Original Article

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Effect of Clonidine on Postoperative Nausea and Vomiting in Breast Cancer Surgery: A Double-Blind Randomized Clinical Trial

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Abstract

Introduction: Postoperative nausea and vomiting (PONV) remains among the most common complications after general anesthesia and may delay postoperative recovery. Therefore, the present study evaluated the effects of preoperative oral clonidine versus placebo on PONV among patients undergoing breast cancer surgery.

Methods: This double-blind, randomized, placebo-controlled clinical trial was conducted in 2020 at Faghihi Hospital, Shiraz, Iran. Sixty-eight patients (aged 28–70 years) scheduled for breast cancer surgery were randomized (1:1) using block randomization to receive either oral clonidine (0.2 mg) or an identical placebo 2 h before surgery. The primary outcome was the incidence and severity of PONV during the first 60 min after surgery. Secondary outcomes included perioperative systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and recovery-room duration. Data analysis was conducted using SPSS (version 23.0), and t-test, Mann-Whitney U, Chi-square test, Fisher's exact test and repeated measures ANOVA.

Results: A total of 68 women (n=34 per group) completed the trial. The mean age was 46.62 ± 10.86 years in the clonidine group and 50.47 ± 9.46 years in the placebo group. The proportion of PONV-free patients was higher with clonidine than with placebo (82.35% vs. 61.76%), although the difference was not significant (p=0.05). Clonidine significantly reduced perioperative SBP, DBP, MAP, and HR and shortened recovery-room stay by 16 min (86±27 vs. 102±33 min; p=0.04).

Conclusion: Preoperative oral clonidine did not significantly reduce PONV after breast cancer surgery, although a clinically relevant trend was observed. Clonidine improved perioperative hemodynamic profiles and reduced recovery-room duration. The lack of statistical significance for the primary outcome may reflect limited statistical power, warranting confirmation in larger randomized trials.

Key words: Breast Neoplasms, Clonidine, Hemodynamic monitoring, Nausea and Vomiting, Surgery

Introduction

Cancer remains a major global cause of morbidity and mortality, with an estimated 19.3 million new cancer cases and almost 10 million cancer-related deaths worldwide in 2020 (1). Among malignancies affecting women, breast cancer represents one of the most important public health challenges and continues to impose a substantial clinical and economic burden worldwide (2). Breast cancer is the most commonly diagnosed malignancy among women globally and remains a leading cause of cancer-related mortality in women (3). Over recent decades, the incidence of breast cancer has increased in many regions, partly because of population aging, changes in reproductive and lifestyle-related risk factors, and improved detection (4).

Surgery remains a central component of breast cancer treatment, including breast-conserving surgery, mastectomy, axillary procedures, and reconstructive approaches when clinically indicated (5). General anesthesia is frequently used for breast cancer surgery, and postoperative recovery may be complicated by nausea, vomiting, pain, shivering, hypothermia, respiratory events, and hemodynamic

disturbances (6). Postoperative nausea and vomiting (PONV) is among the most common and distressing complications following anesthesia and surgery and may impair patient comfort and quality of recovery, delay discharge, prolong post-anesthesia care unit stay, and increase the risk of unplanned hospital admission (7). Although the incidence of PONV is approximately 30% in unselected surgical patients, it may reach 80% in high-risk individuals. Female sex, nonsmoking status, a history of PONV or motion sickness, volatile anesthetic exposure, postoperative opioid use, and certain types of surgery are among the most consistently recognized independent risk factors for PONV(6).

Female patients undergoing breast and gynecologic surgery are particularly susceptible to PONV, and recent reviews have emphasized that sex, surgical type, anesthetic technique, and perioperative opioid exposure all contribute to PONV risk. Breast cancer surgery is therefore a clinically relevant high-risk setting for PONV, especially because most patients are female and commonly receive general anesthesia and perioperative opioids (5). The clinical impact of PONV extends beyond patient discomfort, as it can delay oral intake, prolong post-anesthesia care unit stay, increase the need for rescue medication, delay discharge, and reduce patient satisfaction (6).

Current consensus guidelines recommend individualized PONV risk assessment, reduction of modifiable baseline risk factors, and multimodal prophylaxis in patients at moderate or high risk. Despite the availability of established antiemetic agents, including 5-hydroxytryptamine type 3 receptor antagonists, corticosteroids, dopamine antagonists, anticholinergics, and neurokinin-1 receptor antagonists, PONV remains incompletely controlled in many high-risk surgical populations (6). This persistent clinical challenge has encouraged investigation of adjunctive perioperative agents that may reduce PONV indirectly through opioid-sparing, anxiolytic, sympatholytic, sedative, or anesthetic-sparing mechanisms (8).

Clonidine is a centrally acting α2-adrenergic agonist that reduces sympathetic outflow and is associated with sedative, anxiolytic, analgesic-sparing, and hemodynamic effects relevant to perioperative care (9). Since clonidine can reduce anesthetic and opioid requirements and modulate sympathetic responses, it has been investigated as a potential adjunct for improving postoperative recovery and reducing PONV (10).

Evidence regarding the antiemetic efficacy of clonidine remains limited and appears to vary across clinical settings. A recent systematic review and meta-analysis revealed that clonidine premedication reduced postoperative vomiting in selected pediatric surgical populations, particularly after ophthalmic surgery (11); however, the available studies were heterogeneous with respect to surgical procedure, comparator, and clonidine dose. More recently, a randomized study comparing clonidine with dexmedetomidine in children undergoing abdominal surgery showed no statistically significant difference in PONV between the two agents (12). Although earlier trials reported potential benefits of clonidine in breast cancer surgery, ear surgery, and pediatric appendectomy, these studies were conducted more than a decade ago and used different routes, doses, anesthetic protocols, and patient populations (13, 14). In contrast, other studies have failed to demonstrate a consistent clinically decisive benefit, suggesting that clonidine's antiemetic effect may depend on patient population, surgical type, anesthetic protocol, route of administration, and dose (15, 16). Route of administration is particularly important, because intravenous clonidine provides more predictable systemic exposure, whereas oral clonidine may be influenced by absorption variability and bioavailability (10, 17). A previous breast cancer surgery trial reported that although intravenous clonidine significantly increased the number of PONV-free patients, whether a fixed preoperative oral dose provides a comparable effect remains uncertain (13).

Accordingly, the efficacy of clonidine for PONV prevention, and particularly that of a fixed preoperative oral dose in adult breast cancer surgery, remains uncertain and requires further evaluation.

The present double-blind randomized clinical trial was designed to evaluate whether a single preoperative oral dose of clonidine reduces the incidence and severity of PONV compared with placebo in patients undergoing breast cancer surgery under general anesthesia. Secondary objectives were to assess the effect of oral clonidine on perioperative hemodynamic variables and recovery-room duration.

Methods

Trial design:

This double-blind, randomized clinical trial evaluates the effect of clonidine versus placebo on PONV in patients undergoing breast cancer surgery.

In this study, the CONSORT reporting guideline is followed.

Participants

Patients aged 15 to 70 categorized with American Society of Anesthesiologists (ASA) classification I and II, who were scheduled for breast cancer surgery under general anesthesia at Faqihi Hospital, were included in the study. Although patients aged 15–70 years were eligible, the actual age range of the enrolled participants was 28–70 years. On the day before the operation, the patients met with an anesthesiologist at the anesthesia clinic. The study excluded patients with a history of nausea and vomiting after surgery, those who had taken anti-emetic medications such as ondansetron or dexamethasone within 24 h before surgery, individuals with a history of motion sickness, drug sensitivity to propofol, hyper-sensitivity to clonidine, concurrent use of beta-blocker drugs affecting heart rate (HR), systolic blood pressure (SBP) below 100 mmHg, history of myocardial infarction, usage of tricyclic antidepressants, and those with a history of kidney failure.

Intervention:

Patients were given either a 0.2 mg clonidine tablet or a placebo 2 h before the operation. Afterward, they received midazolam (0.03-0.06 mg/kg) and fentanyl (2-4 µg/kg) as premedication, followed by induction with propofol (1-3 mg/kg) and atracurium (0.5 mg/kg). Intubation was then performed using a suitable tracheal tube. The maintenance drugs used during the operation were propofol at a dose of 50-150 micrograms/kg/min, Remifentanil at a dose of 0.1-0.4 micrograms/kg/min, and Morphine at a dose of 0.1-0.15 mg/kg. Mechanical ventilation with capnography was used to maintain a 30-35 end-tidal CO_2. The anesthesiology resident monitored the patient's blood pressure and HR while administering anesthesia. No additional anti-nausea medications, such as dexamethasone or ondansetron, were given to the patients. Of 76 patients assessed for eligibility, 68 eligible patients were randomized. All randomized patients were analyzed in their originally assigned groups; therefore, the primary analysis followed the intention-to-treat principle (Figure 1).

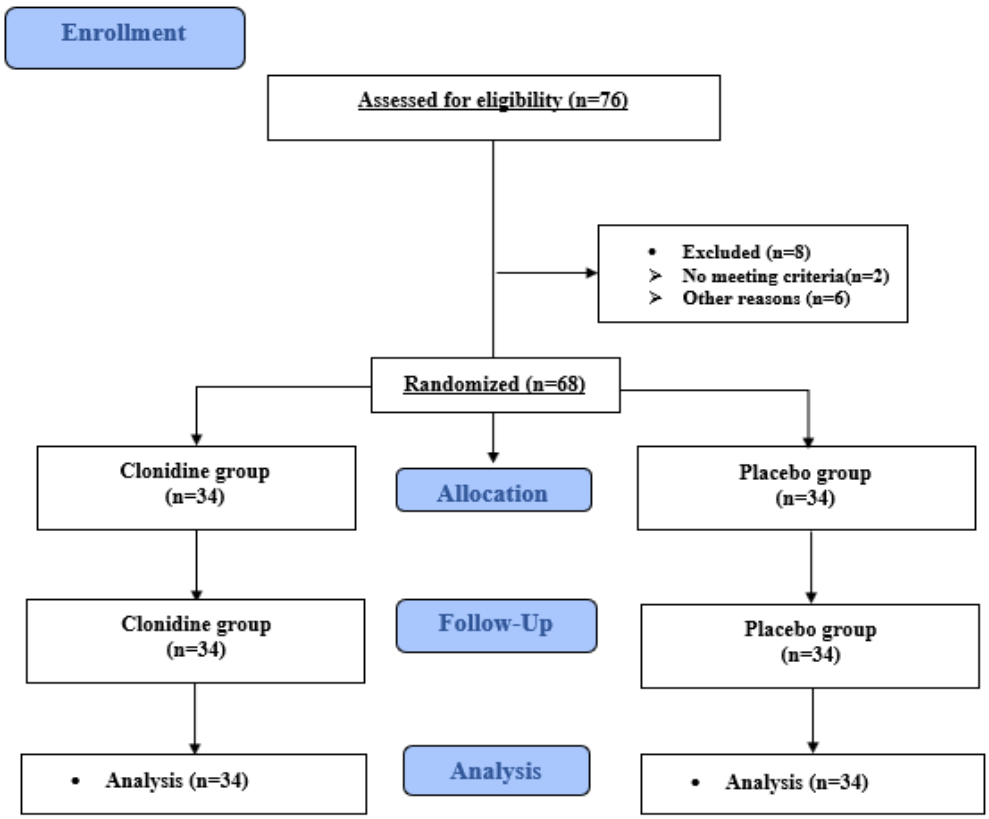


Figure 1. CONSORT flow diagram

Outcomes:

The primary outcome of the study was the incidence and severity of PONV during the first 60 min after surgery. Patients were assessed and categorized into one of four groups based on their symptoms: asymptomatic, nausea, belching, or vomiting. Secondary outcomes included hemodynamic stability and recovery duration. To assess these, hemodynamic parameters—SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), and HR—were continuously monitored in the operating room and recovery room and surgical ward up to 24 h postoperatively. Additionally, the total duration of each patient's stay in the recovery room was recorded as a secondary endpoint. Nurse satisfaction was assessed as an exploratory secondary outcome at the end of the patient's recovery-room stay by the recovery-room nursing staff. Satisfaction was recorded using a four-category ordinal scale: completely satisfied, satisfactory, unsatisfactory, and highly unsatisfactory. This assessment reflected the nurse's overall perception of the patient's early recovery course, including nausea, vomiting, agitation, hemodynamic condition, and ease of postoperative care. The scale was not previously validated and was used as an institutional clinical assessment.

Safety outcomes included clinically significant hypotension, bradycardia, and the need for pharmacologic intervention. Clinically significant hypotension was defined as SBP below 90 mmHg or a reduction of more than 20% from baseline requiring intervention. Clinically significant bradycardia was defined as a HR below 50 beats/min or bradycardia requiring treatment. The need for vasopressor therapy or atropine was recorded as a treatment-related safety outcome. In addition, rescue antiemetic treatment with ondansetron 4 mg IV was permitted if patients developed clinically significant nausea, repeated retching, persistent vomiting, or patient-requested treatment for intolerable symptoms during the postoperative period.

Sample Size:

Based on the previous study by Oddby-Muhrbeck et al. (13), which reported PONV-free rates of 37% in the placebo group and 67% in the clonidine group, we assumed an increase in PONV-free patients from 40% in the placebo group to 65% in the clonidine group. Considering 80% power, a two-sided type I error rate of 0.05, and an anticipated dropout rate of 15%, the required sample size was calculated as 68 patients in total, with 34 patients in each group.

Randomization and Blinding:

Sixty-eight participants were randomly assigned in a 1:1 ratio to the clonidine group or placebo group, with 34 patients in each group through block randomization. The random sequences were generated using a blocked randomization list from www.sealedenvelope.com, with 17 blocks of size 4, before patient enrollment, by a research team member who was not involved in patient recruitment, intervention administration, perioperative care, outcome assessment, or data analysis. Treatment assignments were placed in sequentially numbered, opaque, sealed envelopes. The envelopes were securely stored and opened sequentially only after eligibility had been confirmed and the patient had been enrolled. The envelope was opened by the designated drug-preparation personnel, who prepared either the clonidine tablet or the identical-looking placebo according to the allocation. Patients, anesthesiology residents, nurses in the recovery room and surgical ward, outcome assessors, and data analysts remained blinded to treatment allocation throughout the study.

Statistical Analysis: Continuous variables were presented as mean ± SD. We used an independent sample t-test and Mann-Whitney U test to analyze continuous variables. Categorical variables were represented as numbers and percentages. Differences in categorical outcome variables were compared using the Chi-square test and Fisher's exact test. For analyzing data collected over time, we used repeated measures ANOVA. Data analysis was conducted using SPSS (version 23.0) software (SPSS Inc., Chicago, IL, USA (United States of America)). A *P*-value of 0.05 or less was considered statistically significant, and Bonferroni correction was applied to the *P*-value if needed.

Results

The baseline characteristics of the breast cancer surgery patients in the study groups were comparable, and no statistically significant differences were found ($p>0.05$). Additionally, none of the patients in either group were smokers or experienced nausea and vomiting before the operation (Table 1).

Table 2 compares the incidence and severity of PONV in the recovery room at various times

between the clonidine and placebo groups. While the number of patients without PONV symptoms was higher in the clonidine group at all times, this difference was not statistically significant. A total of 28 (82.4%) patients were symptom-free in the clonidine group, compared to 21 (61.8%) patients in the placebo group (p=0.05).

Table 1. Baseline Characteristics of the Study Patients.

	Clonidine group (n=34)	**Placebo group (n=34)**	***P*-value**
Age (*year*)	46.62±10.86	50.47±9.46	0.12
Weight (*Kg*)	67.97±9.47	66.53±8.10	0.47
SBP (*mmHg*)	122.79±10.51	125.70±9.76	0.24
DBP (*mmHg*)	74.35±7.18	76.85±6.93	0.14
MAP (*mmHg*)	90.50±7.46	93.13±7.26	0.14
HR (*beats/min*)	75.85±9.99	79.17±9.95	0.20
Previous Chemotherapy	13(38.23)	14(41.17)	>0.99

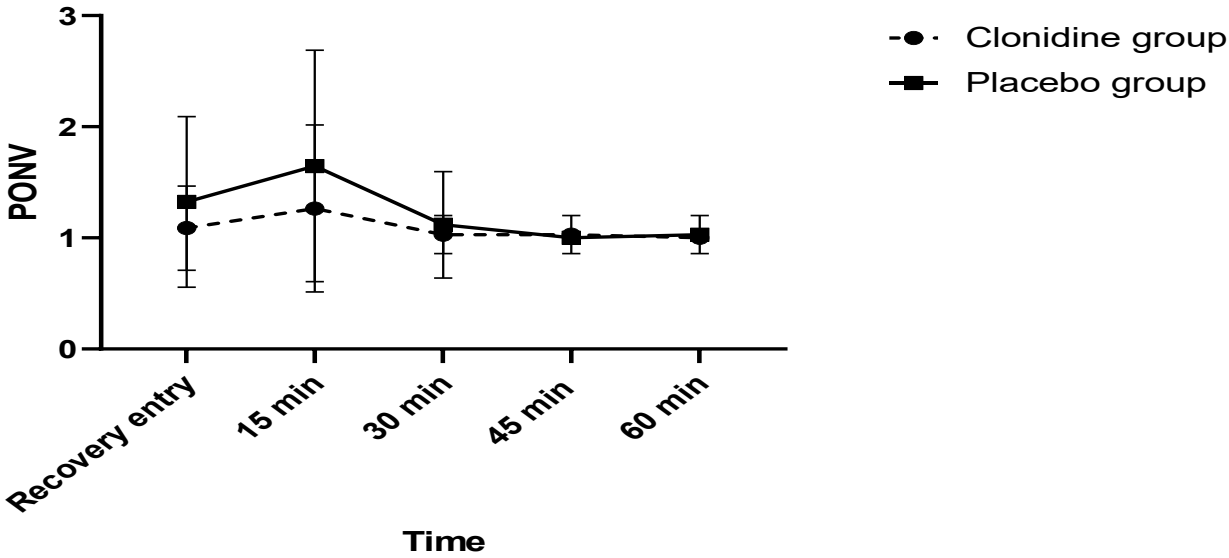
The values indicate mean± SD or frequency (percentage)
SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, HR: Heart Rate

Table 1. Comparing postoperative nausea and vomiting (PONV) incidence status in the recovery room between the studied groups.

	Clonidine group (n=34)	**Placebo group (n=34)**	***P*-value**
Recovery entry			
No PONV	32 (94.1)	28 (82.4)	0.41
Nausea only	1 (2.9)	2 (5.9)	
Retching	1 (2.9)	3 (8.8)	
Vomiting	0 (0)	1 (2.9)	
15 minutes			
No PONV	30(88.2)	23(67.6)	0.13
Nausea only	0(0)	3(8.8)	
Retching	3(8.8)	5(14.7)	
Vomiting	1(2.9)	3(8.8)	
30 minutes			
No PONV	33(97.1)	32(94.1)	0.49
Nausea only	1(2.9)	0(0)	
Retching	0(0)	2(5.9)	
Vomiting	0(0)	0(0)	
45 minutes			
No PONV	33(97.1)	34(100)	>0.99
Nausea only	1(2.9)	0(0)	
Retching	0(0)	0(0)	
Vomiting	0(0)	0(0)	
60 minutes			
No PONV	34(100)	33(97.1)	>0.99
Nausea only	0(0)	1(2.9)	
Retching	0(0)	0(0)	
Vomiting	0(0)	0(0)	
In Total			
Free of PONV	28(82.4)	21(61.8)	0.05
Not free of PONV	6(17.6)	13(38.2)	

PONV categories were defined as follows: No PONV = absence of nausea, retching, or vomiting; Nausea only = subjective sensation of nausea without retching or vomiting; Retching = involuntary retching or dry heaving without expulsion of gastric contents; Vomiting = expulsion of gastric contents.
The values are indicated as a frequency (percentage)

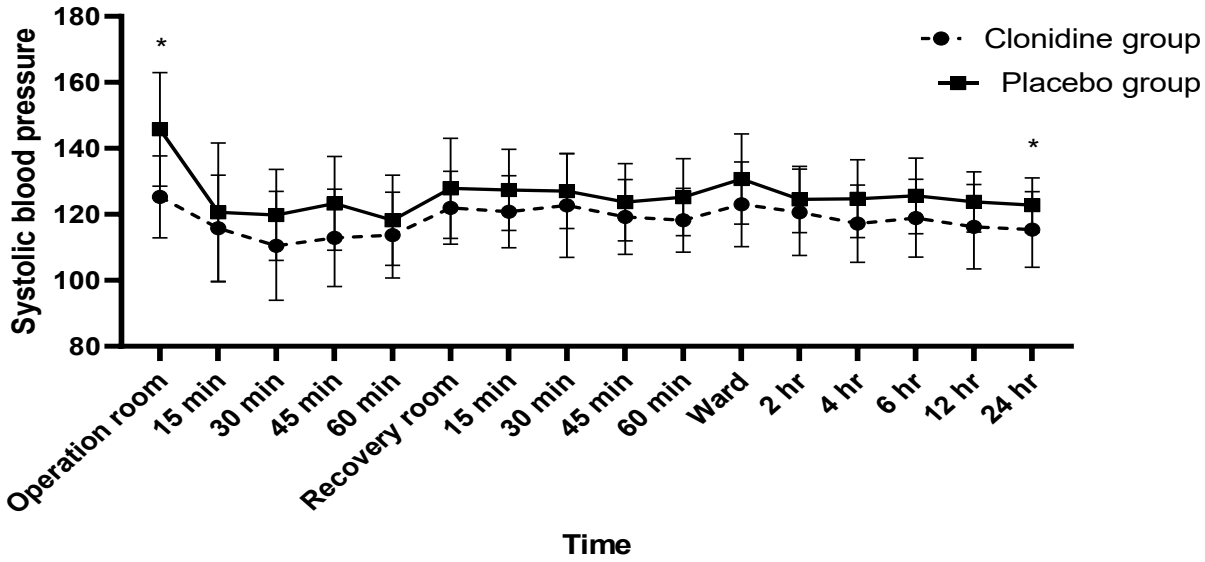
Figure 2 illustrates the changes in PONV severity during the first 60 min of recovery in the clonidine and placebo groups. Postoperative nausea and vomiting severity decreased significantly over time in both groups (time effect, $p<0.001$), indicating progressive postoperative recovery. However, neither the overall difference between treatment groups (group effect, $p=0.06$) nor the group-by-time interaction (interaction effect, $p=0.12$) reached statistical significance, suggesting that the temporal pattern of PONV recovery was comparable between groups.



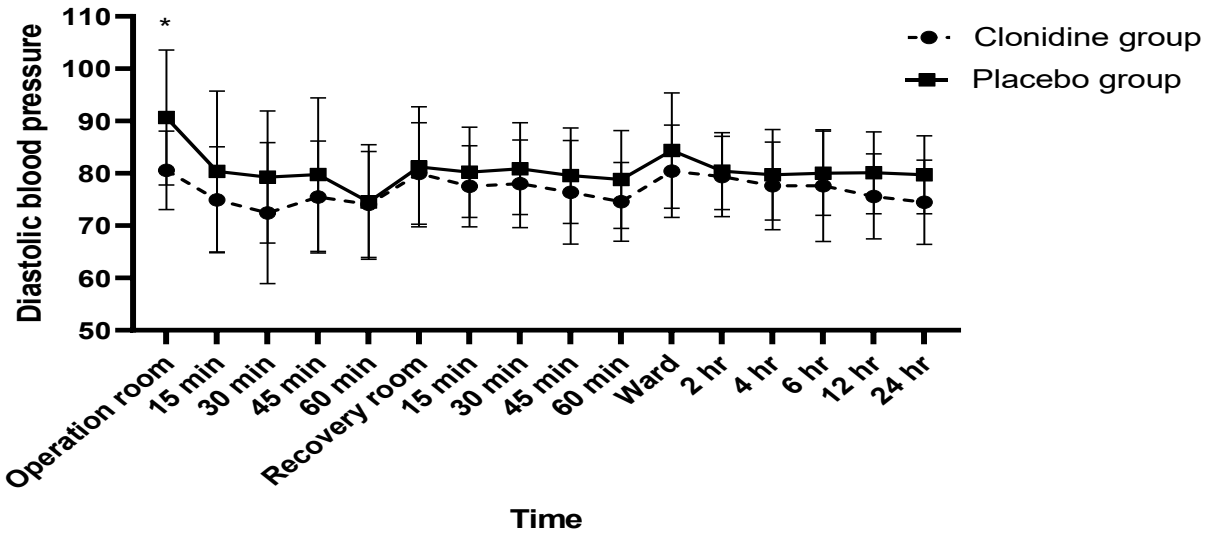
Time effect $p<0.001$*, Interaction (group*time) effect $p=0.12$, Group effect $p=0.06$
Bonferroni correction P-value=0.01
*Indicates significant P-value

Figure 2. Comparison of postoperative nausea and vomiting (PONV) severity over time in the recovery room in the studied groups.

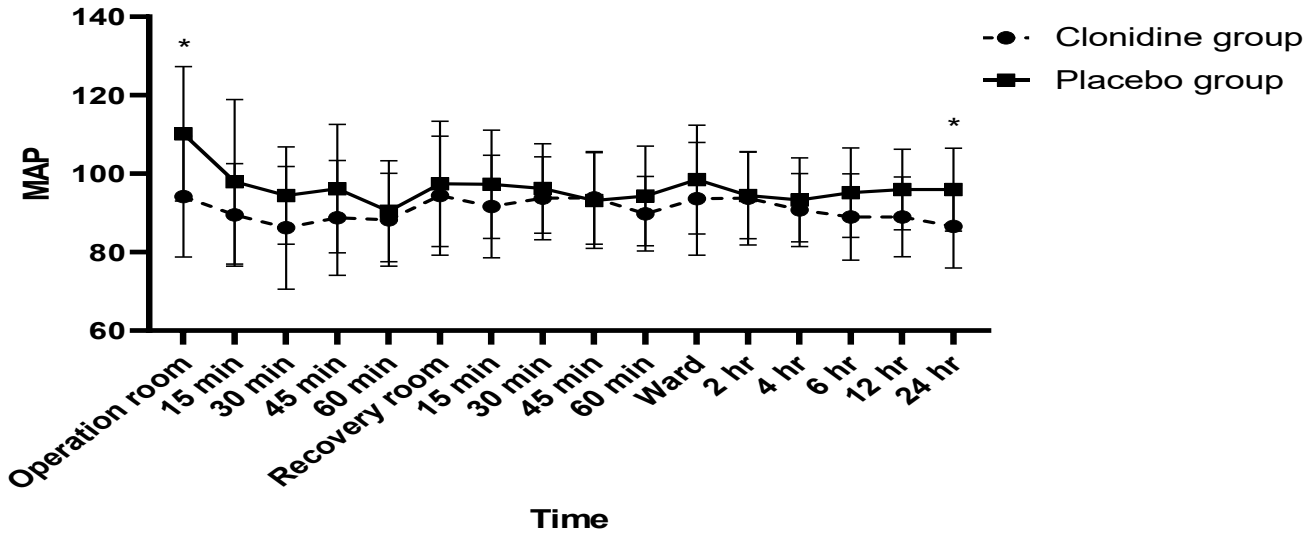
Figure 3 demonstrates the perioperative changes in SBP, DBP, MAP, and HR in the two study groups. All four hemodynamic parameters changed significantly over time (time effect, $p<0.001$ for all variables). Compared with placebo, patients receiving clonidine had significantly lower overall SBP ($p<0.001$), DBP ($p=0.006$), MAP ($p=0.004$), and HR ($p<0.001$), indicating a significant overall treatment effect. However, no significant group-by-time interactions were observed for SBP ($p=0.12$), DBP ($p=0.25$), MAP ($p=0.13$), or HR ($p=0.20$), suggesting that the temporal patterns of perioperative hemodynamic changes were comparable between groups. Bonferroni-adjusted post hoc analyses demonstrated significantly lower SBP at the beginning of surgery and 24 h postoperatively, lower DBP at the beginning of surgery, lower MAP at the beginning of surgery and 24 h postoperatively, and lower HR at the beginning of surgery, 15 and 30 min intraoperatively, and 30 min after admission to the recovery room in the clonidine group. These findings are consistent with the expected sympatholytic effects of clonidine during the perioperative period.



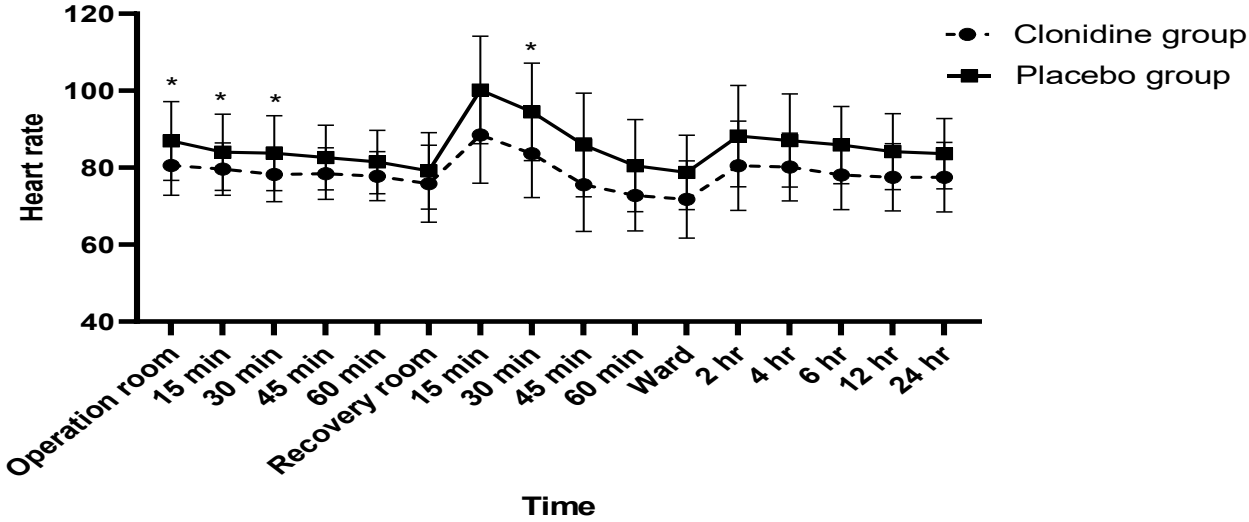
Time effect $p<0.001$*, Interaction (group*time) effect $p=0.12$, Group effect $p<0.001$*
Bonferroni correction *P*-value=0.003
$P_{t=OR}<0.001$*, $P_{t=24\ hr.\ ward}=0.003$*



Time effect $p<0.001$*, Interaction (group*time) effect $p=0.25$, Group effect $p=0.006$*
Bonferroni correction *P*-value=0.003
$P_{t=OR}<0.001$*



Time effect $p<0.001$*, Interaction (group*time) effect $p=0.13$, Group effect $p=0.004$*
Bonferroni correction P-value=0.003
$P_{t=OR}<0.001$*, $P_{t=24\ hr.\ ward}=0.001$*



Time effect $p<0.001$*, Interaction (group*time) effect $p=0.20$, Group effect $p<0.001$*
Bonferroni correction P-value=0.003
$P_{t=OR}=0.001$*, $P_{t=15min\ OR}<0.001$*, $P_{t=30min\ OR}=0.001$*, $P_{t=30\ min\ Recovery}=0.001$*

Figure 3. Hemodynamic changes over time in the studied groups.
*Indicates significant P-value

In addition, patients in the clonidine group had a significantly shorter duration of stay in the recovery room compared to those in the placebo group (86±27 min vs. 102±33 min, respectively; $p=0.04$).

Complete nurse satisfaction was numerically higher in the clonidine group than in the placebo group, 82.4% versus 64.7%, respectively; however, the overall difference in nurse satisfaction categories was not statistically significant ($p=0.37$; Table 3).

No prophylactic antiemetic medication, including ondansetron or dexamethasone, was administered before or during surgery. Rescue ondansetron 4 mg IV was permitted postoperatively according to the predefined rescue criteria. Furthermore, no patient in either group developed clinically significant hypotension or bradycardia requiring

discontinuation of the intervention or additional postoperative monitoring. No patient required atropine for bradycardia. No patient in either group required vasopressor therapy or atropine. No serious adverse event related to clonidine was observed.

Table 3. Comparing nurse satisfaction in the recovery room in the studied groups.

	Clonidine group (n=34)	Placebo group (n=34)	*P*-value
Completely satisfied	28(82.4)	22(64.7)	0.37
Satisfactory	2(5.9)	2(5.9)	
Unsatisfactory	3(8.8)	7(20.6)	
Highly unsatisfactory	1(2.9)	3(8.8)	

The values are indicated as a frequency (percentage).

Discussion

In this double-blind randomized clinical trial, a single preoperative oral dose of clonidine was associated with a higher proportion of PONV-free patients after breast cancer surgery compared with placebo; however, this difference was not significant (p=0.05). Specifically, 82.4% of patients in the clonidine group remained free of PONV compared with 61.8% of patients in the placebo group, corresponding to a 20.6% absolute difference between groups.

Although the P-value was borderline, the observed 20.6% absolute difference in PONV-free patients may still be clinically meaningful. Given the modest sample size, the study may have been underpowered to detect statistical significance for this effect size. Accordingly, the findings should be interpreted by considering both clinical importance and statistical uncertainty rather than relying solely on the P-value (6, 18).

The present findings are clinically relevant because PONV remains a frequent and distressing postoperative complication that can impair recovery quality, delay discharge readiness, increase rescue-medication use, and reduce patient satisfaction (6, 19). The high-risk nature of the present study population may partly explain the reason clonidine produced a clinically apparent yet statistically non-significant reduction in PONV. All patients in this trial were women undergoing breast cancer surgery under general anesthesia, and perioperative opioid administration was part of the anesthetic protocol. Female sex, nonsmoking status, history of motion sickness or previous PONV, volatile anesthetic exposure, postoperative opioid use, and type of surgery are among the most important recognized predictors of PONV (5, 6, 19). A recent study in patients undergoing breast cancer surgery reported that 61% of patients experienced nausea and vomiting within the first 24 h after surgery, confirming that this population remains highly vulnerable to PONV (20). That study also showed that postoperative opioid use, motion sickness or previous PONV, and age were significantly associated with PONV after breast cancer surgery (20). Therefore, the 38.2% PONV rate observed in the placebo group of the present trial should be interpreted within the context of a surgical population with intrinsically elevated baseline PONV risk.

In patients at high risk of PONV, current consensus guidelines recommend reducing modifiable baseline risk factors and implementing multimodal prophylaxis rather than relying on a single antiemetic intervention (6). Accordingly, oral clonidine should not be considered a substitute for established evidence-based antiemetic prophylaxis in women undergoing breast cancer surgery, particularly when multiple PONV risk factors are present (6, 13). Instead, the present findings suggest that oral clonidine may serve as an adjunctive component of a multimodal prevention strategy, although its clinical benefit remains uncertain and should be confirmed in adequately powered randomized controlled trials (11, 12).

The difference between our findings and previous clonidine studies deserves careful consideration. Oddby-Muhrbeck et al. previously reported that clonidine reduced PONV in women undergoing breast cancer surgery, making their trial one of the most directly comparable studies to the present work (13). However, an important methodological difference is that Oddby-Muhrbeck et al. evaluated intravenous clonidine, whereas the present study used a fixed oral dose of 0.2 mg administered 2 h before surgery. This distinction is clinically important, since intravenous administration provides more predictable systemic exposure, whereas oral

administration may be influenced by gastrointestinal absorption, first-pass metabolism, and interindividual pharmacokinetic variability. Dose may also have contributed to the discrepancy between studies, as the present trial used a fixed 0.2 mg oral dose rather than weight-based dosing. A fixed dose may result in variable effective exposure across patients with different body weights, metabolic profiles, and perioperative physiologic conditions. These considerations support the need for future studies comparing oral versus intravenous clonidine and fixed-dose versus weight-based regimens in breast cancer surgery.

Previous studies have reported inconsistent findings regarding the effect of clonidine on PONV, suggesting that its antiemetic efficacy may depend on the clinical setting (11, 12). A recent systematic review demonstrated that clonidine reduced postoperative vomiting in selected pediatric surgical populations, although substantial heterogeneity was observed across procedures, dosing regimens, and comparators (11). Earlier randomized trials also reported reduced PONV following oral clonidine premedication in patients undergoing ear surgery and pediatric appendectomy (14, 16); however, these findings may not be directly applicable to adult women undergoing breast cancer surgery due to important differences in baseline PONV risk, anesthetic techniques, perioperative opioid exposure, and surgical stress (6, 19).

Comparative evidence also suggests that clonidine may be less effective than established antiemetic agents in some surgical settings (6, 21). For instance, a randomized trial in patients undergoing thyroidectomy reported a higher incidence of PONV among patients receiving clonidine than among those receiving ondansetron (21). Consistent with current consensus recommendations, these findings suggest that clonidine should be considered, at most, an adjunct to evidence-based multimodal prophylaxis rather than a replacement for established first-line antiemetic agents (6).

The pharmacologic profile of clonidine provides a plausible explanation for the secondary outcomes observed in the present study. Clonidine is a centrally acting α2-adrenergic receptor agonist that reduces sympathetic outflow, resulting in dose-dependent decreases in blood pressure and HR through sympatholytic mechanisms (10, 17). Consistent with these established pharmacodynamic effects, oral clonidine was associated with significantly lower SBP, DBP, MAP, and HR at several perioperative time points compared with placebo. These findings confirm the expected biologic activity of the administered oral dose and are in agreement with previous perioperative studies of clonidine (9, 13). However, the term "hemodynamic stability" should be interpreted cautiously because the present study primarily demonstrated lower hemodynamic values rather than directly assessing hemodynamic variability or clinically significant hypotensive, hypertensive, bradycardic, or tachycardic events. Therefore, a more accurate interpretation is that oral clonidine produced the expected sympatholytic hemodynamic effects during the perioperative period. This distinction is clinically important because excessive hypotension or bradycardia may be undesirable in susceptible patients, particularly those with underlying cardiovascular disease or impaired autonomic compensation (10). In the present study, patients with SBP below 100 mmHg, previous myocardial infarction, beta-blocker therapy affecting HR, and other relevant contraindications were excluded, which may have reduced the likelihood of clinically significant hemodynamic adverse events.

Another important finding was the significantly shorter post-anesthesia care unit (PACU) stay in the clonidine group compared with the placebo group. Patients receiving oral clonidine remained in the PACU for 86 ± 27 min, whereas those receiving placebo remained for 102 ± 33 min, representing a statistically significant reduction of approximately 16 min. This finding may partly reflect the lower frequency of PONV symptoms observed in the clonidine group, although the primary PONV outcome did not reach statistical significance. It may also be attributable to the pharmacologic effects of clonidine, including its sedative, anxiolytic, opioid-sparing, and sympatholytic properties, which may facilitate smoother emergence from anesthesia and earlier fulfillment of PACU discharge criteria (9, 10). Nevertheless, postoperative recovery is influenced by multiple perioperative factors, including pain control, opioid consumption, residual sedation, hemodynamic status, and institutional discharge protocols, rather than by PONV alone (6, 19). Therefore, the shorter PACU stay observed in the present study should be interpreted as an exploratory secondary outcome and not as direct evidence of an antiemetic effect.

The trend toward higher nurse satisfaction in the clonidine group may also support the possibility of

smoother early recovery, although this outcome did not reach statistical significance. In the present study, complete nurse satisfaction was reported in 82.4% of patients in the clonidine group compared with 64.7% in the placebo group; however, the overall comparison was not statistically significant. This non-significant trend should be interpreted cautiously given that nurse satisfaction is a subjective secondary outcome that may be influenced by nausea, pain, agitation, hemodynamic parameters, and institutional workflow. Nevertheless, the direction of this finding is consistent with the shorter recovery-room duration and may warrant further evaluation in future trials using validated recovery-quality instruments.

The present findings should also be interpreted within the context of evolving strategies for the prevention and management of PONV. Contemporary consensus guidelines emphasize individualized risk assessment, multimodal prophylaxis, opioid-sparing anesthetic techniques, total intravenous anesthesia when appropriate, and rescue treatment using an antiemetic from a different pharmacologic class than that used for prophylaxis (6). Given its sympatholytic and opioid-sparing properties, clonidine may be better viewed as an adjunctive component of a broader multimodal perioperative recovery strategy rather than as a primary antiemetic intervention (9, 10). Recent evidence regarding α2-adrenergic agonists, particularly dexmedetomidine, suggests that this drug class may reduce the incidence of PONV in selected patients undergoing general anesthesia. However, these findings should not be directly extrapolated to oral clonidine because of important differences in receptor selectivity, pharmacologic potency, route of administration, and pharmacokinetic characteristics (10).

A recent randomized comparative study evaluated dexmedetomidine and clonidine for the prevention of PONV in pediatric patients undergoing abdominal surgery, highlighting the continued interest in α2-adrenergic agonists as potential perioperative adjuncts for PONV prevention (12). However, current evidence remains insufficient to support routine use of clonidine as a first-line antiemetic agent, particularly in high-risk patients undergoing breast cancer surgery. Instead, contemporary consensus guidelines recommend evidence-based multimodal prophylaxis using established antiemetic agents according to the patient's baseline risk profile (6, 11).

The main strength of the present study is its double-blind randomized placebo-controlled design in a clinically relevant high-risk surgical population. Another strength is the assessment of both the primary PONV outcome and secondary perioperative outcomes, including hemodynamic parameters, recovery-room duration, and nurse satisfaction. However, several limitations should be acknowledged. First, although the observed 20.6% absolute difference in PONV-free patients may be clinically meaningful, the sample size may have been insufficient to confirm statistical significance for the primary outcome. Second, the study assessed only a fixed oral dose of clonidine and did not compare oral administration with intravenous administration. Third, the single-center design may limit generalizability to other institutions with different anesthetic protocols, recovery-room discharge criteria, and antiemetic practices. Future multicenter randomized trials should evaluate oral and intravenous clonidine regimens, compare fixed and weight-based dosing, apply validated PONV risk stratification tools, and assess clonidine as part of a multimodal prophylaxis strategy. Fourth, although the Apfel simplified risk score was not prospectively calculated for each participant, several of its major components were either uniform or controlled by design. All participants were female, all were nonsmokers, and patients with previous PONV or motion sickness were excluded. However, since postoperative opioid exposure was not incorporated into a formal participant-level Apfel score, we could not present Apfel score distributions or perform Apfel-adjusted sensitivity analyses.

Conclusion

In conclusion, preoperative oral clonidine did not significantly reduce PONV after breast cancer surgery, although the 20.6% absolute increase in PONV-free patients suggests a potentially clinically meaningful trend. Clonidine was associated with lower perioperative blood pressure and HR values and a shorter recovery-room stay, findings consistent with its sympatholytic and perioperative adjunctive pharmacologic profile. Overall, these findings suggest that oral clonidine should not be considered a primary substitute for standard PONV prophylaxis in high-risk breast surgery patients; however, it may have value as an adjunctive perioperative medication. Larger adequately powered randomized trials are needed to determine whether oral clonidine has a reproducible, clinically

meaningful antiemetic effect and to define its optimal route, dose, timing, and role within multimodal perioperative care.

Ethics approval and consent to participate

The study protocol followed the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.635). All patients provided written informed consent. This study was registered in the Iranian Registry of Clinical Trials (IRCT20141009019470N99), where the trial protocol can be accessed.

Consent for Publication

Not applicable.

Data Availability Statement

All data will be available upon reasonable request.

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Author's Contribution

AA and **SH**: study conception, proposal writing, manuscript drafting, and revising. **AK** and **HR**: proposal preparation, data collection, manuscript writing. **MS**: study conception, proposal writing, and manuscript revising. **NA**: study design, data analysis, and data curation. **MB**: data analysis, interpretation of analysis, results writing, and manuscript editing and preparation.

Conflict of Interest

The present article was extracted from the thesis written by Dr. Shabnam Heydarinejad. All other authors declare no conflicts of interest.

Declaration of Generative Artificial Intelligence in Scientific Writing

As English is not the authors' native language, Grammarly was used solely to improve the English language, grammar, spelling, punctuation, and overall readability of the manuscript. No generative AI was used to generate scientific content, analyze data, interpret results, or draw conclusions. The authors take full responsibility for the accuracy and integrity of the final manuscript.

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