J Anesth (2011) 25:917–922
DOI 10.1007/s00540-011-1241-1

REVIEW ARTICLE

Management of postoperative nausea and vomiting in women scheduled for breast cancer surgery

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Received: 21 June 2011 / Accepted: 14 September 2011 / Published online: 1 October 2011

Abstract Breast cancer surgery performed under general anesthesia is associated with a high incidence of postoperative nausea and vomiting (PONV). A number of approaches are available for the management of PONV after breast cancer surgery. First, the risk factors related to patient characteristics, surgical procedure, anesthetic technique, and postoperative care can be reduced. More specifically, the use of propofol-based anesthesia can reduce the incidence of PONV. Secondly, a wide range of prophylactic antiemetics, including butyrophenones (droperidol), benzamides (metoclopramide), glucocorticoids (dexamethasone), clonidine, a small dose of propofol, and serotonin receptor (SR) antagonists (ondansetron, granisetron, tropisetron, dolasetron, ramosetron, and palonosetron), are available for preventing PONV. Thirdly, antiemetic therapy combined with granisetron and droperidol or dexamethasone, and a multimodal management strategy which includes a package consisting of dexamethasone, total intravenous anesthesia with propofol, and ondansetron are highly effective in preventing PONV. Unfortunately, the use of glucocorticoids and SR antagonists for preventing PONV is not permitted in Japan according to national health insurance guidelines. Fourth, electro-acupoint stimulation at the P6 point (Nei-Guwan) as a non-pharmacologic therapy is as effective as ondansetron for preventing PONV. Knowledge of the risk factors for PONV, antiemetics, and a non-pharmacologic approach are needed for the management of PONV in women undergoing breast cancer surgery.

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Keywords Complications · Vomiting · Antiemetics · Combination · Electro-acupoint stimulation

Introduction

Worldwide, breast cancer is the most frequent malignant neoplasm in women and the leading cause of death from cancer for middle-aged women [1]. Since 1990, morbidity and mortality related to breast cancer has shown an increasing trend in Japan and, consequently, the number of breast cancer surgeries performed under general anesthesia is increasing [2]. Between 60 and 80% of patients undergoing mastectomy (with axillary dissection) experience postoperative nausea and vomiting (PONV) during the first 24 h after the induction of general anesthesia when no prophylactic antiemetic has been provided [3, 4]. PONV predispose to the aspiration of gastric contents, wound dehiscence, psychological distress, and delayed recovery and discharge times [5–8].

The vomiting reflex is a complex act coordinated by the vomiting center in the brainstem, which receives stimuli from the periphery via afferent neurons of the vagus nerves in the autonomic nervous system or centrally via the chemoreceptor trigger zone (CTZ), area postrema (AP), or nucleus of the solitary tract. Many transmitters, such as dopamine, histamine, muscarine, and serotonin, are involved in the process [5–8].

Antiemetics commonly used for preventing PONV act at various stages of the emetic pathways by blocking different neuroreceptors [5–8]. The most commonly used approaches to manage PONV following breast cancer surgery reported in published trials include: (1) the reduction of risk factors for PONV; (2) use of antiemetics; (3) combination and multimodal management strategies; (4) electro-acupoint stimulation at the P6 point as a non-pharmacologic technique.

Reduction of risk factors for PONV

Factors affecting PONV after mastectomy (with axillary dissection) are the patient's characteristics, the surgical procedure, the anesthetic technique, and postoperative care [5–8]. The incidence of PONV is threefold higher in males than females due to increased gonadotropin, estrogen, and plasma progesterone levels in women during their menstrual cycles [9]. Patients with a history of motion sickness and/or previous PONV are at increased risk for developing emetic symptoms because of a low threshold for vomiting [10]. Cigarette smoking confers protection against PONV due to the presence of an antiemetic substance in tobacco smoke [11], and thus the incidence of PONV is lower in smokers than in non-smokers [12]. Surgical risk factors for PONV are the site and the duration of surgery [5–8]. In a large study of 18,000 ambulatory patients, mastectomy (with axillary dissection) was associated with an increased risk of PONV [13]. Each 30-min increase in the duration of surgery increases the risk for PONV by 60%, so that a baseline risk of 10% is increased by 16% after 30 min [13]. Anesthesia-related factors for PONV include the choice of preanesthetic medication and anesthetic agents [nitrous oxide (N_2O), propofol] [5–8]. Premedication with opioids (morphine, fentanyl) increases the incidence of PONV by stimulating the central nervous system (CNS) opioid receptors [14]. The use of N_2O causes PONV by stimulating CNS catecholamine release [14] and by changes in middle ear pressure, resulting in traction on the membrane of the round window and consequent stimulation of the vestibular system [15]. The incidence of PONV is higher in patients receiving N_2O than in those receiving anesthetics or analgesics without N_2O [16, 17]. The use of propofol for maintenance of anesthesia has a positive effect on reducing PONV [18]: PONV is less frequent when propofol is administered compared with inhalational anesthetics [19]. Postoperative risk factors for PONV are pain, dizziness, ambulation, oral intake, and analgesics (opioids), all of which increase the incidence of PONV in women undergoing mastectomy (with axillary dissection) as well as other surgical procedures [5–8]. Consequently, avoiding these risk factors for PONV would result in fewer PONV episodes after breast cancer surgery.

Antiemetics

Antiemetics used to prevent PONV following breast cancer surgery include butyrophenones (droperidol), benzamides (metoclopramide), glucocorticoids (dexamethasone), clonidine, a small dose of propofol, and serotonin receptor (SR) antagonists (ondansetron, granisetron, tropisetron,

Table 1 Antiemetics

Classification	Regimen	Dose, route	Timing of administration	References
Butyrophenones	Droperidol	1.25 mg, i.v.	Immediately after induction of anesthesia	[2]
		20 μg/kg, i.v.	End of surgery	[20]
Benzamides	Metoclopramide	10 mg, i.v.	Immediately before induction of anesthesia	[25]
Corticosteroids	Dexamethasone	4 mg, i.v.	Immediately after induction of anesthesia	[28]
		4–8 mg, i.v.	End of surgery	[29]
α_2-adrenergic agonists	Clonidine	2 μg/kg, i.v.	Immediately before induction of anesthesia	[31]
Hypnotics	Propofol	0.5 mg/kg, i.v.	End of surgery	[21, 36]
Serotonin receptor (SR) antagonists	Ondansetron	4–8 mg, i.v.	Immediately after induction of anesthesia	[2, 28, 36]
		4 mg, i.v.	End of surgery	[37]
	Granisetron	40 μg/kg, i.v.	Immediately before induction	[38, 39]
		2 mg, orally	1 h before surgery	[40]
		1 mg, i.v.	Just before induction of anesthesia	[41, 42]
	Tropisetron	2–5 mg, i.v.	Immediately before induction of anesthesia	[43]
	Dolasetron	12.5 mg, i.v.	15 min before end of surgery	[44]
	Ramosetron	0.1–0.3 mg, i.v.	End of surgery	[45]
		0.1 mg, orally	1 h before surgery	[46]
	Palonosetron	0.075 mg, i.v.	Immediately before induction of anesthesia	[47]

i.v. Intravenously

dolasetron, ramosetron, and palonosetron) (Table 1). Unfortunately, the use of glucocorticoids and SR antagonists for preventing PONV is not permitted in Japan according to the national health insurance guidelines.

Butyrophenones possess antiemetic activity due to their antagonism at dopamine receptors [20]. Droperidol has been widely accepted as the first-line therapy in the management of PONV [5–8]. Droperidol 20 μg/kg administered intravenously (i.v.) at the end of surgery is effective in preventing PONV after mastectomy (with axillary dissection) [21]. Female patients receiving droperidol 1.25 mg i.v. immediately after the induction of anesthesia experience less PONV than those receiving placebo [2]. When used at large doses (>2.5 mg), droperidol produces undesirable adverse effects, including drowsiness, dysphoria, restlessness, and extrapyramidal signs [5–8]. In 2001, the U.S. Food and Drug Administration (FDA) issued warnings on droperidol-related adverse events because of its dysrhythmogenic effects, such as prolonged QT syndrome [22]. However, after careful evaluation of all reports submitted to the FDA, Habib and Gan [23] concluded that none of the cases in which arrhythmia occurred after small doses of droperidol (<1.25 mg) provided evidence of a cause-and-effect relationship.

Benzamides have both central [chemoreceptor trigger zone (CTZ) and AP vomiting centers] and peripheral (gastrointestinal tract) antiemetic actions by blocking dopaminergic receptors and by increasing esophageal sphincter tone and promoting gastric motility, thereby preventing the delayed gastric emptying produced by the opioid analgesics [24]. Metoclopramide is an antiemetic used widely in clinical practice [5–8]. However, in women scheduled for breast cancer surgery, metoclopramide 10 mg administered i.v. immediately before the induction of anesthesia does not reduce the incidence of PONV [25]. Higher doses (>0.2 mg/kg) of metoclopramide are associated with extrapyramidal reactions, such as akathisia and motor restlessness [5–8].

Dexamethasone is an inexpensive and effective antiemetic drug with minimal adverse effects after a single-dose administration [26]. The exact mechanism by which dexamethasone exerts it antiemetic action is not fully understood, but possibilities include central or peripheral inhibition of the synthesis of prostaglandins or changes in the permeability of the blood–brain barrier to serum proteins [26, 27]. Dexamethasone 4 mg administered i.v. immediately after the induction of anesthesia is effective as prophylaxis against PONV after mastectomy (with axillary dissection) [28]. Similarly, dexamethasone 4–8 mg administered i.v. at the end of surgery reduces the incidence of PONV [29].

The α_2-adrenergic agonist clonidine has a number of beneficial effects, including an enhancement of postoperative analgesia of opioids and a reduction of anesthetic and/or opioid requirements during perioperative periods [30]. Co-induction with i.v. clonidine 2 μg/kg is effective for the prevention of PONV after breast cancer surgery without any increase in postoperative sedation [31]. The mechanism of its antiemetic action is unknown, but it is probably multifactorial. The reduced need for anesthetics and/or opioids during clonidine treatment decreases the incidence of PONV [31]. Clonidine inhibits catecholamine release, which in turn triggers emetic symptoms, thereby contributing to the reduction of PONV [5–8, 14].

Propofol possesses direct antiemetic properties [32] that are not a result of the lipid emulsion in its formulation [33]. Although the exact mechanism by which propofol acts as an antiemetic is not known, it is considered to have vagolytic properties [33]. The results obtained in an experimental model indicate the possibility that the antiemetic property of propofol is associated with the reduced levels of serotonin in the AP and cerebrospinal fluids [34]. A small dose (0.5 mg/kg) of propofol administered i.v. at the end of surgery reduces the incidence of PONV [35] and is as effective as droperidol for the prevention of PONV in women receiving general anesthesia (sevoflurane and air in oxygen) for mastectomy (with axillary dissection) [21].

SR antagonists (ondansetron, granisetron, tropisetron, dolasetron, ramosetron, and palonosetron) are highly effective in preventing PONV after breast cancer surgery [2, 25, 28, 36–47]. Palonosetron, a novel SR antagonist with a greater binding affinity and longer half-life than other SR antagonists, has recently been approved in the USA for managing PONV [48]. The actions of SR antagonists involve both central and peripheral mechanisms mediating the control of emetic symptoms. Centrally, SR antagonists bind competitively and selectively to serotonin receptors in the CTZ. In addition to their central effects, they also block receptors in the gastrointestinal tract, which prevents the action of serotonin and inhibits emetic symptoms [49]. When administered i.v. immediately after the induction or at the end of surgery, ondansetron 4–8 mg reduces the incidence of PONV [2, 29, 37, 38] and is as effective as droperidol 1.25 mg [2]. Prophylactic granisetron administered i.v. (40 μg/kg) immediately before the induction of anesthesia or given orally (2 mg) 1 h before surgery also reduces the incidence of PONV [38–40]. The antiemetic efficacy of granisetron 40 μg/kg is superior to that of traditional antiemetics, namely, droperidol 1.25 mg and metoclopramide 10 mg, as prophylaxis against PONV [25]. Female patients receiving granisetron 1 mg i.v. immediately before the induction of anesthesia experience less PONV than those receiving droperidol 1.25 mg i.v. [41], and granisetron 1 mg administered i.v. just before the induction of anesthesia is as effective as ondansetron 4 mg for the prevention of PONV [42]. Tropisetron 2–5 mg administered i.v. immediately before the induction of

anesthesia is also effective for preventing PONV [43]. Dolasetron 12.5 mg administered i.v. 15 min prior to the end of anesthesia reduces the incidence of PONV [44]. Ramosetron 0.3 mg administered i.v. at the end of surgery is more effective than granisetron 3 mg for the long-term prevention of PONV [45]. Preoperative oral disintegration of a ramosetron 0.1 mg tablet is as effective as ramosetron 0.1 mg administered i.v. at the end of surgery [46]. Palonosetron 0.075 mg administered i.v. immediately before the induction of anesthesia reduces the incidence of PONV [47]. SR antagonists are generally well tolerated with few adverse effects [6, 7]. Because they have no affinity for dopaminergic receptors, muscarinic cholinergic receptors, and histamine receptors, they are not associated with sedation and/or anticholinergic effects [6, 7]. Headache is the most commonly reported adverse event in clinical trials of SR antagonists for PONV after breast cancer surgery [2, 25, 28, 36–47]. In Japan, SR antagonists (e.g., US$100.00 for ondansetron 3 mg) are much more expensive than traditional antiemetics (US$1.80 for droperidol 1.25 mg and US$0.60 for metoclopramide 10 mg). This higher cost may delay the widespread use of SR antagonists as antiemetics.

NK-1R antagonists, such as aprepitant, competitively inhibit the binding of substance P, which plays an important role in emesis as a ligand for NK-1Rs located in the nucleus tractus solitarius and the AP of the CNS [50]. Therefore, aprepitant may be effective in the prevention of PONV after breast cancer surgery due to its ability to block input from emetic stimuli to the CNS. However, no published articles are yet available on the use of NK-1R antagonists in women undergoing mastectomy (with axillary dissection).

Combination and multimodal management strategies

None of the currently available antiemetics are entirely effective, perhaps because most of them act by blocking one type of receptor. Therefore, a combination of antiemetics with different sites of activity would be more effective than an antiemetic alone [51]. Combination antiemetic therapy is effective for preventing PONV in women undergoing breast cancer surgery [41, 52, 53] (Table 2). In terms of PONV prevention, the efficacy of combined granisetron 3 mg and droperidol 1.25 mg administered i.v. immediately before the induction of anesthesia is superior to that of each drug alone [54]. Dexamethasone decreases chemotherapy-induced emesis when used in combination with SR antagonists (e.g., ondansetron) [55]. The combination therapy of granisetron 40 μg/kg plus dexamethasone 8 mg is more effective than granisetron alone, administered i.v. immediately before the induction of anesthesia, in reducing the incidence of PONV [53]. Similarly, adding dexamethasone 5 mg to granisetron 1 mg administered i.v. immediately before the induction of anesthesia increases the antiemetic efficacy of granisetron alone as prophylaxis against PONV [41]. The mechanism by which dexamethasone enhances the antiemetic efficacy is unknown, but it is hypothesized that corticosteroids may reduce serotonin levels in neural tissue by depleting its precursor tryptophan, the anti-inflammatory properties of corticosteroids may prevent the release of serotonin in the gut, and/or dexamethasone may potentiate the main effect of other antiemetics by sensitizing the pharmacologic receptor [55–57].

The choice of a multimodal regimen for preventing PONV is based on its efficacy and safety [4, 5, 57]. The multimodal management strategy, which includes a package consisting of dexamethasone, total intravenous anesthesia with propofol, and ondansetron, is highly effective for preventing PONV in women undergoing breast cancer surgery [58] (Table 2).

Non-pharmacologic therapy

Acupressure and acupuncture have been evaluated as non-pharmacologic methods for the prevention of PONV [5–8]. In acupressure, manual stimulation is applied, whereas in acupuncture, the skin is pierced with a needle. Most published articles indicate the efficacy of acupressure and acupuncture at the P6 point (Nei-Guwan) located between the flexor tendons three fingerbreadths below the hand–wrist crease. These non-pharmacologic techniques are

Table 2 Combination and multimodal management strategies

Classification	Regimen	Dose, route	Timing of administration	References
Combination	Granisetron + droperidol	3 mg, i.v. + 1.25 mg, i.v.	Immediately before induction of anesthesia	[52]
	Granisetron + dexamethasone	1 mg, i.v. + 5 mg, i.v.	Immediately before induction of anesthesia	[41]
	Granisetron + dexamethasone	40 μg/kg, i.v. + 8 mg	Immediately before induction of anesthesia	[53]
Multimodal (package)	Dexamethasone	8 mg, orally	1–2 h before surgery	[58]
	TIVA with propofol	–	–	
	Ondansetron	4 mg, i.v.	20 min before end of surgery	

TIVA Total intravenous anesthesia

more effective than placebo for the prevention of PONV within 6 h postoperatively [59]. Electrical stimulation on the P6 point during the surgical procedure was found to be more effective than placebo for preventing PONV in women undergoing breast cancer surgery and as effective as ondansetron 4 mg administered i.v. at the induction of anesthesia [60]. In contrast, the application of acupuncture at the P6 point for 20 min before or immediately after the induction of anesthesia does not decrease the incidence of PONV [61].

Current best and novel approaches available to Japanese anesthesiologists for managing PONV after breast cancer surgery

The first step is to reduce the risk factors associated with patient characteristics, the surgical procedure, anesthetic technique, and postoperative care. Specifically, the use of propofol-based anesthesia can reduce the incidence of PONV. Secondly, prophylactic antiemetics, including butyrophenones (droperidol), benzamides (metoclopramide), glucocorticoids (dexamethasone), clonidine, a small dose of propofol, and SR antagonists (ondansetron, granisetron, tropisetron, dolasetron, ramosetron and palonosetron) are available for preventing PONV. Thirdly, antiemetic therapy combined with granisetron and droperidol or dexamethasone, and multimodal management strategy, which includes a package consisting of dexamethasone, total intravenous anesthesia with propofol, and ondansetron, are highly effective in the prevention of PONV. Unfortunately, the use of glucocorticoids and SR antagonists for preventing PONV is not permitted in Japan according to the national health insurance guidelines. Fourthly, electro-acupoint stimulation at the P6 point (Nei-Guwan) as a non-pharmacologic therapy is as effective as ondansetron for preventing PONV.

Conclusion

Knowledge of the risk factors for PONV, antiemetics, and a non-pharmacologic approach is needed for the management of PONV in women undergoing breast cancer surgery.

Conflict of interest The author has no conflict of interest to declare in relation to the information contained in this article.

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