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Antiemetic efficacy of dexmedetomidine versus dexmedetomidine-dexamethasone combination in patients undergoing breast surgery

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Abstract

Objective: To compare the antiemetic efficacy of dexmedetomidine alone versus combined dexmedetomidine–dexamethasone on incidence of postoperative nausea and vomiting (PONV) in patients undergoing breast surgery.

Methods: A total of 149 patients (aged 20–65 years) were assigned to receive normal saline (control group, n = 50), dexmedetomidine 0.5 μg/kg (DEX group, n = 49), or a combination of dexmedetomidine 0.5 μg/kg and dexamethasone 5 mg (dual group, n = 50) at 30 minutes prior to the end of surgery. The primary outcome measure was the incidence of PONV in the post-anesthesia care unit (PACU).

Results: During the first 24 hours after surgery, the incidence of PONV was significantly higher in the control group than in the DEX and dual groups (70% vs. 20% and 12%, respectively), with no intergroup difference observed between the DEX and dual groups. In the PACU, the incidence of PONV differed significantly among the control, DEX, and dual groups (12%, 4%, and 3%, respectively).

Conclusion: Dexmedetomidine alone and in combination with dexamethasone significantly reduced PONV with similar antiemetic efficacies in female patients during the first 24 hours after breast surgery.

Clinical trial registration: ClinicalTrials.gov (NCT 02550795).

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Introduction

Postoperative nausea and vomiting (PONV) is an extremely common and highly undesirable complication of general anesthesia,[1] and in the United States, hundreds of millions of dollars are spent annually to reduce PONV.[2] Female gender, non-smoking status, use of opioids, and previous history of motion sickness or PONV are considered strong risk factors for PONV.[3] Thus, women undergoing breast surgery under general anesthesia are highly susceptible to PONV, which reportedly occurs in up to 70% of these patients during the first 24 hours after surgery without antiemetic prophylaxis.[4] Because the etiology of PONV is multifactorial, a combination of antiemetics and adjuvants with different mechanisms is recommended rather than single-antiemetic prophylaxis.[1,5,6]

Dexmedetomidine is a highly selective α_2-receptor agonist initially introduced as a sedative and anxiolytic agent. Recent clinical studies have demonstrated the antiemetic activity of pre- or postoperative dexmedetomidine use after various types of surgical procedure.[7–10] A meta-analysis of the efficacy of dexmedetomidine on PONV also reported that dexmedetomidine at 0.5 or 1.0 μg/kg effectively reduced the incidence of PONV compared with placebo.[11] Glucocorticoids may exert an antiemetic effect by inhibiting inflammatory mediators and by interacting with serotonin, neurokinin, α-adrenergic receptors, and other receptors.[12] Furthermore, several studies have shown that dexamethasone enhances the antiemetic efficacies of 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists.[13,14] However, the antiemetic efficacy of dexmedetomidine in combination with dexamethasone has not been reported to date. The objective of this prospective, randomized, double-blinded study was to investigate the antiemetic efficacy of dexmedetomidine alone versus a dexmedetomidine–dexamethasone combination for PONV prophylaxis in female patients during the first 24 hours after breast surgery.

Materials and methods

This was a randomized, controlled, double-blind trial with three parallel groups. The study protocol was approved by the ethics committee of Gil Hospital, Incheon, South Korea (GCIRB 2014-154; August. 2014) and all subjects provided written informed consent prior to participation.

Subjects

A total of 150 female patients aged 20 to 65 years, of American Society of Anesthesiologists physical status 1 or 2, and scheduled for elective breast surgery under general anesthesia were enrolled in the study between September 2015 and August 2016. The following exclusion criteria were applied: diabetes mellitus; treatment with antiemetics or glucocorticoids; history of chemotherapy or radiation therapy; body mass index >30 kg/m^2; or uncontrolled cerebrovascular, cardiovascular, gastrointestinal, renal, or hepatic disease.

The risk for PONV was assessed using the Apfel scoring system, which allocates 1 point for each of the following factors: female gender, previous PONV or motion sickness, non-smoker, and planned postoperative opioid use.[1] Patients were randomized in a 1:1:1 ratio to receive normal saline (control group, n = 50), dexmedetomidine 0.5 μg/kg (DEX group, n = 50), or a combination of dexmedetomidine 0.5 μg/kg with dexamethasone 5 mg (dual group, n = 50) using a randomization list generated in Excel 2007 (Microsoft Office, Redmond, WA, USA) without stratification.

Anesthesia

Intramuscular midazolam 2 mg and glycopyrrolate 0.2 mg were administered to all patients as premedication 30 minutes prior to induction of anesthesia. On arrival in the operating room, pulse oximetry, electrocardiography, and noninvasive blood pressure monitoring were initiated. Anesthesia was induced using alfentanil 10 to 15 μg/kg, lidocaine 0.5 mg/kg, propofol 1.5 to 2 mg/kg, and rocuronium bromide 0.8 mg/kg. Following orotracheal intubation, anesthesia was maintained using 1.5% to 2.5% sevoflurane in 60% O_2/air, targeting a bispectral index between 40 and 60. For all patients, intravenous patient-controlled analgesia (PCA) was provided for 48 hours postoperatively using an Accufuser® (Wooyoung Meditech, Seoul, Korea) and 100 ml of normal saline containing fentanyl 600 μg and ketorolac 180 mg. PCA was administered at a basal infusion rate of 2 ml/hour, intermittent bolus dose of 0.5 ml, and a 15-minute lock-out time.

Study drugs and evaluation of PONV

The study drugs comprised a syringe containing 50 ml of dexmedetomidine (2 μg/ml) or normal saline and a syringe containing 1 ml of dexamethasone (5 mg/ml) or normal saline. An anesthesiologist unaware of group assignment administered 1 ml of dexamethasone or normal saline 30 minutes before the end of skin closure followed by infusion of 0.25 ml/kg of dexmedetomidine 0.5 μg/kg or normal saline over 10 minutes. The study drugs were prepared by an independent researcher, while the investigators responsible for evaluating the results of the study were blinded to the group assignment.

The incidence of vomiting, use of rescue antiemetics, and analgesic requirements were recorded at 0 to 1 hours after surgery in the postanesthetic care unit (PACU). The severity of nausea was evaluated using an 11-point numerical rating scale (NRS) (0 = no symptoms; 10 = worst symptoms imaginable). Ramosetron 0.3 mg was administered to patients with nausea >5 points on the NRS or to those who requested an antiemetic. Pain score was also assessed using an 11-point NRS. Intravenous fentanyl 50 μg was administered to patients who reported pain >5 points on the NRS. Mean arterial pressure (MAP), heart rate (HR), and Ramsay sedation score (1 = agitated, anxious, or restless; 2 = oriented, cooperated, and tranquil; 3 = responsive to verbal commands only; 4 = asleep, brisk response to a loud auditory stimulus or a light glabella tap; 5 = sluggish response to a glabella tap or loud auditory stimulus; 6 = no response to a loud auditory stimulus or a light glabella tap) were recorded. Over-sedation was defined as a Ramsay sedation score > 4. Shivering was recorded by nursing staff unaware of group allocations when patients experienced fasciculation or tremor in more than one muscle group without voluntary limb activity.

At 6 and 24 hours after surgery, the incidence and severity of PONV were assessed using the Rhodes Index of nausea, vomiting, and retching (Table 1).[15]

Table 1. Rhodes Index of nausea, vomiting, and retching at 6 to 24 hours after surgery.

	Score				
Items	4	3	2	1	0
How many times did you vomit?	>7	5–6	3–4	1–2	0
How much distress did you have from retching or dry heaves?	Severe	Great	Moderate	Mild	None
How much distress did you have from vomiting?	Severe	Great	Moderate	Mild	None
How long did you feel nauseated or sick to your stomach?	>4 hours	2–3 hours	1–2 hours	<1 hour	0 hours
How much distress did you have from nausea or feeling sick to your stomach?	Severe	Great	Moderate	Mild	None
How much did you vomit?	3 cups	2–3 cups	1/2–2 cups	0–1/2 cups	0
How many times did you feel nausea or sick to your stomach?	>7	5–6	3–4	1–2	0
How many times did you have periods of retching or dry heaves?	>7	5–6	3–4	1–2	0

Statistical analysis

Study sample size was calculated based on the results of a previous study in patients undergoing mastectomy in which the incidence of PONV in a placebo-control group in the PACU after surgery was 44%.[16] Forty-six patients were required per group for a power of 80% at an α-error of 0.017 to detect a 30% difference between two groups. Thus, assuming a dropout rate of 10%, 150 patients were recruited.

Statistical analysis was performed using SPSS software ver. 18.0 (SPSS Inc., Chicago, IL, USA). Results are expressed as means $\pm$ standard deviations, medians (interquartile ranges), or number of patients. The Kolmogorov–Smirnov test was used to assess the normality of continuous variable distributions. Categorical data were analyzed using the χ^2 test and, for multiple comparisons among the three study groups, P-values < 0.017 ($=0.05/3$) were considered statistically significant. One-way ANOVA with Bonferroni's correction was used to analyze normally distributed continuous variables and the Kruskal–Wallis test with Bonferroni's correction was used to analyze non-normally distributed continuous variables. P-values of < 0.05 determined using the one-way ANOVA or the Kruskal–Wallis test were considered statistically significant.

Results

Patient allocation and demographics

Of the 150 enrolled patients, one patient in the DEX group was excluded from the analysis because of a change in surgical plan (Figure 1). Thus, 49 patients were assigned to the DEX group and 50 patients each were assigned to the control and dual groups. Patient characteristics are summarized in Table 2. Duration of surgery and risk scores for PONV were similar across the three study groups.

Hemodynamic data and pain score in the PACU

Hemodynamic variables and adverse events in the PACU are presented in Table 3. HR differed among the groups ($P < 0.001$), and was significantly lower in the DEX and dual

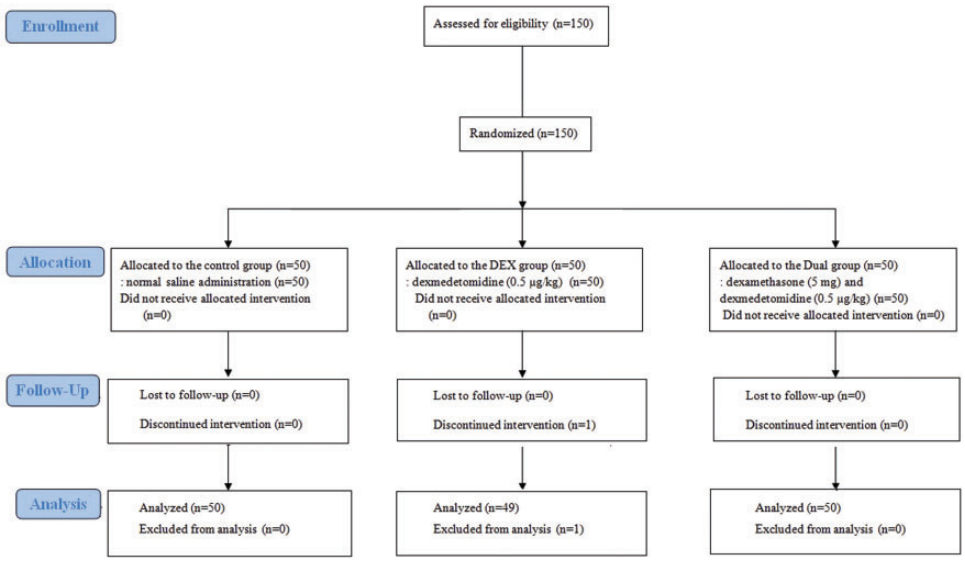

Figure 1. Flow diagram of patient allocation.

Table 2. Patient characteristics.

	Control group (n = 50)	DEX group (n = 49)	Dual group (n = 50)	*P*-value
Age (years)	48.7 ± 6.4	48.2 ± 7.1	48.4 ± 7.5	0.918
BMI (kg/m^2)	24.1 ± 2.8	24.4 ± 3.4	23.1 ± 2.9	0.066
Duration of surgery (min)	168 ± 39	155 ± 35	157 ± 39	0.201
Hypertension (n)	6 (12)	13 (27)	6 (12)	0.083
Apfel score for PONV (n)				0.422
3	44 (88)	46 (94)	43 (86)	
4	6 (12)	3 (6)	7 (14)	

Values are means ± SDs or number of patients (%). Control group, patients administered normal saline; DEX group, patients administered dexmedetomidine (0.5 μg/kg); Dual group, patients administered with dexmedetomidine (0.5 μg/kg) and dexamethasone (5 mg); BMI, body mass index; PONV, postoperative nausea and vomiting. The risk score for PONV was assessed using the Apfel scoring system, which allocates 1 point to each of four factors (female gender, previous PONV or motion sickness, non-smoking status, and planned postoperative opioid use).

groups than in the control group ($P = 0.001$ and $P = 0.002$, respectively). No patient had significant bradycardia (HR < 50 beats/minute). The incidence of shivering differed among the three groups ($P = 0.03$) and was significantly lower in the dual group than in the control group ($P = 0.014$).

Incidence of PONV and Rhodes Index score

The incidence of PONV and Rhodes Index scores is summarized in Table 4. At 24 hours after surgery, the incidence of PONV was significantly higher in the

Table 3. Hemodynamic data and pain score in the post anesthesia care unit.

	Control group (n = 50)	DEX group (n = 49)	Dual group (n = 50)	*P*-value
Mean arterial pressure (mmHg)	102 ± 14	97 ± 15	95 ± 14	0.058
Heart rate (beats/min)	74 ± 9	67 ± 11*	67 ± 10*	<0.001
Shivering (n)	8 (16)	3 (6)	1 (2)*	0.030
Over-sedation (n)	4 (8)	1 (2)	4 (8)	0.357
Pain score (NRS)	4.5 [3–6]	3 [3–3.5]	3 [2.5–5]	0.050
Rescue analgesic requirement (n)	14 (28)	11 (22)	12 (24)	0.804
Rescue fentanyl dosage (μg)	0 [0–50]	0 [0–0]	0 [0–12.5]	0.489

Values are means ± SDs, number of patients (%) or medians [interquartile ranges]. Control group, patients administered normal saline; DEX group, patients administered dexmedetomidine (0.5 μg/kg); Dual group, patients administered dexmedetomidine (0.5 μg/kg) and dexamethasone (5 mg); Over-sedation was defined as a Ramsay sedation score of >4; NRS, an 11-point numerical rating scale (0–10); Rescue analgesics, administration of fentanyl 50 μg when a patient complained of pain of >5 points on the NRS. *$P < 0.05/3$ vs. control group.

Table 4. Incidences of postoperative nausea and vomiting (PONV).

	Control group (n = 50)	DEX group (n = 49)	Dual group (n = 50)	*P*-value
During 24 hours after surgery				
PONV	35 (70)	20 (41)*	12 (24)*	<0.001
0–1 hour PONV (in the PACU)				
PONV	12 (24)	4 (8)	3 (6)	0.013
Nausea (n)	12 (24)	4 (8)	3 (6)	0.013
Severity of nausea (NRS)	0 [0–0.25]	0 [0–0]	0 [0–0]	0.113
Vomiting (n)	4 (8)	0 (0)	0 (0)	0.017
Rescue antiemetics (n)	10 (20)	2 (4)	2 (4)	0.007
1–6 hours after surgery				
PONV	30 (60)	19 (39)	10 (20)*	<0.001
Nausea	30 (60)	19 (39)	9 (18)*	<0.001
Vomiting	15 (30)	6 (12)	1 (2)	<0.001
Rhodes Index	5 [0–12]	0 [0–5.5]*	0 [0–0.5]*	<0.001
6–24 hours after surgery				
PONV	25 (50)	14 (29)	6 (12)*	<0.001
Nausea	25 (50)	14 (29)	6 (12)*	<0.001
Vomiting	9 (18)	5 (10)	1 (2)	0.029
Rhodes Index	3.5 [0–13]	0 [0–3.5]*	0 [0–0]*	<0.001

Values are number of patients (%) or medians [interquartile ranges]. Control group, patients administered normal saline; DEX group, patients administered dexmedetomidine (0.5 μg/kg); Dual group, patients administered dexmedetomidine (0.5 μg/kg) and dexamethasone (5 mg); PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; NRS, nausea intensity score evaluated using an 11-point numerical rating scale (0–10). *$P < 0.05/3$, vs. control group.

control group than in the DEX and dual groups (70% vs. 20% and 12%, respectively; $P = 0.0046$ and < 0.001, respectively) with no intergroup difference observed between the DEX and dual groups. In the PACU, the incidence of PONV was significantly different among the control, DEX, and dual groups (12%, 4%, and 3%,

respectively; $P = 0.013$). The use of rescue antiemetics also differed in the three groups ($P = 0.007$). At 1 to 6 hours and from 6 to 24 hours after surgery, the incidence of PONV was significantly lower in the dual group than in the control group (both $P < 0.001$). Rhodes Index scores at 1 to 6 hours and at 6 to 24 hours after surgery were also lower in both the DEX group ($P = 0.005$ and 0.006, respectively) and the dual group (both $P < 0.001$) compared with the control group, but no difference was observed between the DEX and dual groups. Furthermore, the incidence of nausea at 1 to 6 hours and at 6 to 24 hours after surgery was similar in the DEX and dual groups. Four patients in the control group, three in the DEX group, and 0 in the dual group discontinued PCA because of PONV, and one patient in the control group received diclofenac 75 mg as a rescue analgesic.

Discussion

In this prospective randomized study, dexmedetomidine alone and a dexmedetomidine–dexamethasone combination effectively reduced PONV and showed similar antiemetic efficacies during the first 24 hours after surgery in patients undergoing breast surgery.

PONV is caused by vagal stimulation of the gastrointestinal area and stimulation of cortical/thalamic emesis center, vestibular nerve, and chemoreceptor trigger zone outside of the blood–brain barrier. Several receptor systems trigger PONV in the emetic center and chemoreceptor trigger zone, and these same receptor systems are also targeted in the treatment of PONV. Histamine, 5-HT_3, acetylcholine, dopamine type 2, substance P, neurokinin, several opioid receptors, and other biomolecules are associated with the control of emesis or vomiting.[5] Commensurate with the multifactorial etiology of PONV, current evidence indicates that multimodal antiemetic therapies are more effective in the prevention of PONV than is any single therapy.[1,5]

The Rhodes Index is a reliable and valid patient self-reporting tool to assess nausea, vomiting, and retching and consists of eight items with 5 scales (0–4).[15] This index has been shown to be a highly reliable method for evaluating gastrointestinal distress after ambulatory surgery ($\alpha = 0.897$).[17]

Dexmedetomidine use as an antiemetic in the present study was not according to the packaging label, and the mechanisms responsible for the antiemetic effect of dexmedetomidine remain unclear. In addition to modulation of neurotransmitters, clinical studies support an opioid- and anesthetic-saving effect as the underlying mechanism of the antiemetic effect of dexmedetomidine.[8,16,18,19] Given that the onset and peak effect times of dexmedetomidine are 5 minutes and 15 minutes, respectively,[20] dexmedetomidine was administered at the end of surgery in the present study, as in a previous clinical study of dexmedetomidine.[16] In the present study, administration of dexmedetomidine at the end of surgery had little effect on intraoperative opioid or anesthetic consumption. Moreover, the use of rescue opioids in the PACU did not differ among the three study groups, indicating that the dose of dexmedetomidine used might not have been high enough to demonstrate an opioid-sparing effect. In a previous study, a bolus of dexmedetomidine 0.5 μg/kg significantly reduced tramadol requirements after breast surgery in patients who did not receive PCA.[16] A further large-scale study in patients receiving opioid-based PCA may therefore be required to elucidate the opioid-sparing effect of dexmedetomidine. Taken together, the major mechanism of the antiemetic effects of dexmedetomidine observed in the present study might be attributable to the modulation of neurotransmitters. In a previous animal

study, dexmedetomidine reduced evoked 5-HT release in the dorsal and median raphe nucleus, and it has been suggested that postsynaptic α_{2A}-receptors on 5-HT cell elements, functioning as heteroreceptors, might directly mediate the dexmedetomidine-induced modulation of 5-HT release.[19] In addition, dexmedetomidine might modulate dopamine release by dose-dependently decreasing extracellular dopamine levels in the nucleus accumbens[21] and suppressing the histamine-induced expression of the pro-inflammatory cytokine interleukin-6.[22]

Earlier clinical studies indicated that dexamethasone combined with ondansetron, droperidol, or ramosetron increased antiemetic efficacy compared with any of these antiemetics used alone.[14,23] The antiemetic effect of dexamethasone may be associated with its anti-inflammatory effect attributed to the inhibition of inflammatory mediators (e.g., prostaglandins or substance P), inhibition of 5-HT expression, suppression of the hypothalamus–pituitary–adrenal axis, and activation of α_2-adrenoreceptors.[12] In the present study, dexamethasone was administrated 30 minutes prior to the end of surgery and the timing of administration might have affected its antiemetic efficacy, especially during the early postoperative period, because dexamethasone has a relatively long onset time with a time-lag between injection and maximum antiemetic effect of approximately 2 hours.[24] For this reason, it is recommended that dexamethasone is administered prior to surgery and not used as a rescue antiemetic. Thus, in the present study, delayed dexamethasone administration might explain why the addition of dexamethasone to dexmedetomidine did not induce any additive antiemetic effects in the PACU.

In the present study, the incidence of postanesthetic shivering was lower in the dual group than in the control group. Dexmedetomidine suppresses vasoconstriction, which is related to the shivering threshold. In a previous study of 90 females undergoing abdominal hysterectomy, shivering incidence and intensity were lower in patients who received a loading dose of 1 μg/kg dexmedetomidine followed by an infusion of 0.4 μg/kg/hour compared with patients who received normal saline.[25] Similarly, Yu et al.[10] compared dexmedetomidine 0.5 μg/kg with meperidine 0.5 mg/kg and reported that dexmedetomidine showed a better safety profile for anti-shivering in patients undergoing Cesarean delivery.

The present study had several limitations. First, PONV prophylaxis was not used as a control group. Although immediate rescue antiemetic use was planned in the PACU, PONV prophylaxis should have been administered to susceptible patients. Second, the incidence of nausea (24%) in the placebo-control group was markedly lower than that observed in the previous study (44%) of Kim et al.,[16] which was used for the sample size calculation. As a result of this low incidence of nausea and relatively small sample size, statistical significance was not observed in the difference in antiemetic effect between the DEX and dual groups. Further larger-scale studies are therefore needed to permit the generalization of our results. Another limitation was the timing of dexamethasone administration. The antiemetic effect of dexamethasone is observed at approximately 1 to 2 hours after injection, which may have affected the incidence of PONV at 0 to 1 hour after surgery in the present study. However, because the incidence of PONV was different among the three groups and slightly lower in the treatment groups than in the control group in the PACU, the influence of timing of dexamethasone administration may have been minimal.

In conclusion, dexmedetomidine (0.5 μg/kg) alone and combined with dexamethasone (5 mg) significantly reduced

PONV with similar antiemetic efficacies in female patients during the first 24 hours after breast surgery. The mechanism of the antiemetic effect of dexmedetomidine may be attributable to neurotransmitter modulation.

Declaration of conflicting interest

The author(s) declare that there is no conflict of interest.

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