV, Felgate CC, Palmer JL, et al. Determination of ondansetron in plasma and its pharmacokinetics in the young and elderly. J Pharm Sci 1991;80:868-71.
46. Roila F, Del Favero A. Ondansetron clinical pharmacokinetics. Clin Pharmacokinet 1995;29:95-109.
47. Theodosopoulou P, Staikou C, Fassoulaki A. Preoperative versus intraoperative antiemetic strategies in patients undergoing laparoscopic cholecystectomy: A randomised double-blind study. Eur J Anaesthesiol 2023;40:769-76.
48. Lu D, Wang Y, Zhao T, et al. Successful implementation of an enhanced recovery after surgery (ERAS) protocol reduces nausea and vomiting after infratentorial craniotomy for tumour resection: a randomized controlled trial. BMC Neurol 2020;20:150.
49. Borgeat A, Wilder-Smith OH, Saiah M, et al. Subhypnotic doses of propofol possess direct antiemetic properties. Anesth Analg 1992;74:539-41.
50. Wuhrman E, Clark M. Use of ephedrine for the short-term treatment of postoperative nausea and vomiting: a case report. J Perianesth Nurs 2011;26:305-9.
51. Mishra A, Srivastava VK, Prakash R, et al. Perioperative Anxiolysis and Analgesic Effect after Premedication with Melatonin and Pregabalin in Total Hip Arthroplasty under Spinal Anaesthesia: A Prospective Comparative Trial. Adv Biomed Res 2023;12:185.

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