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The Impact of Intraoperative Active Warming on Postoperative Nausea and Vomiting: A Pre-specified and Exploratory Analysis of a Dual-Center, Prospective Randomized Controlled Trial

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Abstract

Background

Postoperative nausea and vomiting are common after noncardiac surgery. This study evaluated whether intraoperative active warming reduces the risks of postoperative nausea and vomiting and severe postoperative nausea and vomiting within 24 hours after surgery, and explored whether intraoperative core temperature change mediates this effect.

Methods

In this dual-center, prospective randomized controlled trial, 974 adults undergoing hepatobiliary, urologic, gastrointestinal, or thyroid surgery at Qingdao Municipal Hospital and Yantai Yuhuangding Hospital between August 15, 2023, and August 31, 2024, were randomly assigned to passive warming or active warming. Outcomes were analyzed by intention-to-treat and per-protocol principles. Multivariable logistic regression identified factors associated with postoperative nausea and vomiting. Mediation analysis examined whether intraoperative core temperature change explained the treatment effect.

Results

In the intention-to-treat population, postoperative nausea and vomiting within 24 hours occurred in 55 of 487 patients (11.29%) in the active warming group and 110 of 487 (22.59%) in the passive warming group (relative risk 0.50; 95% confidence interval 0.37–0.67; $P < 0.001$). Severe postoperative nausea and vomiting occurred in 18 (3.70%) versus 44 (9.03%) patients (relative risk 0.41; 95% confidence interval 0.24–0.70; $P < 0.001$). Per-protocol analyses were consistent. Active warming was associated with a smaller decline in intraoperative core temperature. Female sex, coronary artery disease, and higher intraoperative sufentanil dose were associated with higher risk. A smaller decline in core temperature was associated with lower risk. Mediation analysis suggested partial mediation by intraoperative core temperature change, but these findings are hypothesis-generating.

Conclusions

Intraoperative active warming reduced the risks of postoperative nausea and vomiting and severe postoperative nausea and vomiting within 24 hours after noncardiac surgery. Attenuation of the intraoperative decline in core temperature may partially contribute to this benefit.

Trial registration:

Chinese Clinical Trial Registry, ChiCTR2300074633, 2023-08-11, prospectively registered.

1. Introduction

Postoperative nausea and vomiting (PONV) is among the most common and distressing complications following anesthesia and surgery. It substantially compromises the quality of recovery, prolongs hospitalization, and increases healthcare costs; therefore, its prevention and management are essential components of high-quality perioperative care. Without prophylactic measures, PONV occurs in approximately 20%–30% of patients, with an incidence of up to 80% among those at high risk[1].

Postoperative nausea (PON) is defined as the subjective sensation of an urge to vomit after surgery. Postoperative vomiting (POV) refers to the forceful expulsion of gastric contents through the mouth, with retching generally included within this outcome. PONV encompasses postoperative nausea and/or vomiting. Complete response, a composite endpoint, is defined as the absence of vomiting or retching and no requirement for rescue antiemetic medication during a prespecified postoperative time window.

Previous clinical studies have suggested that opioid-free anesthesia and acupoint application therapy may reduce the incidence of PONV. In contrast, intraoperative hypotension, intraoperative hypothermia, a history of gastrointestinal surgery, greater opioid consumption, and longer surgical duration have been identified as independent risk factors for PONV[1,2].

Optimizing PONV management is therefore an important aspect of improving the quality of perioperative care. Previous studies have demonstrated that preoperative prewarming and intraoperative active warming using forced-air warming systems and warming blankets can effectively reduce the incidence of intraoperative hypothermia[3–7].Accordingly, this dual-center, prospective randomized controlled trial aimed to evaluate the effect of intraoperative active warming on the risks of PONV and severe PONV within 24 h after noncardiac surgery. We further explored whether intraoperative core temperature change might contribute to the association between active warming and a reduced risk of PONV.

2. Methods

2.1 Study standardization and participant enrollment

This dual-center, prospective, randomized controlled trial was prospectively registered with the Chinese Clinical Trial Registry before enrollment of the first participant.A uniform study protocol was implemented at both participating centers. The same standard operating procedures were followed for anesthetic induction and maintenance, intraoperative temperature management, postoperative care, the timing and scoring criteria of PONV assessments, and rescue antiemetic treatment. Before study initiation, personnel involved in anesthesia, nursing care, PONV assessment, and rescue antiemetic administration received standardized training to minimize intercenter differences in clinical practice and outcome assessment.

On the day before surgery, a researcher assessed each potential participant for eligibility according to the predefined inclusion and exclusion criteria. Eligible participants provided written informed consent

after receiving detailed information regarding the study procedures and potential benefits and risks. Enrolled patients were then randomly assigned to either the active warming group (group T) or the passive warming group (group C).

2.2 Warming interventions

In the active warming group, nonsurgical areas of the body were covered with a forced-air warming blanket. The warming unit was initially set to 43°C, and the temperature setting was subsequently adjusted according to changes in core temperature, skin condition, and patient safety. The intervention was intended to maintain a core temperature of at least 36.0°C while preventing the temperature from exceeding 37.5°C. All intravenous fluids were warmed to approximately 37°C using a fluid-warming device before administration.

In the passive warming group, neither prewarming nor active warming devices were used before or during surgery. Passive insulation was provided using an unheated insulating blanket and cap.

All patients entered the operating room after fasting for at least 8 h. The ambient temperature was maintained at 22–25°C in the preoperative holding area and the post-anesthesia care unit (PACU), and at 21–24°C in the operating room.

2.3 Core temperature monitoring

Core temperature was monitored using a nasopharyngeal temperature probe. Baseline nasopharyngeal temperature was recorded before anesthetic induction, followed by measurements at 5-min intervals throughout surgery. The final nasopharyngeal temperature was recorded at the end of surgery.

Intraoperative core temperature change was defined as the lowest intraoperative nasopharyngeal temperature minus the preinduction nasopharyngeal temperature. A more negative value indicated a greater decline in core temperature, whereas a value closer to zero or a positive value indicated better maintenance of core temperature.

2.4 PONV prophylaxis and rescue treatment

To avoid potential interference of prophylactic antiemetics with the primary outcome, prophylactic antiemetic medication was not routinely administered during the study. If PONV occurred, ondansetron was administered as rescue treatment according to the prespecified protocol. The use of any other antiemetic medication for clinical indications was recorded.

2.5 Anesthetic management

Standard intraoperative monitoring included electrocardiography, noninvasive blood pressure measurement, pulse oximetry, and bispectral index (BIS) monitoring. Systolic blood pressure (SBP) and heart rate (HR) were recorded before anesthetic induction. In both groups, anesthesia was induced with intravenous propofol (2 mg/kg), sufentanil (0.5 μg/kg), and rocuronium (0.6 mg/kg). During mechanical

ventilation, the respiratory rate was adjusted according to the end-tidal carbon dioxide concentration to maintain an end-tidal carbon dioxide level of 30–35 mmHg throughout surgery.

2.6 Analysis populations and protocol deviations

The primary efficacy analysis was conducted in the intention-to-treat (ITT) population, which included all randomized patients analyzed according to their original group assignments. Patients who crossed over to the alternative intervention remained in their originally assigned groups for the ITT analysis. The per-protocol (PP) analysis excluded patients with major protocol deviations, intervention crossover, transfer to the intensive care unit, refusal of follow-up, or non-evaluable primary outcome data.

Patients randomized to the passive warming group were not informed of their group allocation. If a patient assigned to this group requested active warming before anesthetic induction, active warming was provided for ethical reasons and to ensure patient comfort. These patients remained in the passive warming group for the ITT analysis but were excluded from the PP analysis as intervention crossovers.

For patients with missing primary outcome data who could not be contacted for follow-up, the absence of PONV was imputed in the ITT analysis according to the prespecified rule. Because this approach could underestimate the incidence of PONV, a supplementary PP sensitivity analysis was performed to assess the robustness of the primary findings with respect to protocol deviations and the handling of patients with non-evaluable outcome data.

2.7 Reporting guideline

This study was reported in accordance with the CONSORT 2010 statement.

3. Outcome Measures

The primary outcome was the cumulative incidence of PONV within the first 24 h after surgery. Events occurring during the PACU stay were included in this cumulative 24-h assessment. PONV was assessed using a four-point scale: 0, no nausea; 1, nausea; 2, retching; and 3, vomiting. A score of ≥ 1 was considered indicative of PONV, and patients with a score of ≥ 1 received ondansetron as rescue antiemetic therapy.

The secondary outcomes were the cumulative incidence of severe PONV within 24 h after surgery and intraoperative core temperature change. Severe PONV was defined as more than three episodes of vomiting within 24 h after surgery. Intraoperative core temperature change was calculated as the lowest intraoperative core temperature minus the preinduction core temperature.

4. Statistical Analysis

The sample size was estimated using PASS, version 11.0. Based on preliminary pilot data from our research group, the incidence of PONV within 24 h after surgery was approximately 20.0% in the passive warming group. Active warming was expected to reduce the incidence to 12.6%, corresponding to an

absolute risk reduction of 7.4 percentage points and a relative risk reduction of approximately 37%. With a two-sided α of 0.05, a statistical power (1 − β) of 0.80, and a 1:1 allocation ratio, approximately 780 evaluable patients were required. Allowing for an estimated 20% loss due to attrition, intervention crossover, protocol deviations, or non-evaluable data, the planned sample size was 974 patients, with 487 patients in each group.

All statistical analyses were performed using SPSS, version 27.0. Continuous variables were summarized as the mean ± standard deviation or median (interquartile range), depending on their distributions. Between-group comparisons were performed using the independent-samples *t* test or Mann–Whitney *U* test, as appropriate. Categorical variables were presented as numbers and percentages and compared using the χ^2 test or Fisher's exact test, as appropriate. Treatment effects for the primary outcomes were reported as risk ratios (RRs), absolute risk reductions (ARRs), numbers needed to treat (NNTs), and their corresponding 95% confidence intervals (CIs). All statistical tests were two-sided, and a *P* value < 0.05 was considered statistically significant.

The mediation analysis was exploratory and was performed using the PROCESS macro for SPSS, version 5.0 (Model 4). Direct and indirect effects and their 95% CIs were estimated using 5,000 bootstrap resamples.

A multivariable logistic regression model was constructed with PONV as the dependent variable. After adjustment for covariates including sex and intraoperative opioid consumption, intraoperative core temperature change—calculated as the lowest intraoperative nasopharyngeal temperature minus the preinduction nasopharyngeal temperature—was entered into the model as a continuous independent variable. The adjusted odds ratio and corresponding 95% CI for each 1°C increase in intraoperative core temperature change were calculated.

5. Results

5.1 Participant Enrollment and Group Allocation

Between 2023-08-15 and 2024-08-31, 974 patients undergoing noncardiac surgery were enrolled and randomly assigned in a 1:1 ratio to the passive warming group (group C; *n* = 487) or the active warming group (group T; *n* = 487). The computer-generated randomization sequence was created using SPSS, version 27.0.

The randomization sequence was generated by a researcher who was not involved in participant recruitment, intervention delivery, or outcome assessment and was stratified by study center. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes, which were opened by designated research personnel after patient enrollment. Owing to the nature of the active warming intervention, the attending anesthesiologists could not be blinded to group allocation. However, PACU nurses, postoperative follow-up assessors, and statistical analysts remained blinded to group allocation.

Randomization was performed after the preoperative assessment. Nevertheless, surgery was postponed in some patients on the day of surgery because of unexpected conditions, such as a newly developed febrile infection or an acute elevation in blood pressure. Because these patients did not undergo surgery according to the original schedule, they were excluded from the per-protocol analysis. After their conditions had been adequately controlled, surgery was rescheduled; the patients retained their original treatment assignments and were included in the intention-to-treat analysis.

In group T, 16 patients did not complete the study or were excluded from the PP population: 4 had inadequately controlled preoperative infections, 5 had inadequately controlled preoperative blood pressure, 3 developed new infections before surgery, 1 was transferred to the intensive care unit (ICU) because of inadequate emergence from anesthesia, and 3 were transferred to the ICU because of excessive intraoperative bleeding.

In group C, 38 patients did not complete the study or were excluded from the PP population: 6 had inadequately controlled preoperative infections, 5 had inadequately controlled preoperative blood pressure, 6 developed new infections before surgery, 3 participants were found to have newly identified impaired cardiac function during the final preoperative reassessment after randomization., 7 requested active warming before anesthetic induction, 6 were transferred to the ICU because of inadequate emergence from anesthesia, 4 were transferred to the ICU because of excessive intraoperative bleeding, and 1 participant declined further study follow-up after completion of the 24-hour primary outcome assessment..The primary outcome was available for all 974 randomized participants, including those who discontinued the allocated intervention. All participants were analyzed according to their randomized group.

All 974 randomized patients were retained in the ITT population and analyzed according to their original group assignments. The PP population comprised 920 patients, including 449 in group C and 471 in group T. This final PP sample size remained sufficient according to the a priori sample size calculation performed using PASS. The participant flow diagram is presented in Fig. 1.

5.2 Baseline Characteristics of the Two Groups

The baseline characteristics of the PP population are presented in Table 1. The median age was 65 years (interquartile range [IQR], 58–71) in group C and 67 years (IQR, 57–72) in group T, with no significant between-group difference ($Z = -1.070$, $P = 0.283$). The groups were also generally similar in terms of sex distribution, body mass index (BMI), type and duration of surgery, preinduction core temperature, and histories of hypertension and diabetes mellitus (all $P > 0.05$).

Specifically, group C comprised 250 men and 199 women, whereas group T comprised 244 men and 227 women. The sex distribution did not differ significantly between the groups ($\chi^2 = 1.388$, $P = 0.239$). The median BMI was 24.97 kg/m² (IQR, 23.18–26.72) in group C and 24.98 kg/m² (IQR, 23.34–26.66) in group T ($Z = -0.388$, $P = 0.698$).

The numbers of patients undergoing hepatobiliary, urologic, gastrointestinal, and thyroid surgery were 86, 136, 134, and 93, respectively, in group C and 118, 117, 128, and 108, respectively, in group T. The distribution of surgical types did not differ significantly between the groups ($\chi^2 = 7.181$, $P = 0.066$). No significant between-group differences were observed in surgical duration, preinduction core temperature, or the prevalence of hypertension or diabetes mellitus.

Comparison of baseline characteristics between the two groups (PP population) [Median (IQR) or n (%)]

Table 1

Variable	Group C (n = 449)	Group T (n = 471)	t/Z/χ^2	P value
Age (years)	**65 (58, 71)**	**67 (57, 72)**	**-1.070**	**0.283**
Sex			**1.388**	**0.239**
Male	**250 (55.7)**	**244 (51.8)**		
Female	**199 (44.3)**	**227 (48.2)**		
BMI(kg/m²)	**24.97 (23.18, 26.72)**	**24.98 (23.34, 26.66)**	**-0.388**	**0.698**
Type of surgery			**7.181**	**0.066**
Hepatobiliary	**86 (19.2)**	**118 (25.1)**		
Urological	**136 (30.3)**	**117 (24.8)**		
Gastrointestinal	**134 (29.8)**	**128 (27.2)**		
Thyroid	**93 (20.7)**	**108 (22.9)**		
Duration of surgery (h)	**3.00(2.75, 3.50)**	**3.00(3.00, 3.00)**	**-0.981**	**0.327**
Pre-induction temperature (°C)	**36.50(36.30, 36.70)**	**36.50(36.20, 36.90)**	**-1.755**	**0.079**
History of hypertension			**0.466**	**0.495**
Yes	**159 (35.4)**	**177 (37.6)**		
No	**290 (64.6)**	**294 (62.4)**		
History of diabetes			**3.143**	**0.076**
Yes	**73 (16.3)**	**98 (20.8)**		
No	**376 (83.7)**	**373 (79.2)**		

5.3 Primary Outcome

The incidences of PONV and severe PONV within 24 h after surgery are presented in Table 2. Severe PONV was defined as more than three episodes of vomiting within the first 24 h after surgery [1].

In the primary ITT analysis, the cumulative incidence of PONV within 24 h after surgery was significantly lower in the active warming group than in the passive warming group (55/487 [11.29%] vs. 110/487 [22.59%]; RR = 0.50, 95% CI, 0.37–0.67; $P < 0.001$). The absolute risk reduction was 11.30%, corresponding to an NNT of approximately 9. The incidence of severe PONV was also significantly lower in the active warming group (18/487 [3.70%] vs. 44/487 [9.03%]; RR = 0.41, 95% CI, 0.24–0.70; $P < 0.001$).

The PP sensitivity analysis yielded findings consistent with those of the primary ITT analysis. In the PP population, PONV occurred in 103 of 449 patients (22.94%) in the passive warming group and 53 of 471 patients (11.25%) in the active warming group; 346 and 418 patients, respectively, did not experience PONV. The incidence of PONV was significantly lower in the active warming group ($\chi^2 = 22.298$, $P < 0.001$; RR = 0.49, 95% CI, 0.36–0.67). The absolute risk reduction was 11.69%, corresponding to an NNT of approximately 9. Similarly, the incidence of severe PONV was significantly lower in the active warming group than in the passive warming group (18/471 [3.82%] vs. 42/449 [9.35%]; RR = 0.41, 95% CI, 0.24–0.70; $P < 0.001$).

The consistency of the ITT and PP results supports the robustness of the primary findings with respect to the handling of protocol deviations and intervention crossovers. Both analyses indicated that intraoperative active warming reduced the risks of PONV and severe PONV within 24 h after noncardiac surgery.

Table 2
Comparison of 24-hour postoperative PONV and severe PONV between the two groups

ITT	Outcome	Group C n/N (%)	Group T n/N (%)	RR (95% CI)	ARR	NNT	P
	24 h PONV	110/487 (22.59)	55/487 (11.29)	0.50 (0.37–0.67)	11.30%	9	< 0.001
ITT	24h Severe PONV	44/487 (9.03)	18/487 (3.70)	0.41 (0.24–0.70)	5.34%	19	< 0.001
PP	24 h PONV	103/449 (22.94)	53/471 (11.25)	0.49 (0.36–0.67)	11.69%	9	< 0.001
PP	24h Severe PONV	42/449 (9.35)	18/471 (3.82)	0.41 (0.24–0.70)	5.53%	19	< 0.001

5.4 Secondary Outcome

Intraoperative core temperature change was defined as the lowest intraoperative core temperature minus the preinduction core temperature. A more negative value indicated a greater decline in core temperature, whereas a value closer to zero or a positive value indicated better maintenance of core temperature.

Because intraoperative core temperature change was not normally distributed in either group, the groups were compared using the Mann–Whitney *U* test. The median core temperature change was − 0.50°C (IQR, − 1.00 to − 0.30) in group C and − 0.20°C (IQR, − 0.40 to 0.00) in group T. The value was significantly higher—and therefore less negative—in group T than in group C (Z = − 14.522, P < 0.001), indicating that active warming significantly attenuated the intraoperative decline in core temperature among patients undergoing noncardiac surgery (Table 3).

Unless otherwise specified, all subsequent analyses were based on the PP population.

Comparison of the magnitude of core temperature change between the two groups [Median (IQR)]

Table 3

Variable	Group C (n = 449)	Group T (n = 471)	Z	P value
Magnitude of temperature change (°C)	**-0.50 (-1.00, -0.30)**	**-0.20 (-0.40, 0.00)**	**-14.522**	**<0.001**

5.5 Factors Associated With PONV Within 24 Hours

To further investigate factors associated with PONV within 24 h after surgery, a multivariable binary logistic regression model was constructed with the occurrence of PONV within 24 h as the dependent variable. Sex, histories of hypertension, diabetes mellitus, coronary heart disease (CHD), and smoking, intraoperative sufentanil dose, and intraoperative core temperature change were entered as independent variables.

The Hosmer–Lemeshow goodness-of-fit test indicated that the model fitted the data adequately (χ^2 = 3.565, df = 8, P = 0.894). The results of the multivariable logistic regression analysis are presented in Table 4.

Female sex was independently associated with PONV within 24 h. Compared with male patients, female patients had significantly higher odds of developing PONV (OR = 2.100, 95% CI, 1.442–3.059; P < 0.001). A history of CHD was also associated with increased odds of PONV. Patients with a history of CHD had higher odds of PONV than those without such a history (OR = 1.825, 95% CI, 1.055–3.155; P = 0.031).

A higher intraoperative sufentanil dose was associated with increased odds of PONV. For each 1-μg increase in sufentanil dose, the odds of PONV increased by 9.0% (OR = 1.090, 95% CI, 1.058–1.123; P < 0.001).

Intraoperative core temperature change was inversely associated with the odds of PONV. Each 1°C increase in the core temperature change value was associated with 73.7% lower odds of PONV (OR = 0.263, 95% CI, 0.176–0.392; $P < 0.001$). Because positive values indicated an increase in core temperature and negative values indicated a decrease, this finding suggests that a greater intraoperative decline in core temperature was associated with higher odds of PONV within 24 h. Conversely, better maintenance of intraoperative core temperature may be associated with lower odds of PONV.

No statistically significant associations were observed between PONV within 24 h and histories of hypertension, diabetes mellitus, or smoking (all $P > 0.05$).

Table 4

Hosmer-Lemeshow Test

Step	Chi-square	df	P value
1	3.565	8	0.894

Multivariable logistic regression analysis of factors associated with 24-hour postoperative PONV

Variable	β	SE	Waldχ^2	P value	OR	95%CI
Sex (Female vs. Male)	0.742	0.192	14.972	<0.001	2.100	1.442–3.059
History of hypertension (Yes vs. No)	-0.207	0.201	1.069	0.301	0.813	0.548 ~ 1.204
History of diabetes (Yes vs. No)	0.129	0.241	0.288	0.592	1.138	0.710–1.825
History of CHD (Yes vs. No)	0.601	0.279	4.632	0.031	1.825	1.055–3.155
Smoking history (Yes vs. No)	-0.465	0.241	3.720	0.054	0.628	0.392–1.008
Intraoperative sufentanil (μg)	0.086	0.015	31.998	<0.001	1.090	1.058–1.123
Temperature change (°C)	-1.337	0.204	42.984	<0.001	0.263	0.176–0.392
Constant	-5.198	0.795	42.740	<0.001	0.006	

5.6 Exploratory Mediation Analysis

To further explore the potential mechanism underlying the association between active warming and a lower likelihood of PONV within 24 h after surgery, an exploratory mediation analysis was performed. The warming intervention was specified as the independent variable (X: 0 = passive warming and 1 = active warming), the occurrence of PONV within 24 h as the dependent variable (Y: 0 = no PONV and 1 = PONV), and intraoperative core temperature change as the mediator (M). A positive value of M indicated an increase in core temperature, whereas a negative value indicated a decrease.

The analysis was conducted using the PROCESS macro, version 5.0 (Model 4), in SPSS, version 27.0. Because Y was binary, a binary logistic regression model was specified for Y, whereas a linear regression model was used for M. Sex, history of CHD, and intraoperative sufentanil dose were included as covariates to control for potential confounding. Direct and indirect effects and their 95% CIs were estimated using 5,000 bootstrap resamples. An effect was considered statistically significant when its bootstrap CI did not include zero.

The path-analysis results are presented in Table 5. After adjustment for the covariates, the warming intervention remained significantly associated with intraoperative core temperature change. Compared with passive warming, active warming increased the core temperature change value by 0.42°C, indicating a smaller intraoperative decline in core temperature (X→M: coefficient = 0.42, $P < 0.001$). Core temperature change also remained significantly associated with PONV after adjustment for the intervention and covariates (M→Y: logistic regression coefficient = − 1.10, $P < 0.001$). Thus, better maintenance of core temperature, represented by a higher core temperature change value, was associated with lower log odds of PONV.

The direct-effect estimate of active warming on PONV was − 0.50 (95% bootstrap CI, − 0.91 to − 0.08). Because the CI did not include zero, the direct effect was statistically significant. The indirect-effect estimate through intraoperative core temperature change was − 0.47 (95% bootstrap CI, − 0.70 to − 0.27), and its CI also excluded zero, indicating a statistically significant indirect effect.

This mediation analysis was prespecified in the study protocol as an exploratory supplementary analysis to assess whether intraoperative core temperature change might mediate the association between active warming and PONV within 24 h. However, it was not explicitly listed in the clinical trial registration. The findings suggest that the association between active warming and lower odds of PONV may be partially mediated by attenuation of the intraoperative decline in core temperature. Because mediation analysis relies on assumptions including the absence of unmeasured confounding and correct model specification, these results should be interpreted as hypothesis-generating rather than confirmatory evidence of a causal mechanism. The path coefficients among X, M, and Y are illustrated in Fig. 2.

Effect Type	Effect	se	95% LLCI	95% ULCI
Direct effect (X → Y)	-0.50	0.21	-0.91	-0.08
Indirect effect (X → M → Y)	-0.47	0.11	-0.70	-0.27
Note: Confidence intervals that do not contain zero indicate statistical significance.				

Table 5 Bootstrap analysis of direct and indirect effects

6. Discussion

This study evaluated the effect of intraoperative active warming on postoperative nausea and vomiting. Compared with passive warming, active warming significantly reduced the cumulative incidence of PONV within 24 h after surgery as well as the incidence of severe PONV. The primary ITT analysis and PP sensitivity analysis yielded consistent findings, supporting the robustness of the results with respect to the handling of protocol deviations and intervention crossovers. Furthermore, the exploratory mediation analysis suggested that attenuation of the intraoperative decline in core temperature might partially mediate the association between active warming and a lower likelihood of PONV.

Previous studies have shown that perioperative hypothermia is associated with various adverse postoperative outcomes, including shivering, coagulation abnormalities, an increased risk of surgical-site infection, and delayed postoperative recovery. Active warming is widely used to maintain perioperative normothermia and reduce hypothermia-related complications. However, evidence regarding whether active warming can reduce PONV remains limited. Extending previous research on perioperative temperature management, our findings suggest that maintaining a more stable intraoperative core temperature may not only reduce traditional hypothermia-related complications but also be associated with a lower incidence of PONV.

The biological mechanisms underlying the observed reduction in PONV remain uncertain. By attenuating the intraoperative decline in core temperature, active warming may improve thermal comfort and reduce cold-related discomfort and postoperative shivering, which could contribute to better early postoperative recovery[8–11]. However, whether these effects account for the reduction in PONV was not examined in this study. Although experimental and critical-care studies have implicated changes in sympathetic activity, splanchnic perfusion, gastrointestinal function, and serotonergic signaling [12–16], evidence derived from septic shock, animal models of intestinal ischemia–reperfusion, and cellular or pharmacogenomic studies may not be directly applicable to the modest changes in core temperature observed during elective noncardiac surgery. Moreover, we did not assess intestinal perfusion, lactate concentrations, serotonin levels, autonomic function, gastrointestinal motility, inflammatory responses, or oxidative stress. Therefore, the present findings do not support any specific biological pathway, and these potential mechanisms should be regarded as hypotheses requiring evaluation in studies incorporating dedicated mechanistic endpoints.

The exploratory mediation analysis suggested that intraoperative core temperature change might partially mediate the association between active warming and a lower likelihood of PONV within 24 h. This finding provides statistical support for the possibility that attenuation of the intraoperative decline in core temperature contributes to the effect of active warming. Nevertheless, mediation analysis relies on several assumptions, including the absence of unmeasured confounding, correct model specification, and an appropriate temporal sequence between the mediator and outcome. Although this analysis was prespecified in the study protocol, it was not explicitly included in the clinical trial registration. The results should therefore be interpreted as exploratory and hypothesis-generating rather than as confirmatory evidence of a causal mechanism.

From a clinical perspective, PONV adversely affects postoperative comfort, early mobilization, the resumption of oral intake, and patient satisfaction. Current PONV prevention strategies rely primarily on risk assessment and pharmacological antiemetic prophylaxis; however, these measures do not completely eliminate PONV. Active warming is a relatively simple, nonpharmacological, and readily implementable perioperative intervention. Our findings suggest that enhanced intraoperative temperature management may serve as a useful adjunct to multimodal PONV prevention strategies, although it should not replace standard antiemetic prophylaxis.

The primary analysis was conducted according to the ITT principle, with a PP analysis performed as a sensitivity analysis. The closely similar findings of the two analyses support the robustness of the primary conclusion. The study was conducted at two centers that used standardized procedures for anesthesia, nursing care, PONV assessment, and rescue antiemetic treatment. Personnel at both centers also underwent standardized training before study initiation, which helped minimize intercenter differences in clinical practice and outcome assessment. However, center effects and center-by-treatment interactions were not formally modeled. Consequently, the influence of residual center-level differences on the treatment-effect estimates cannot be completely excluded.

This study has several limitations. First, although the mediation analysis was prespecified in the study protocol, it was not explicitly included in the clinical trial registration; its findings should therefore be regarded as exploratory and hypothesis-generating. Second, apart from the PP analysis, no additional sensitivity analyses adjusted for study center or baseline covariates were performed. The potential influence of residual center-level differences or covariate imbalance therefore cannot be entirely excluded. Third, not all established risk factors for PONV were comprehensively captured, including a history of PONV or motion sickness, postoperative opioid consumption, prophylactic antiemetic use, and postoperative pain intensity. Fourth, stress and inflammatory responses, gastrointestinal motility, and emesis-related biomarkers were not directly assessed; therefore, the specific biological mechanisms through which active warming may influence PONV could not be established. Fifth, the small number of patients with missing primary-outcome data were classified as not having experienced PONV in the ITT analysis. This approach may have underestimated the incidence of PONV and introduced bias, although the PP sensitivity analysis yielded findings consistent with those of the ITT analysis.

Finally, the study was conducted at two centers with relatively standardized perioperative practices. The generalizability of the findings to other surgical populations, anesthetic techniques, and healthcare settings therefore requires further investigation.

Future studies should validate these findings in larger, multicenter trials involving more diverse surgical populations. Mediation hypotheses, model specifications, covariate-selection strategies, and planned sensitivity analyses should be explicitly prespecified at the trial-registration stage. Future research should also systematically collect information regarding previous PONV or motion sickness, perioperative opioid exposure, antiemetic use, pain scores, and anesthetic exposure and incorporate mechanistic biomarkers to further elucidate how active warming may influence PONV.

7. Conclusions

In conclusion, compared with passive warming, intraoperative active warming reduced the incidence of PONV and severe PONV within 24 h after noncardiac surgery. The exploratory mediation analysis suggested that attenuation of the intraoperative decline in core temperature might partially account for this association. As a practical, nonpharmacological perioperative intervention, active warming may serve as a useful adjunct to multimodal PONV prevention strategies. Further large-scale, multicenter studies are warranted to confirm these findings and elucidate the underlying mechanisms.

Declarations

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of Yantai Yuhuangding Hospital (approval no. 2023 – 305) and was conducted in accordance with the Declaration of Helsinki. Eligible participants provided written informed consent after receiving detailed information regarding the study procedures and potential benefits and risks.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contribution

Y.J.: conceptualization, data curation, writing – original draft; Q.L. and J.W.: investigation, data curation; C.S. and X.L.: supervision, funding acquisition, writing – review and editing. All authors have read and approved the final version of the manuscript.

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The authors have nothing to report.

References

(1) Gan, T. J.; Jin, Z.; Ayad, S.; Belani, K. G.; Habib, A. S.; Meyer, T. A.; Urman, R. D.; Andrew, B. Y.; Bergese, S. D.; Chung, F.; Diemunsch, P.; Kovac, A. L.; Candiotti, K.; Englesakis, M.; Grant, M. C.; Hedrick, T. L.; Huang, H.; Kranke, P.; Lloyd, S. J.-A.; Manahan, M. A.; Minkowitz, H. S.; Philip, B. K.; Phillips, B. J.; Simpson, K. D.; Stever, J. Fifth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting: Executive Summary. *Anesth. Analg.***2022**, 10.1213/ANE.0000000000007816. https://doi.org/10.1213/ANE.0000000000007816.

(2) Stoops, S.; Kovac, A. New Insights into the Pathophysiology and Risk Factors for PONV. *Best Pract. Res. Clin. Anaesthesiol.***2020**, *34* (4), 667–679. https://doi.org/10.1016/j.bpa.2020.06.001.

(3) Yoo, J. H.; Ok, S. Y.; Kim, S. H.; Chung, J. W.; Park, S. Y.; Kim, M. G.; Cho, H. B.; Song, S. H.; Cho, C. Y.; Oh, H. C. Efficacy of Active Forced Air Warming during Induction of Anesthesia to Prevent Inadvertent Perioperative Hypothermia in Intraoperative Warming Patients: Comparison with Passive Warming, a Randomized Controlled Trial. *Medicine (Baltimore)***2021**, *100* (12), e25235. https://doi.org/10.1097/MD.0000000000025235.

(4) Recio-Pérez, J.; Miró Murillo, M.; Martin Mesa, M.; Silva García, J.; Santonocito, C.; Sanfilippo, F.; Asúnsolo, A. Effect of Prewarming on Perioperative Hypothermia in Patients Undergoing Loco-Regional or General Anesthesia: A Randomized Clinical Trial. *Medicina (Mex.)***2023**, *59* (12), 2082. https://doi.org/10.3390/medicina59122082.

(5) Grote, R.; Wetz, A.; Bräuer, A.; Menzel, M. Short Interruptions between Pre-Warming and Intraoperative Warming Are Associated with Low Intraoperative Hypothermia Rates. *Acta Anaesthesiol. Scand.***2020**, *64* (4), 489–493. https://doi.org/10.1111/aas.13521.

(6) *Effect of preoperative warming on intraoperative hypothermia and postoperative functional recovery in total hip arthroplasty: a randomized clinical trial - Minerva Anestesiologica 2024 January-February;90(1-2):41-50*. https://www.minervamedica.it/en/journals/minerva-anestesiologica/article.php?cod=R02Y2024N01A0041 (accessed 2025-12-13).

(7) Ding, N.; Yang, J.; Wu, C. Comparison of Prewarming plus Intraoperative Warming with Intraoperative Warming Alone in Patients Undergoing Minimally Invasive Thoracic or Abdominal Surgery: A Systematic Review and Meta-Analysis. *PLOS ONE***2024**, *19* (9), e0310096. https://doi.org/10.1371/journal.pone.0310096.

(8) *Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 Genotype and Use of 5-HT3 Receptor Antagonists: 2026 Update - PubMed*. https://pubmed.ncbi.nlm.nih.gov/41979467/ (accessed 2026-06-28).

(9) *Involvement of 5-HT1B/1D receptors in the inflammatory response and oxidative stress in intestinal ischemia/reperfusion in rats - PubMed*. https://pubmed.ncbi.nlm.nih.gov/32574671/ (accessed 2026-06-28).

(10) Pan, W.-T.; Ji, M.-H.; Ma, D.; Yang, J.-J. Effect of Perioperative Autonomic Nervous System Imbalance on Surgical Outcomes: A Systematic Review. *Br. J. Anaesth.***2025**, *135* (3), 608–622. https://doi.org/10.1016/j.bja.2025.06.004.

(11) Haugen, M.; Dammen, R.; Svejda, B.; Gustafsson, B. I.; Pfragner, R.; Modlin, I.; Kidd, M. Differential Signal Pathway Activation and 5-HT Function: The Role of Gut Enterochromaffin Cells as Oxygen Sensors. *Am. J. Physiol. Gastrointest. Liver Physiol.***2012**, *303* (10), G1164-1173. https://doi.org/10.1152/ajpgi.00027.2012.

(12) Cao, S.; Daniels, M.; Hah, J. M.; Hao, D. A&A Pro-Con Debate: Opioid-Free Versus Opioid-Conventional for Patients Undergoing General Anesthesia. *Anesth. Analg.***2026**, *143* (1), 21–26. https://doi.org/10.1213/ANE.0000000000007800.

(13) Habes, Q. L. M.; van Ede, L.; Gerretsen, J.; Kox, M.; Pickkers, P. Norepinephrine Contributes to Enterocyte Damage in Septic Shock Patients: A Prospective Cohort Study. *Shock***2018**, *49* (2), 137–143. https://doi.org/10.1097/SHK.0000000000000955.

(14) Lee, J. M.; Lee, S. H.; Gim, D. H.; Lee, S. Y.; Choi, K. H.; Ahn, J. H.; Hong, Y. J.; Kim, H. K.; Lee, K. Y.; Choo, E. H.; Jeon, K.-H.; Kim, H.; Kang, M. G.; Koh, J.-S.; Joh, H. S.; Park, T. K.; Yang, J. H.; Song, Y. B.; Choi, S.-H.; Gwon, H.-C.; Hahn, J.-Y.; Multicenter FLOW-CMD investigators. Coronary Microvascular Dysfunction and Cardiovascular Outcomes (Multicenter FLOW-CMD Registry): A Prospective, Multicentre Cohort Study in South Korea. *Lancet***2026**, *407* (10545), 2319–2328. https://doi.org/10.1016/S0140-6736(26)00666-5.

(15) Yang, J.; Liao, T.; Luo, J.; Ma, A.; He, J.; Li, H.; Liu, R.; Yu, Y.; Peng, J. Impact of Opioid Free Anesthesia on Postoperative Nausea and Vomiting, Chronic Pain, and Quality of Recovery in Patients Undergoing Video-Assisted Thoracoscopic Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *BMC Anesthesiol.***2026**. https://doi.org/10.1186/s12871-026-04028-y.

(16) Zhang, Y.; Xian, X.; Wang, F.; Zhou, B.; Wang, Y.; Wang, P.; Li, Y.; Wu, Y. Opioid-Free Anesthesia Improved the Quality of Recovery After Thyroidectomy Through Pre-Emptive and Preventive Analgesia: A Randomized Controlled Trial. *Drug Des. Devel. Ther.***2025**, *19*, 5243–5254. https://doi.org/10.2147/DDDT.S520856.

Figures

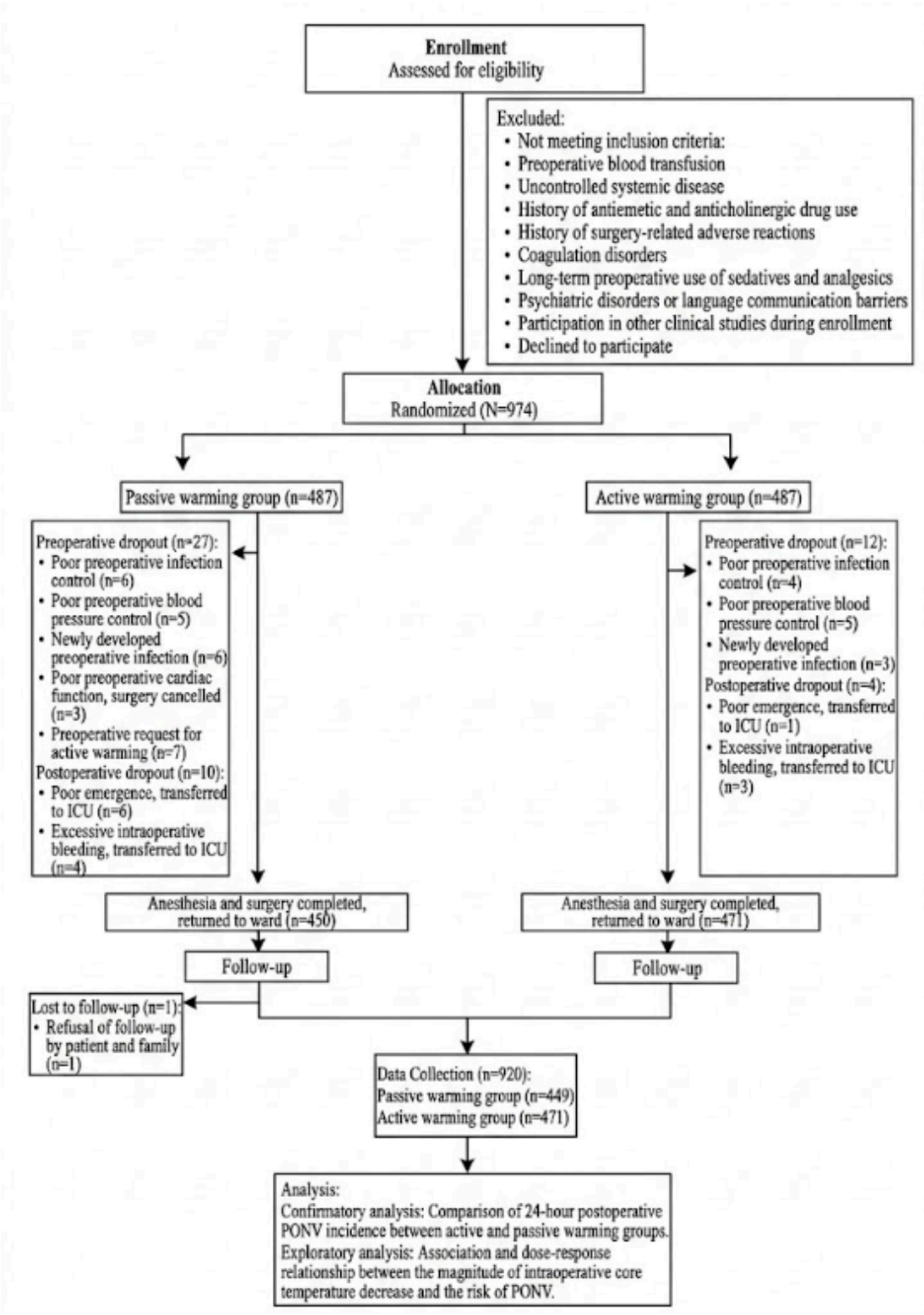
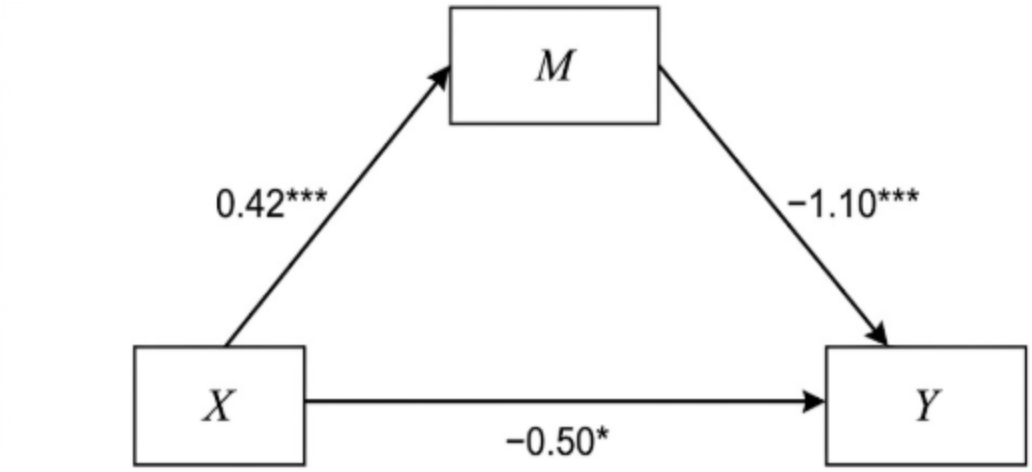


Figure 1

CONSORT Flow Diagram of the Study



Note: Path coefficients are standardized / unstandardized regression coefficients; where, the X→M path is a linear regression coefficient, and the M→Y and X→Y paths are Logit coefficients for Logistic regression.
***$P < 0.001$; **$P < 0.01$; *$P < 0.05$; the same applies hereinafter.

Figure 2

Path diagram for the mediating effect of the magnitude of temperature change (M) between