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Acupuncture combined with ondansetron for prevention of postoperative nausea and vomiting in high-risk patients undergoing laparoscopic gynaecological surgery: A randomised controlled trial

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Abstract

Background: Consensus guidelines recommend the use of multiple antiemetics as prophylaxis in patients at high risk of postoperative nausea and vomiting (PONV), but the evidence regarding combining acupuncture and antiemetics as a multimodal approach was of very low quality.

Objective: This study aimed to assess the effect of combinations of acupuncture with ondansetron versus ondansetron alone for PONV prophylaxis in women at a high risk.

Methods: This parallel, randomised controlled trial was conducted in a tertiary hospital in China. Patients who had three or four PONV risk factors on the Apfel simplified risk score, undergoing elective laparoscopic gynaecological surgery for benign pathology, were recruited. Patients in the combination group received two sessions of acupuncture treatment and 8 mg intravenous ondansetron, whereas those in the ondansetron group received ondansetron alone. The primary outcome was the incidence of PONV within 24 h postoperatively. Secondary outcomes included the incidence of postoperative nausea, postoperative vomiting, adverse events etc.

Results: Between January and July 2021, a total of 212 women were recruited, 91 patients in the combination group and 93 patients in the ondansetron group were included in the modified intention-to-treat analysis. In the first 24 h postoperatively, 44.0% of the patients in the combination group and 60.2% of the patients in the ondansetron group experienced nausea, vomiting, or both (difference, −16.3% [95% CI, −30.5 to −2.0]; risk ratio, 0.73 [95% CI, 0.55–0.97]; $p = 0.03$). However, the results of the secondary outcomes showed that compared to ondansetron alone, acupuncture together with ondansetron was only effective in reducing nausea but did not have a significant impact on vomiting. The incidence of adverse events was similar between the groups.

Shiyan Yan, Mingjun Xu and Xuan Zou contributed equally to this work.

Conclusion: Acupuncture combined with ondansetron as a multimodal prophylaxis approach is more effective than ondansetron alone in preventing postoperative nausea in high-risk patients.

KEYWORDS
5-HT3 receptor antagonists, acupuncture, CAM, complementary and alternative medicine, multimodal prophylaxis, ondansetron, PONV, postoperative nausea and vomiting, surgery

INTRODUCTION

Postoperative nausea and vomiting (PONV) is a common and unpleasant adverse event following surgery and anaesthesia. Without effective prophylaxis, PONV affects approximately 30% of general surgical patients.[1] PONV can contribute to surgical wound complications, dehydration, aspiration of gastric contents, and is also associated with delayed hospital discharge time and increased healthcare costs.[2–4] Risk factors such as female gender, postoperative opioid use, and laparoscopy can result in an increased incidence of PONV in high-risk patients, with a PONV rate of up to 80%.[2,5,6] Existing treatment involves prophylactic and symptomatic administration of antiemetic drugs, such as metoclopramide, ondansetron, and aprepitant;[7] for high-risk patients, multimodal antiemetic therapies have been proposed in recent consensus guidelines for the management of PONV.[7] However, even with multimodal antiemetic prophylaxis, the incidence of PONV remains as high as 60%–70% in these patients.[8,9]

Due to the limited effect of antiemetics, interest has emerged in nonpharmacological therapies for their potential value and minimal adverse effects in preventing PONV.[10–12] Acupuncture and its related techniques such as electro-acupuncture, acupressure, and transcutaneous electrical stimulation have been demonstrated to be effective for the prevention and treatment of PONV.[13–16] A Cochrane review reported that Neiguan (PC6) stimulation could reduce the incidence of PONV and the need for rescue antiemetics when compared with sham treatment.[17] However, most previous studies enrolled a general population, few data are available on the effectiveness of acupuncture in high-risk patients. Moreover, the evidence regarding combining acupoint stimulation and antiemetics as a multimodal approach for preventing PONV is inconclusive due to study limitations.[7,17] Therefore, we designed a randomised controlled trial to investigate the effectiveness of acupuncture in combination with ondansetron as a multimodal prophylaxis approach for PONV. We focused on high-risk patients who may benefit most from such an intervention.

Key summary

Summarise the established knowledge on this subject

- Prevention of postoperative nausea and vomiting (PONV) remains challenging in high-risk patients.
- New multimodal antiemetic therapies are needed for the prophylaxis of PONV.
- Acupuncture has proven efficacy in the prevention of PONV.
- The added value of acupuncture based on the antiemetic effect of drugs is unclear.

What are the significant and/or new findings of this study?

- The combination of acupuncture and ondansetron further reduced the incidence of postoperative nausea in high-risk patients.
- The antiemetic effect of acupuncture was more pronounced in the early postsurgical phase.
- This multimodal approach had a good safety profile.

MATERIALS AND METHODS

This trial was a prospective, randomised controlled single-centre study comparing the prophylactic effects of acupuncture-ondansetron combination on a single dose of ondansetron in patients at high risk of PONV. The study was reviewed and approved by the institutional review boards of Beijing University of Chinese Medicine (2020BZYLL0602) and the coordinating hospital (2020-KY-055-01) (See Supplement S1). The study was conducted in compliance with the Declaration of Helsinki and registered in the Chinese Clinical Trial Registry (ChiCTR2100042486). Written informed consent was obtained from all participants.

Setting and study population

The study was conducted at Beijing Obstetrics and Gynaecology Hospital. Eligible patients were women who were scheduled to undergo gynaecological surgery under total intravenous anaesthesia (TIVA), aged 18–65 years, American Society of Anaesthesiologists (ASA) physical status class I or II, expected use of postoperative opioids for analgesia, had three or all four of the Apfel risk factors for PONV (female gender, non-smoking status, history of PONV and/or motion sickness, and use of postoperative opioids), anticipated surgical duration (from induction of anaesthesia to surgical wound closure) ≥1 h.

Exclusion criteria were as follows: pregnancy, lactation or having menses; smoking; undergoing surgery for malignant pathology; nausea, vomiting, or both within 24 h before surgery; use of antiemetics, opioids, or glucocorticoids within 24 h before surgery; allergy to ondansetron or metoclopramide; eczema or infection over the acupoint skin area; severe renal or liver malfunction, central nervous system injury, vertebrobasilar artery insufficiency, vestibular disease, coagulation disorder or other kinds of hemopathy; participated in other studies within 3 months.

Study treatment

Patients allocated to receive acupuncture in combination with ondansetron (combination group) were given two sessions of acupuncture (30–60 min before surgery in the ward and immediately after awakening from anaesthesia in the Post-anaesthesia Care Unit [PACU]), and 8 mg intravenous ondansetron (0–30 min before wound closure). Patients in the control group (ondansetron group) received ondansetron only.

Acupuncture treatment

Acupuncture treatment was administrated at bilateral Neiguan (PC6), Hegu (LI4), Zusanli (ST36) and Sanyinjiao (SP6). Participants were in the supine position, following skin disinfection, Hwato brand disposable needles (size 0.25 × 40 or 0.25 × 25 mm, Suzhou Medical Appliance) were inserted into the acupoints slowly and vertically. The detailed location of acupoints and insertion depth of needles are shown in the Supplement S2. After *deqi* (sensation of aching, soreness, heaviness, swelling, or numbness at acupoints) was attained, manipulation including twisting, lifting and thrusting on the needles was performed at each acupoint for 30 s. Afterwards, the needles were retained for 30 min. The acupuncture intervention protocol was based on a previous literature review[18] and expert consensus.[19] All acupuncture treatments were performed by certified acupuncturists who had at least 3 years of clinical experience.

Anaesthesia and perioperative management

All participants received TIVA and endotracheal intubation. After overnight fasting, patients were wheeled into the operating room, monitoring procedures including non-invasive blood pressure, ECG, pulse oximetry and heart rate were performed, the bispectral index (BIS) monitors were placed. Following the insertion of the intravenous line, a crystalloid solution was started. Anaesthesia was induced with remifentanil, propofol, midazolam and/or etomidate, and maintained with propofol and remifentanil. After confirming the loss of consciousness, intravenous cisatracurium was used for muscle relaxation. Afterwards, Endotracheal intubation was performed, and a ventilator was connected to control breathing. All patients received 8 mg ondansetron (Qilu Pharmaceutical, Shandong, China) 0–30 min before surgical wound closure for PONV prophylaxis.

After surgery, the patients were transported to the PACU, and were extubated after the restoration of normal respiratory function. Following extubation, patients in the combination group received one session of acupuncture. The patients were monitored in the PACU, and were sent back to the ward when their vital signs were stable and the Steward wake-up score ≥4. Postoperative pain was managed by sufentanil and was administered via patient controlled intravenous analgesia (PCIA). The PCIA pump was filled with 100 μg sufentanil diluted in 100 mL of 0.9% saline, with a loading dose of 0 mL, background dose of 2 mL/h, a single dose of 0.5 mL/h, lockout interval 10 min, and use time of 24 h. The amount of sufentanil used was recorded at 6, 24 h postoperatively. For antiemetic rescue therapy, 10 mg intravenous metoclopramide was administered to patients who reported unbearable postoperative nausea or vomiting. Participants were encouraged to restrain from using other medications for the management of PONV and postoperative pain throughout the trial, and details were recorded on the concomitant medication form if used.

RANDOMISATION AND MASKING

Eligible participants were randomly assigned to 2 groups with 1:1 ratio using permuted block randomisation (block size of 4). The randomisation sequence was generated by an independent statistician with SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA), procedure PROC PLAN. The allocation was concealed in identical sequentially numbered, sealed opaque envelopes. After obtaining informed consent from each patient, the envelope was opened in numerical order by a study coordinator not involved in the outcome assessments or treatment. Baseline and follow-up assessments were performed by blinded outcome assessors who had received specialised training. Considering the convenience and time schedule of PONV information collection, the incidence of PONV was recorded by nurses who received specialised training. Communication between assessors and patients was restricted to a minimum to avoid potential bias. The acupuncturists, clinical trial coordinator and patients knew the treatment allocation, while the anaesthetists, clinical staff involved in perioperative care, outcome assessors and statisticians were blinded.

Assessments and outcomes

The primary outcome was the incidence of PONV within 24 h postoperatively.[20] The secondary outcomes were as follows: the incidence of postoperative nausea (PON), postoperative vomiting (POV) and PONV; severity of nausea and pain; the number of episodes of vomiting or retching (with an interval of 5 minutes defining separate episodes)[21]; participants' satisfaction with PONV management; average amount of postoperative sufentanil administered; mean time to first postoperative exhaust.

The data of incidence of PON, POV, PONV, the severity of nausea and pain, the number of episodes of vomiting or retching were collected at 6, 24, and 48 h after the end of surgery; satisfaction on PONV management was assessed at 24 and 48 h after surgery; and the average number of analgesics administered was recorded at 6 and 24 h postoperatively. Nausea was defined as a subjectively uncomfortable sensation in the upper stomach with an involuntary urge to vomit. Vomiting and retching were defined as the powerful sustained contraction of abdominal muscles with or without the expulsion of gastric content, respectively.[22] Severity of PON as well as pain were measured using visual analogue scales (VAS), which 0 indicated no symptoms and 10 the worst imaginable symptoms; satisfaction on PONV management was also rated by VAS (0 = very dissatisfied to 10 = most satisfied imaginable). A preplanned subgroup analysis according to the history of acupuncture, history of PONV and/or motion sickness, comorbidity, age, and Apfel score was performed for the primary outcome. Post-hoc, we also analysed a number of new patients with the onset of PONV in different follow-up time periods.

Surgery- and anaesthesia-related profiles such as the duration of anaesthesia and surgery, extubation time after surgery, and duration of stay in the PACU were also documented. Adverse events (AEs) were collected and categorised by anaesthetists and acupuncturists as treatment-related or non-treatment-related. All AEs were managed by related clinical specialists.

STATISTICAL ANALYSIS

Based on a previous study, the incidence of PONV within 24 h in high-risk patients was 65% in the ondansetron group and expected to be 45% when combined with acupuncture.[9] It was calculated that a sample size of 94 participants per group would provide 80% power to detect a between-group difference of 20%, with a two-sided significance level of 5%. To accommodate a dropout rate of 10%, the sample size was increased to 105 per group and 210 participants in total were needed.

All analyses were based on the modified intention-to-treat (mITT) population of all randomly assigned patients with no major protocol violations, that is, duration of operation less than 1 h, did not receive allocated intervention, or were converted to other types of surgery or anaesthesia. The primary outcome was described as treatment effects with risk ratios and numbers needed to treat (NNT) and assessed by the Chi-square test. A sensitivity analysis based on the population excluding the operation cancelation patients was conducted to validate the robustness of the primary outcome. For comparisons of secondary outcomes, the incidence of PON, the incidence of POV, the number of episodes of vomiting or retching, and satisfaction on PONV management were analysed by Chi-Square tests; the severity of PON and postoperative pain was assessed using *t* tests. Average amount of analgesics administered, mean time to first postoperative exhaust, and average amount of rescue antiemetic drugs used were analysed by Wilcoxon rank sum tests. Predefined subgroup analyses were conducted using a logistic regression model including the interaction of group and subgroup factors to examine the incidence of PONV within 24 h postoperatively for history of acupuncture, history of PONV and/or motion sickness, had comorbidity or not, age, and Apfel score. Considering that all patients' primary outcomes were collected, no missing data was imputed. Two-sided $p < 0.05$ was considered to be statistically significant, statistical analyses were performed with SAS, version 9.4.

Role of the funding source

The study sponsor played no role in the study design, data collection, data analysis, or writing of the report. All authors had full access to the data of the study and approved the final manuscript for submission.

RESULTS

Baseline characteristics

334 women screened for eligibility between January and July 2021, of whom 122 did not meet the criteria (65 were ineligible, 57 declined to participate), and 212 were randomly allocated to receive intravenous ondansetron or in combination with acupuncture (Figure 1). Among the randomised participants, 28 were excluded from the mITT analysis set (18 duration of surgery less than 1 h, 2 converted to inhalation-intravenous combined anaesthesia, 4 cancelled surgery, 2 did not receive ondansetron, 2 withdrew from study with no follow-up data). Thus, data from 184 participants (91 in the combination group, 93 in the ondansetron group) were analysed and presented in this article.

Baseline demographic characteristics as well as surgery- and anaesthesia-related details were similarly distributed across both treatment groups (Table 1). The mean age of the included participants was 42.7 years (SD, 11.2), 62 (33.7%) participants had prior exposure to acupuncture, 47 (25.5%) had comorbidities. All participants underwent laparoscopic gynaecological surgery (mean duration 88.7 min) and received 8 mg intravenous ondansetron before wound closure.

Treatment outcomes

There was a significant between-group difference for the primary outcome; the incidence of PONV within 24 h after surgery was 44.0% in the combination group and 60.2% in the ondansetron group (difference, −16.3% [CI, −30.5 to −2.0]; risk ratio, 0.73 [CI, 0.55–0.97]; $p = 0.03$) (Table 2). This means that 6.2 (CI, 3.3–49.8) patients would need to be given combination treatment to avoid one patient experiencing PONV in the first 24 h. The results of the sensitive analyses were consistent (Table 1). If we split postoperative nausea and vomiting, the incidence of nausea (combination group vs. ondansetron group: 44.0% vs. 60.2%; difference, −16.3% [CI, −30.5 to −2.0];

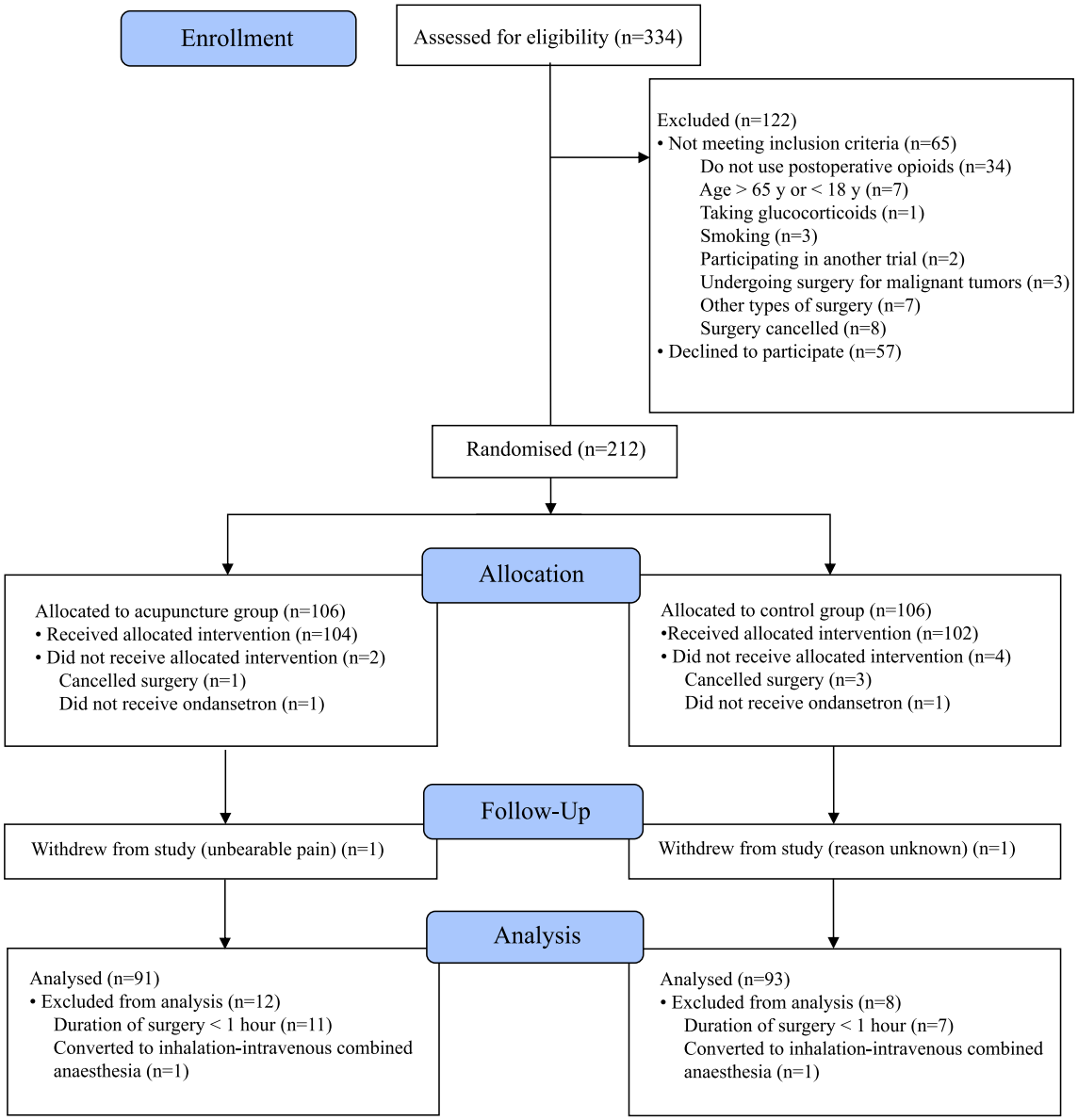

FIGURE 1 The flow chart.

risk ratio, 0.73 [CI, 0.55–0.97]; $p = 0.03$) but not vomiting (combination group vs. ondansetron group: 27.5% vs. 23.7%; difference, 3.82 [CI, −8.78–16.41]; risk ratio, 1.16 [CI, 0.71–1.90]; $p = 0.67$) was lower in the combination group.

In different follow-up time periods, no significant differences in the incidence of PON, POV, or PONV were detected between the two groups (0–6, 6–24, and 24–48 h) (Table 2). A between group difference of −13.2% (CI, −27.4–1.0, $p = 0.07$) was observed in the incidence of PONV and PON 6 h after surgery, but was insignificant. Similarly, the number of new patients with the onset of PONV in different follow-up time periods was lower in the combination group, but the difference was not significant either (Table 2). The credibility and expectancy of participants, the number of episodes of vomiting, mean dosage of analgesics used, mean time to first exhaustion after surgery, and usage of rescue antiemetics were similar between the groups. No differences were found in the visual analogue scales with respect to the severity of PON, severity of postoperative pain, and satisfaction on PONV management between the two groups throughout the study period (Table 2). There was no evidence that the incidence of PONV within 24 h in the combination group differed in subgroup analyses (Figure 2).

A total of 16 AEs were reported, no significant between-group difference was observed. Acupuncture-related AEs were reported in one patient (pain at acupoint after treatment) but were mild and self-limiting. No serious AEs occurred in either group (Table 3).

DISCUSSION

This randomised, controlled clinical trial demonstrated that the combination of acupuncture with ondansetron is more effective than the latter alone in reducing the incidence of PONV in highly

TABLE 1 Baseline characteristics of participants in the modified intention-to-treat (mITT) analysis.

	Combination group (n = 91)	Ondansetron group (n = 93)	Total (n = 184)
Age (years): *n* (%)			
<50	61 (67·0)	68 (73·1)	129 (70·1)
50–65	30 (33·0)	25 (26·9)	55 (29·9)
Mean (SD)	41·9 (12·4)	43·6 (9·9)	42·7 (11·2)
Range	(18·0, 64·0)	(23·0, 64·0)	(18·0, 64·0)
Race: *n* (%)			
Han	89 (97·8)	84 (90·3)	173 (94·0)
Others	2 (2·2)	9 (9·7)	11 (6·0)
Education years: Mean (SD)	14·5 (3·3)	14·2 (3·6)	14·4 (3·5)
BMI: Mean (SD)	23·6 (3·9)	23·6 (3·7)	23·6 (3·8)
History of acupuncture: *n* (%)			
Yes	35 (38·5)	27 (29·0)	62 (33·7)
No	56 (61·5)	66 (71·0)	122 (66·3)
Comorbidity: *n* (%)			
Yes	26 (28·6)	21 (22·6)	47 (25·5)
No	65 (71·4)	72 (77·4)	137 (74·5)
History of PONV and/or motion sickness: *n* (%)			
Yes	54 (59·3)	52 (55·9)	106 (57·6)
No	37 (40·7)	41 (44·1)	78 (42·4)
ASA grade: *n* (%)			
PI normal healthy patient	7 (7·7)	8 (8·6)	15 (8·2)
P2 mild systemic disease	84 (92·3)	85 (91·4)	169 (91·8)
Apfel risk score: *n* (%)			
3	38 (41·8)	41 (44·1)	79 (42·9)
4	53 (58·2)	52 (55·9)	105 (57·1)
CEQ score, mean (SD)			
Credibility	0·16 (2·29)	−0·06 (2·73)	..
Expectancy	0·24 (2·39)	−0·02 (2·95)	..
Surgical site: *n* (%)			
Ovary	17 (18·7)	18 (19·4)	35 (19·0)
Oviduct	1 (1·1)	0 (0·0)	1 (0·5)
Uterus	9 (9·9)	13 (14·0)	22 (12·0)
Ovary and oviduct	14 (15·4)	12 (12·9)	26 (14·1)
Ovary and uterus	9 (9·9)	9 (9·7)	18 (9·7)
Oviduct and uterus	10 (11·0)	22 (23·7)	32 (17·3)
Ovary, oviduct and uterus	31 (34·1)	19 (20·4)	50 (27·2)
Surgery time (min): *n* (%)			
60–120	76 (83·5)	84 (90·3)	160 (87·0)
>120	15 (16·5)	9 (9·7)	24 (13·0)
Mean (SD)	91·0 (31·2)	86·3 (23·9)	88·7 (27·8)
Range	(60·0, 205·0)	(60·0, 160·0)	(60·0, 184·0)

(Continues)

TABLE 1 (Continued)

	Combination group (n = 91)	Ondansetron group (n = 93)	Total (n = 184)
Extubation time (min): Mean (SD)	19·2 (13·8)	19·5 (11·0)	19·4 (12·4)
Duration of PACU stay (min): Mean (SD)	57·3 (17·2)	44·0 (12·3)	50·6 (16·3)

Abbreviations: ASA, American Society of Anaesthesiologists; CEQ, credibility expectancy questionnaire.

TABLE 2 Primary and secondary outcomes.

	Combination group (n = 91)	Ondansetron group (n = 93)	Risk ratio (95% CI)	Difference in risk (%) or means (95% CI)	p value
Primary outcome: *n* (%)					
Incidence of PONV from 0 to 24 h	40 (44·0)	56 (60·2)	0·73 (0·55, 0·97)	−16·3 (−30·5, −2·0)	0·03
Incidence of PONV from 0 to 24 h[a]	46 (44·2)	60 (58·3)	0·76 (0·58, 0·99)	−14·0 (−27·5, −0·5)	0·04
Secondary outcomes: *n* (%)					
Incidence of PONV					
0–6 h	33 (36·3)	46 (49·5)	0·73 (0·52, 1·03)	−13·2 (−27·4, 1·0)	0·07
6–24 h	35 (38·5)	38 (40·9)	0·94 (0·66, 1·34)	−2·4 (−16·5, 11·7)	0·74
24–48 h	12 (13·2)	20 (21·5)	0·61 (0·32, 1·18)	−8·3 (−19·2, 2·6)	0·14
Onset of PONV					
0–6 h	33 (36·3)	46 (49·5)	0·73 (0·52, 1·03)	−13·2 (−27·4, 1·0)	0·07
6–24 h	7 (12·1)	10 (21·3)	0·57 (0·23, 1·38)	−9·2 (−23·6, 5·2)	0·20
24–48 h	5 (9·8)	3 (8·1)	1·21 (0·31, 4·75)	−1·7 (−13·7, 10·3)	1·00
Incidence of nausea					
0–24 h	40 (44·0)	56 (60·2)	0·73 (0·55, 0·97)	−16·3 (−30·5, −2·0)	0·03
0–6 h	33 (36·3)	46 (49·5)	0·73 (0·52, 1·03)	−13·2 (−27·4, 1·0)	0·07
6–24 h	33 (36·3)	37 (39·8)	0·91 (0·63, 1·32)	−3·5 (−17·5, 10·5)	0·74
24–48 h	12 (13·2)	19 (20·4)	0·65 (0·33, 1·25)	−7·2 (−18·0, 3·5)	0·14
Incidence of vomiting					
0–24 h	25 (27·5)	22 (23·7)	1·16 (0·71, 1·90)	3·82 (−8·78, 16·41)	0·55
0–6 h	15 (16·5)	14 (15·1)	1·10 (0·56, 2·14)	1·43 (−9·10, 11·96)	0·79
6–24 h	22 (24·2)	16 (17·2)	1·41 (0·79, 2·50)	7·0 (−4·7, 18·6)	0·24
24–48 h	3 (3·3)	2 (2·2)	1·53 (0·26, 8·96)	1·2 (−3·6, 5·9)	0·68
Severity of nausea, VAS: Mean (SD)[b]					
0–6 h	5·64 (2·96)	5·43 (3·14)	..	0·2 (−1·2, 1·6)	0·77
6–24 h	6·09 (3·18)	5·00 (3·12)	..	1·1 (−0·4, 2·6)	0·15
24–48 h	4·67 (2·90)	3·68 (2·67)	..	1·0 (−1·1, 3·1)	0·34
Number of episodes of vomiting: *M* (P25, P75)[c]					
0–6 h	1·0 (1·0, 1·0)	1·0 (1·0, 1·0)	..	..	0·30
6–24 h	2·0 (1·0, 3·0)	1·5 (1·0, 2·0)	..	..	0·32
24–48 h	1·0 (1·0, 2·0)	1·5 (1·0, 2·0)	..	..	>0·99

TABLE 2 (Continued)

	Combination group (n = 91)	Ondansetron group (n = 93)	Risk ratio (95% CI)	Difference in risk (%) or means (95% CI)	p value
Severity of pain, VAS: Mean (SD)					
0–6 h	5·2 (2·6)	5·1 (2·5)	..	0·01 (−0·7, 0·8)	0·97
6–24 h	4·1 (2·4)	3·9 (2·6)	..	0·2 (−0·6, 0·9)	0·64
24–48 h	3·2 (2·2)	3·1 (2·5)	..	0·1 (−0·6, 0·8)	0·75
Use of postoperative opioids, μg: M (P25, P75)					
0–6 h	12·0 (12·0, 13·0)	12·0 (11·0, 13·0)	..	..	0·91
6–24 h	36·0 (29·0, 36·0)	36·0 (30·5, 36·0)	..	..	0·47
Use of rescue medicine: n (%)					
0–6 h	3 (3·3)	5 (5·4)	0·61 (0·15, 2·49)	−2·08 (−7·95, 3·79)	0·49
6–24 h	10 (11·0)	5 (5·38)	0·46 (0·15, 1·40)	5·6 (−2·3, 13·5)	0·16
24–48 h	0 (0·0)	1 (1·08)	1·01 (0·99, 1·03)	−1·2 (−3·2, 1·0)	>0·99
Time to first exhaust, min: M (P25, P75)	1385·0 (1157·3, 1724·3)	1387·0 (1082·5, 1704·0)	..	..	0·77
Patient satisfaction score: M (P25, P75)					
0–24 h	10·0 (7·0, 10·0)	9·0 (7·0, 10·0)			0·22
24–48 h	10·0 (8·0, 10·0)	10·0 (8·0, 10·0)	..	..	0·84

[a]Sensitivity analysis.

[b]In patients who had nausea.

[c]Average episode for each patient who had vomiting.

susceptible patients. Specifically, compared with ondansetron alone, acupuncture combined with ondansetron was more effective in preventing postoperative nausea, but not postoperative vomiting. Our study also showed that this combination is a safe modality which did not increase the risk of adverse events.

The latest consensus guideline suggested that multimodal prevention strategies should be implemented in routine clinical practice to avoid inadequate prophylaxis in moderate- to high-risk patients. However, new preventive modalities that differ from those currently in use are needed since the risk of PONV remains high in surgical patients with three or four risk factors.[8,23] The evidence on the combination of antiemetic drugs for PONV prevention is robust, but the fear of possible drug-related adverse effects, such as hypotension, extrapyramidal effects, and prolongation of the QT interval, might be part of the reasons why many patients do not receive sufficient PONV prophylaxis.[24–27] Acupuncture as a nonpharmacological approach has been proven to be effective in preventing PONV.[7,17,28] Some studies also showed that acupoint stimulation or acupoint injection in combination with antiemetic drugs could lead to a further reduction in PONV incidence,[29–31] but the quality of evidence remains very low according to the latest Cochrane review and consensus guidelines. Besides, few acupuncture studies have focused on high risk patients, and to the best of our knowledge, no study to date has investigated the combination of acupuncture and antiemetic drugs as a multimodal prevention strategy in patients at high-risk of PONV.

In our study, we identified and enrolled patients at high-risk of PONV using the Apfel simplified risk score, and a 16.3% absolute risk reduction (relative risk reduction: 26.9%, NNT: 6.2) of PONV rate was observed in the combination group 24 h postoperatively. For patients with different baseline risks for PONV, acupuncture combined with ondansetron delivered a further relative risk reduction of 17.8% in patients with three Apfel risk factors and 32.7% in those with four within 24 h after surgery when compared with ondansetron alone. These results were in agreement with previous studies that one preventative modality could reduce the incidence of PONV by about 20–26% and confirmed that acupuncture was as effective as well-established antiemetics.[7,17,32] Notably, the results of subgroup analysis showed that in patients with four risk factors, the relative risk reduction was as high as 32.7%, suggesting that acupuncture is more effective in patients with higher risks. However, since few studies have investigated the effect of acupuncture in high-risk patients or compared the effect among patients at different risks, this finding needs to be validated in future trials. In a previous meta-analysis, Som et al. found that dexamethasone combined with a 5-Hydroxytryptamine type 3 (5-HT3) receptor antagonist had a better effect in PONV preventing than the 5-HT3 antagonist alone, with the number needed to treat at 6.6 in 24 h postoperatively.[33] Our result also showed that the acupuncture-ondansetron combination had a similar effect (NNT = 6.2), supporting previous research that acupuncture combined with antiemetic had a prophylactic effect similar to the combination of different antiemetic drugs.[30] As with

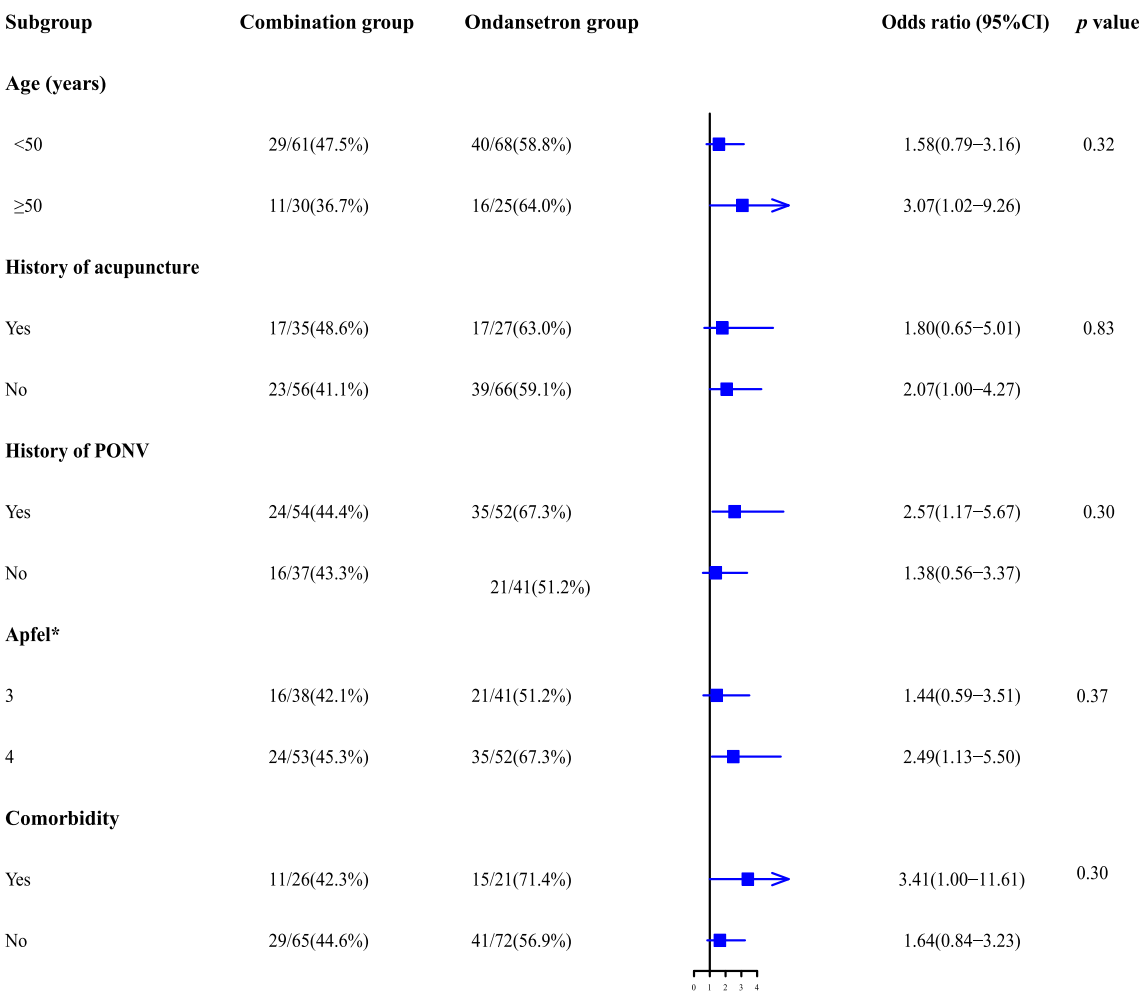

FIGURE 2 Forest plot of subgroup analysis. Predefined subgroup analyses were conducted using a logistic regression model including the interaction of group and subgroup actors to examine incidence or PONV within 24 h postoperative for history of acupuncture, history of PONV and/or motion sickness, had comorbidity or not, age, and Apfel score. PONV, postoperative nausea and vomiting. *Higher score indicates higher baseline risk of PONV.

TABLE 3 Adverse events in the two groups, *n* (%).

	Combination group (*n* = 91)	Ondansetron group (*n* = 93)	*p* value
Pain at acupoints after treatment	1 (1·1)	0 (0·0)	0·50
Abdominal pain	3 (3·3)	2 (2·2)	0·68
Stomach ache	1 (1·1)	0 (0·0)	0·50
Skin rash	2 (2·2)	4 (4·3)	0·68
Sharp pain at surgical wound	0 (0·0)	2 (2·2)	0·50
Periodic low heat	1 (1·1)	0 (0·0)	0·50
Total	8 (8·8)	8 (8·6)	>0·99

many studies,[17,34,35] treatment-related AEs of acupuncture were minor and self-limiting in our study. Though the direct head to head comparisons between acupuncture in combination with drugs and drug combinations are rare, but with a relative reduction of PONV similar to antiemetics and less adverse events, the acupuncture-antiemetic multimodal prophylaxis regimen might be a promising alternative in future clinical practice.

No significant differences in the incidence of PONV were found in different follow-up time periods; we speculate that this may be because the incidence of PONV naturally decreases over time, and the sample size calculated for the primary outcome was underpowered for these secondary outcomes. In addition, patients in the combination group of our study received two 30-min sessions of manual acupuncture, as acupuncture has a dose-dependent effect,[36] the antiemetic effect of the combination group might be better if we prolong the duration and/or increase the number of treatment sessions, but this hypothesis also needed to be tested in future research. Nevertheless, the PONV rate was 13.2% lower in the combination group when compared with ondansetron group in 6 h post-surgery, and the post-hoc analysis revealed that new patients with the onset of PONV in 6–24 h after surgery was 9.2% lower in the combination group, suggesting that acupuncture is effective in both the early and

late postoperative period. A recent trial also showed that acupuncture is effective in reducing PONV incidence at both 6 and 24 h after operation.[37]

Given that few patients vomit without experiencing nausea, the result of PON was the same as the PONV result; the acupuncture-ondansetron combination had an anti-nausea effect when compared with ondansetron alone, but failed to demonstrate a significant decrease in the incidence of vomiting. This supported previous finding which showed that acupuncture was more effective in reducing nausea than in decreasing vomiting and retching.[9,13,38] However, since there have been few studies investigating the effect of combining acupuncture and antiemetic drugs, further research is needed to investigate the possible underlying mechanisms.

This study was open-labelled and a sham acupuncture control was not employed, though we blinded other investigators including the anaesthetists, outcome assessors and statisticians throughout the trial to minimise the risk of bias, a possible placebo effect on the findings cannot be excluded. This design was chosen for the following considerations: the beneficial effect of acupuncture over sham acupuncture for PONV prophylaxis has been well-established,[7] and we intended to focus primarily on the overall effect of acupuncture-drug combination over the antiemetic drug alone. Since eligible placebo control and blinding remain common methodological problems in clinical studies involving nonpharmacologic therapy,[38,39] and acupuncture is a highly complex intervention which placebo effect is an inherent component of its overall therapeutic effects,[40,41] we decided not to perform sham acupuncture in the monotherapy group. Although the active control group used in our study cannot exclude the placebo effect of acupuncture, it is a standard antiemetic care that is widely used in clinical practice.[7] Moreover, treatments are inevitably accompanied by a placebo effect, and it is the overall effect of the treatment that is important to the patient. Therefore, our study design still provides valuable information on the practical use of acupuncture.

Though the prophylactic effect of acupuncture was investigated, as discussed above, the mechanisms are not completely understood. PONV is a complex physiologic phenomenon involving central and peripheral receptor mechanisms, and multiple neurophysiologic pathways.[42] Studies have suggested that the mechanisms of acupuncture in reducing the incidence of PONV might probably involve a serotonin transmission change or an effect on beta-endorphin release in the cerebrospinal fluid.[43]

Our trial has several limitations. First, as few previous studies used manual acupuncture or tested the combination effect of acupuncture and ondansetron, the sample size calculation in our study was based on a previous study that had a different design.[9] Therefore, our trial may have resulted in inaccurate effect size estimates, and the 95% CI of the primary outcome was wide. A larger population is needed to validate our results and to gain a more accurate effect size estimate. Second, as discussed above, we did not use a sham acupuncture control because we planned to evaluate the overall effect of acupuncture combined with a commonly used antiemetic drug in clinical practice. Third, we did not conduct a longer follow-up. Nevertheless, 48 h postoperatively is a typical duration for studies for PONV as most PONV occurs within this time period.[44,45] Finally, patients in our study all received gynaecological surgeries, thus may limit the generalisability of the findings to other populations.

CONCLUSION

In summary, acupuncture in combination with ondansetron as a multimodal prophylaxis approach may decrease the incidence of PONV in high-risk patients. Particularly, acupuncture combined with ondansetron was more effective in preventing postoperative nausea but not postoperative vomiting compared with ondansetron alone. This trial provides relatively high-quality evidence for guideline recommendations and clinical practice. Future research is needed to confirm the results based on a larger sample size and to evaluate the generalisability of the results to other populations.

AUTHOR CONTRIBUTIONS

Cunzhi Liu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Shiyan Yan: Conceptualisation, Data curation, Formal analysis, methodology, software, writing – review and editing. Mingjun Xu: Conceptualisation, Resources, Supervision, Writing – review and editing. Xuan Zou: Conceptualisation, Data curation, Investigation, Writing – review and editing. Zhiyi Xiong: Investigation, Writing – original draft. Hewen Li: Investigation, Writing – review and editing. Jingwen Yang: Resources, Writing – review and editing. Wenchao Cao: Investigation, Resources, Writing – review and editing. Ziqiong Zhu: Resources, Writing – review and editing. Cunzhi Liu: Conceptualisation, Funding acquisition, Project administration, Resources, Supervision, Writing – review and editing. All authors reviewed the final manuscript and approved the final manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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