Original Article

Comparison of granisetron, metoclopramide and gastric decompression for prevention of postoperative nausea and vomiting after fast track cardiac anesthesia

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Abstract

BACKGROUND: Different methods have been suggested to prevent postoperative nausea and vomiting (PONV), but the efficacy of these methods has not been fully studied in fast track cardiac anesthesia (FTCA).

METHODS: In a randomized double blind clinical trial study, 120 patients aged 18-70 years with ASA II or III, undergoing elective cardiac surgery, were selected. They were divided randomly into four groups. In group M, group G and group P, intravenous (IV) metoclopramide (0.1 mg/kg), granisetron (0.01 mg/kg), and normal saline were administered, respectively, about thirty minutes before extubation in the intensive care unit (ICU). In group N, a nasogastric (NG) tube was inserted after tracheal intubation in the operating room and removed about thirty minutes before extubation in the ICU. The incidence and severity of nausea and the episodes of vomiting were recorded by a blinded investigator at the time of extubation and performed regularly for a maximum of 24 hours. Assessment of severity of nausea was scored using a visual analogue scale (VAS) device. Data were analyzed by using ANOVA, chi-squared and Kruskal-Wallis and repeated measures tests.

RESULTS: Overall the 24-h incidence of PONV was significantly lower in the G and M groups than in the P and N groups (10% and 16.7% vs. 33.3% and 40%, respectively; P < 0.02). Postoperative rescue medication was significantly less required in the G and M groups compared to the other two groups (P < 0.01). Less satisfaction, according to PONV status, was observed in the P and N groups (P < 0.01).

CONCLUSIONS: According to this study, metoclopramide and granisetron, but not gastric decompression, are effective regimens for preventing PONV after FTCA. Given the economics and a considerable background incidence in patients exhibiting PONV, we suggest metoclopramide as a routine prophylactic antiemetic in FTCA.

KEYWORDS: Cardiac surgical procedures, postoperative nausea and vomiting, granisetron, metoclopramide, gastrointestinal intubation.

Nausea and vomiting are two of the most frequently experienced postoperative side effects, with major concerns for the patients and physicians in the postoperative period.[1] The prevalence of postoperative nausea and vomiting (PONV) may complicate about one third of surgical procedures.[2,3] Information on the incidence of PONV in patients undergoing cardiac surgery is limited, but the reported incidence is around 49%–67%.[4-6] The etiology of PONV is intricate and multifactorial.[7] Risk factors include female gender, non-smoking condition, age, previous history of PONV or motion sickness, and use of particular inhalation agents (nitrous oxide, in particular), simultaneous use of opiate medications and duration of anesthesia and surgery.[8,9] This "big little problem" can result in significant morbidity [2,10,11] and prolong intensive care unit (ICU) stay[3,4] and delay

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discharge after fast track cardiac anesthesia (FTCA).[12] It also reduces patient satisfaction and the efficiency of services. Kogan et al defined FTCA as perioperative anesthetic management aimed at facilitating tracheal extubation within 8–10 hours after surgery and discharge from the ICU on first postoperative day.[12] Most research has been aimed at prevention rather than therapy of established PONV. [13] Furthermore, few trials have been made to address the overall efficacy of a prophylactic strategy. The most common drugs used for the treatment of PONV include butyrophenones, benzamides, histamine receptor antagonists, muscarinic receptor antagonists, and 5-HT3 (5-hydroxy tryptamine 3) receptor antagonists. [14] Nonpharmacologic treatment methods, such as acupuncture, acupressure and supplemental oxygen have also been studied for their efficacy in the prevention of PONV.[14,15] Ondansetron and granisetron are selective 5-HT3 receptor antagonists and provide an efficient treatment for PONV.[16] However, less information is available on the use of granisetron especially in patients undergoing cardiac surgery. Meanwhile, the greater selectivity of granisetron than that of ondansetron for 5-HT3 receptors[16] contributed to choosing it for this study. On the other hand, a nonpharmacological strategy for prevention of PONV is gastric decompression. Gastric distension, especially during manual ventilation, increases intragastric pressure and predisposes to vomiting. Studies assessing the role of gastric decompression in the prevention of PONV after various types of surgeries have reported contradictory results.[17,18] There is still no reliable and efficient medication for the prevention of PONV. With the current tendency of increasing FTCA, the need for an effective antiemetic treatment that provides earlier discharge and the best patient outcome at the most reasonable cost becomes important. Therefore, this prospective, randomized, double-blind, placebo controlled study was conducted to evaluate the efficacy and safety of intravenous metoclopramide versus granisetron and compare them with gastric

decompression or placebo for the prevention of PONV after cardiac surgery.

Methods

After obtaining approval from the Institutional Research Committee and written, informed consent from the patients, we studied 128 consecutive patients undergoing elective cardiac surgery with cardiopulmonary bypass (CPB). Patients who underwent coronary artery bypass grafting, valve-related and combined procedures were included, according to convenience sampling method. Adult patients between 18 and 70 years of age with American Society of Anesthesiologists (ASA) physical status of II or III were eligible to participate in this randomized double blind clinical trial study, during a 2 month period. Patients with past history of hiatus hernia, heartburn, or previous gastric surgery, those with morbid obesity, mental retardation, or psychiatric illness and patients taking antiemetic medication, H2-receptor antagonist, or proton pump inhibitors, were excluded from the study. Other exclusion criteria were patients who were not tracheally extubated within 12 hours after the end of surgery, intraaortic balloon pump (IABP) requirement during surgery, and emergency re-sternotomy. All operations were performed by the same surgical team and with similar method of surgery and anesthesia. Patients were intramuscularly premedicated with morphine (0.1 mg/kg) about 30 to 60 minutes before surgery and were NPO for 8 hours preoperatively. After establishment of peripheral venous and arterial access, patient induction was performed by intravenous administration of fentanyl (4 μg/kg), sodium thiopental (5 mg/kg), and lidocaine (1.5 mg/kg). Pancuronium (0.1 mg/kg) was administered to facilitate tracheal intubation. An anesthesiologist conducted tracheal intubation, and anesthesia was subsequently maintained by administrating isoflurane (0.5-1.5 MAC), 100% oxygen and morphine (0.1 mg/kg). During the cardiopulmonary bypass (CPB), midazolam (1 μg/kg/min after a 1-mg IV bolus)

and fentanyl (2 μg/kg/h) were prescribed. Intraoperatively, fluid administration aimed to maintain a central venous pressure of 5–12 mmHg. Ventilation was adjusted with a tidal volume of 8-10 ml/kg to maintain normocapnia (end-tidal CO_2, 35-40 mmHg). In the case of CPB system, a membrane oxygenator [Affinity, Medtronic, USA] and crystalloid prime solution (including 1 L of Ringer lactate, 500 mL of hemaxel and 60 g of mannitol) were used; and all patients were cooled by 30-32°C. Continuous flows of 2.4-2.8 L/min/m2 were used to maintain perfusion pressure of 50-70 mmHg during CPB. During bypass, the hematocrit was maintained between 20% and 25%. In managing arterial blood gas (ABG), α-stat protocol was used. Rewarming was continued to 37°C before separation from CPB. Discontinuation from CPB was supported by inotropic drugs, if necessary. Neuromuscular block was not antagonized at the end of the surgical procedure. At the end of the surgical operation, the patients were transferred to the cardiac intensive care unit (ICU) and underwent mechanical ventilation. Following establishment of patients' hemodynamic stability and adequate oxygenation, stable metabolic status and adequate mentation, weaning from ventilation and tracheal extubation were performed according to the protocol proposed by the fast-track cardiac care team.[19] Based on a computer-generated randomization table[20] and before induction of anesthesia, the participants were allocated by the anesthesiologist to one of the four groups of antiemetic prophylaxis. It was estimated that with 29 patients per prophylaxis group, a difference of 30% in clinical efficacy comparing with the placebo group could be found with a statistical power of 80% and a cutoff point for significance of 0.05. To compensate for patients not completing the study, we randomized 32 patients to each group. After weaning from the ventilator but before tracheal extubation in ICU, group M received intravenous metoclopramide (0.1 mg/kg) diluted to 5 mL with 0.9% saline. Group G received granisetron [Kytril® Injection, 1 mg/mL] (0.01 mg/kg) in 5 mL of 0.9% saline,

and the placebo group (group P) received 5 mL of 0.9% saline. Study drug was prepared and administered by an anesthesiologist at the investigative site who was not involved in data collection. In group N, a nasogastric (NG) tube was inserted after intubation in the operating room and then, connected to a free drainage bag. It was removed postoperatively in the intensive care unit (ICU) immediately after weaning from the ventilator but before tracheal extubation to avoid any pharyngeal stimulation-induced vomiting. The incidence and severity of nausea and vomiting were recorded by a blinded investigator, who was not involved in anesthetic and ICU care. Severity of nausea was assessed using a visual analogue scale (VAS) device (0 to 10 cm choice) with 0 representing "no nausea" and 10 cm representing "nausea as bad as it can be". Vomiting was scored in accordance with the number of episodes of emesis occurred. Nausea was defined as the unpleasant sensation of the imminent need to vomit without any expulsive muscular movements. Vomiting was defined as forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature. Retching was defined as spasmodic respiratory movements against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents. An emetic episode (EE) was defined as a single vomit or retch or any number of continuous vomits or retches. Observations were recorded after tracheal extubation at the time of zero and then performed hourly for 4 hours and then, every 4 hours until the patient was discharged from the ICU, or for a maximum of 24 hours (VAS0 to VAS24) (figure 1). Time zero was the time when the patient was awake enough to respond Ramsay Sedation Scale of 2 or less [21] and indicate the level of nausea on the VAS (the notion was explained to patients preoperatively). Postoperative pain was managed with intravenous morphine, 2 to 4 mg, boluses if patients asked for analgesics or experienced pain with a VAS pain score of more than 3. Sedation with IV midazolam (2 to 4 mg) was permitted until 30 minutes before
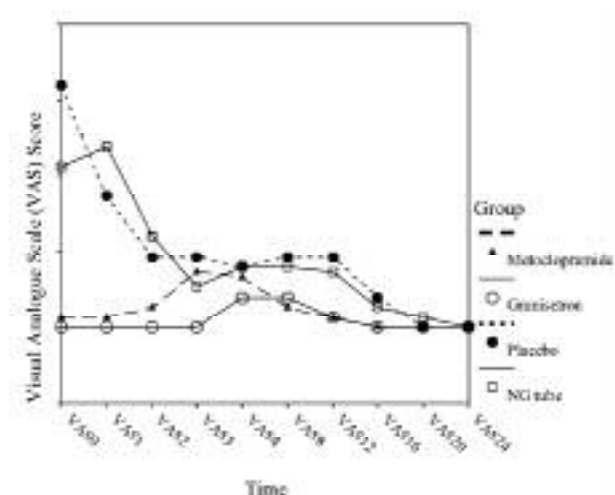
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Figure 1. Postoperative details of nausea severity according to median visual analogue scale (VAS) scores in each group. VAS0, VAS1, VAS2, VAS8, VAS12 and VAS16: P < 0.05, group M and group G versus group N and group P; VAS3 and VAS4: P < 0.05, group G versus group M, group N and group P (for more details see the text).

extubation. All of the subjects were NPO for 6 hours after extubation. First-line rescue medication, in the form of metoclopramide 0.1 mg/kg IV, was administered by the nurse caring for the patient if the patient experienced one EE or more and a score of 4 or more recorded on the nausea. Granisetron (0.01 mg/kg) was prescribed by a blinded attending anesthesiologist as a second-line medication in patients who continued to vomit or experienced persistent nausea 30 minutes after metoclopramide administration. The number of doses of antiemetic given was also recorded. Data collection included patient age, gender, weight, height, smoking status, previous PONV, type of procedure, duration of surgery, duration of CPB, total morphine consumption, duration of ventilation, severity of nausea, number of EE, need for rescue medication and ICU length of stay. Discharge criteria were based on the accelerated-recovery approach.[22] In addition to the 24-h PONV follow-up, patients were asked for satisfaction outcomes according to PONV status in the ICU. Answers were graded from 1 (very satisfied) to 5 (not satisfied at all). Gaussian distribution of vari-

ables was checked by one sample Kolmogorov-Smirnov test. Frequencies were compared by χ^2 and Fisher's exact tests. Differences in continuous variables among the four alternatives were evaluated by an analysis of variance (ANOVA) test or a Kruskal-Wallis test according to variable distribution and category. A Tukey test and Mann-Whitney U-test with Bonferroni's correction were used for post hoc comparisons. Repeated measures analysis was performed to compare groups at different evaluation times. Cumulative incidences of nausea and emesis were examined to eliminate confounding effects of the rescue antiemetic. Parametric data are presented as mean ± SD and nonparametric data as median (interquartile range). In every statistical test, P < 0.05 was considered as statistically significant. The statistical analysis was performed with SPSS for Windows version 11.5.

Results
During a 2 month period, a total of 164 patients were scheduled for cardiac surgery in our institution. Of these patients, 128 met inclusion criteria, provided informed consent, and were qualified for the study. Eight patients were excluded from the data; two because of protocol violation, three for prolonged ventilation after the end of surgery, one required intraoperative IABP and two required re-sternotomy for bleeding. Finally, 120 patients were eligible for the statistical analysis. Patients' characteristics, including demographic data and baseline characteristics are described in table 1. There were no significant differences among the four groups in factors that could modify the incidence of PONV as background factors, factors related to the operation or anesthesia. Average risk of PONV, according to simplified risk score by Apfel and colleagues, [23] was not statistically different among the four groups. There were no significant differences in pain intensity and total dose of postoperative opioids among groups in the ICU. No adverse reactions were reported including asthenia, somnolence, diarrhea, and constipation with granisetron and extrapyramidal side effects with me-

toclopramide. There were no bleeding complications associated with gastric tube insertion in group N. No detrimental complications related to PONV were observed. The overall incidence of PONV, up to 24 hours in the ICU, after FTCA was 33.3% in the placebo group, compared with 40%, 16.7% and 10% in the N, M and G groups, respectively. Prophylactic administration of granisetron or metoclopramide

before the tracheal extubation in the ICU resulted in a significantly smaller proportion of patients with PONV during the 24-h observation period than placebo or nasogastric tube insertion (table 2). Twenty-three (19.2%) patients with PONV were treated with IV metoclopramide and 10 (8.3%) with PONV refractory to metoclopramide were treated with IV granisetron. Overall, fewer patients in group

Table 1. Demographic and morphometric factors and clinical data.

Variable	Group M (n = 30)	Group G (n = 30)	Group N (n = 30)	Group P (n = 30)	P Value
Gender (M/F)	16/14	15/15	14/16	18/12	NS
Age (yr)	50.6 ± 15.2	50.8 ± 14.6	51.2 ± 15.3	50.8 ± 14.9	NS
BMI	26.1 ± 3.9	25.1 ± 4.3	24.1 ± 3.7	23.3 ± 4.1	NS
Previous PONV	3 (10)	1 (3.3)	1 (3.3)	3 (10)	NS
No smoking	23 (76.7)	22 (73.3)	23 (76.7)	24 (80)	NS
ASA physical status (II/III)	12/18	14/16	11/19	13/17	NS
Duration of surgery (minutes)	254.5 ± 52.6	259.7 ± 51.7	256.5 ± 50.4	259.1 ± 53.2	NS
Bypass time (minutes)	88.1 ± 24.3	90.2 ± 22.4	87.4 ± 20.7	93.4 ± 23.1	NS
Average risk of PONV*	2 (2-4)	2 (2-4)	2 (2-4)	2 (2-4)	NS
Surgery					NS
CABG	22	21	20	21	
Valvular	3	5	5	4	
Congenital	4	3	5	4	
Other (e.g., valves + grafts)	1	1	0	1	

Data are presented as the number or means ± SD or number (%) except Apfel's score, which is median (interquartile range).

*According to simplified risk score by Apfel and colleagues, assessed by the number of the four most relevant risk factors, i.e. gender, history of previous PONV, smoking status and postoperative opioids.[23]

Abbreviations: group M, metoclopramide; group G, granisetron; group N, nasogastric tube; group P, placebo; BMI, body mass index; PONV, postoperative nausea and vomiting; ASA, American Society of Anesthesiologists; CABG, coronary artery bypass graft

Table 2. Data relating to the stay in the intensive care unit.

Variable	Group M	Group G	Group N	Group P	P Value
Duration of ventilation (minutes)	310 ± 59	304 ± 62	295 ± 57	314 ± 67	0.99
Time to extubation (minutes)	345 ± 68	337 ± 72	334 ± 71	347 ± 67	0.93
Total morphine consumption (mg)	8.5 ± 1.9	9.2 ± 2.4	10.2 ± 2.8	9.5 ± 2.1	0.52
Total midazolam consumption (mg)	4.9 ± 1.2	5.5 ± 1.4	5.9 ± 1.3	5.2 ± 1.7	0.67
Patients with nausea	5 (16.7)	3 (10)	10 (33.3)	10 (33.3)	0.02*
Patients with emetic episodes	3 (10)	2 (6.7)	5 (16.7)	7 (23.3)	0.29
Patients with PONV	5 (16.7)	3 (10)	12 (40)	10 (33.3)	0.02*
Patients requiring first-line rescue medication	4 (13.4)	2 (6.7)	8 (26.8)	9 (30)	0.02*
Median time† to first emetic event (minutes)	189	206	78	65	0.001*
Patients requiring second-line rescue medication	2 (6.7)	1 (3.35)	3 (10)	4 (13.4)	0.15
Length of ICU stay (hour)	21.1 ± 4.7	20.2 ± 4.1	19.2 ± 3.9	22 ± 4.5	0.91
Satisfaction of patients#	1.9 ± 0.7	2.3 ± 0.9	4 ± 1.3	4.1 ± 1.2	0.01*

Data are presented as means ± SD or number (%).

†time= 0, time from tracheal extubation.

*A significant difference (P<0.05) was found in group M and in group G when compared with the other groups.

#Answers were graded from 1 (very satisfied) to 5 (not satisfied at all).

P value for PONV calculated by chi-squared test; the severity of nausea or vomiting calculated by Mann-Whitney test.

M and group G received rescue medication(s) compared with patients in group P or group N. The median time to first rescue antiemetic was smaller in group P and group N compared with patients in group M and group G. The incidence of EEs after tracheal extubation was not statistically different among the groups (P = 0.29). The median VAS nausea score at 0, 1, 2, 8, 12 and 16 hours was significantly higher in group P and group N than in group M and group G (Figure 1). The peak VAS nausea score was observed later and with less severity in group M and group G than in group P or group N. Patient satisfaction, according to PONV status, in the ICU was considerably superior in group M and group G compared with other groups. There was no difference according to the length of ICU stay among the four groups.

Discussion

PONV is a frequent problem and a potential source of complications after cardiac surgery. Cardiac surgery represents a major procedure associated with many risk factors for nausea and vomiting, including prolonged duration of the surgery,[24] catecholamine administration,[25] large doses of opioids,[26] perioperative hemodynamic instability and gut mucosal hypoperfusion,[27,28] and variable period of mechanical ventilation in ICU. While PONV is an unpleasant experience for every patient, EEs following cardiac surgery may have unfavorable effects such as increased myocardial ischemia and postoperative bleeding. In high risk patients, who can now be identified by simplified and validated risk scores, it may be ethically questionable to wait until they suffer PONV.[8-11] Since FTCA has become popular, clinicians may have more problems with PONV.[22] In this study, surgical and anesthetic factors that may have modified the incidence of PONV were well balanced among groups, so the differences can be attributed to the different antiemetic regimens administered. It has been shown that the different incidences of PONV after most operations are mostly caused by the associated risk factors and less by the operation itself.[24] Thus, instead of selecting patients undergoing just one type of cardiac surgery, we selected patients who underwent a variety of cardiac surgical procedures. More over, we used a validated and simplified risk score, suggested by Apfel and colleagues,[24] to identify and compare patients with an increased risk in the four groups. We also selected a placebo group in our study because there is no common gold standard for preventing PONV.[26] Moreover, we could calculate the overall incidence of PONV in patients avoiding prophylactic antiemetics. We found that metoclopramide and granisetron are equally effective in the prophylaxis of PONV after FTCA. Both drugs reduced the early requirement for rescue antiemetic by one half and significantly reduced the incidence of PONV over the 24-hour study period. Despite early administration of rescue antiemetics to 30% of the placebo group and 26.6% of the NG tube group, the overall incidence of nausea and emesis remained lower in the metoclopramide and granisetron groups for the first 16 hours, indicating a preemptive benefit of prophylaxis (figure 1). However, the VAS nausea score at 3 and 4 hours was fairly higher in metoclopramide group than in granisetron group. This could be due to longer duration of action of granisetron. The median time to first emetic event was considerably longer in metoclopramide and granisetron groups. Therefore, the shape of the curves in figure 1 (the convergence and then the divergence of the curves in group M and group G versus group P and group N) can be better explained. Patient satisfaction has been suggested as the main outcome instead of PONV.[2] In the present study, patients were also more satisfied in the metoclopramide and granisetron groups. For sample size estimation, it was assumed that a difference of 30% in clinical efficacy among groups could be found. However, our study showed only a relatively lower difference between the groups (about 20%). Therefore, our study was effectively underpowered to detect a difference in EEs (P = 0.29). Our observed incidence of PONV was relatively less than ex-

pected from previous studies.[3-6] The background incidence of patients exhibiting PONV (i.e., in patients receiving placebo) was 33.3%. In this group, 33.3% of patients had nausea and 23.3% had vomiting. Grebenik and Allman[4] and Woodward and colleagues [5] have previously reported a 46-49% incidence of nausea and 37-42% incidence of vomiting in their patients after cardiac surgery. Similar data were reported by Halvorsen et al,[6] looking at the effect of dexamethasone on side effects after CABG; they reported that 42% of patients in the control group needed antiemetic rescue therapy on the first postoperative day. This difference could have occurred as a result of the following reasons:

a) Our practice of using low doses of fentanyl (4 µg /kg at the induction and 2 µg/kg/h during CPB time) and low doses of morphine (9.5 ± 2.1 mg during the postoperative period).

b) Our care to avoid the use of drugs with a proemetic profile including N_2O, etomidate, or neostigmine.

c) Gan and colleagues [28] considered the use of gut hypoperfusion during CPB as another possible cause of PONV. The duration of CPB in our patients was relatively short (93.4 ± 23.1 minutes). Hemodynamic parameters were specially monitored with precise controlling of intraoperative hydration and oxygen concentration and vasopressors or vasodilators.

d) High concentration of catecholamines has been advocated as a cause of PONV.[25] However, only 14 (11.6%) patients received mild inotropic support at the time of extubation. The total amount of intraoperative and postoperative inotropic use was similar in the four groups.

e) It is suggested that midazolam has an effective antiemetic property.[29] Indeed, in our study, the patients received midazolam during the CPB and after that in the ICU before extubation.

The treatment of nausea and vomiting appears to be much more cost-effective compared with prophylactically given antiemetics, [12] but this approach is a satisfactory option for patients undergoing surgical procedures with a low frequency of PONV. However, in our study, a significant incidence of PONV and less satisfaction scores were observed in the placebo group comparing with the cases in the metoclopramide and granisetron groups. Therefore, we recommend employing a routine prophylactic regimen in FTCA setting before extubation of patients in ICU. This strategy avoids detrimental effects of EEs in cardiac surgery procedures and the cost of rescue treatments while providing reasonable control of emesis. According to our regimen, metoclopramide 0.1 mg/kg IV is cost-effective in most cases, while granisetron 0.01 mg/kg IV has relatively similar therapeutic effects. However, in our study, the length of the ICU stay was not influenced by the type of antiemetic regimen. This could be due to adoption of discharge criteria according to the accelerated-recovery approach, and not merely considering the PONV status alone. Wattwil et al[30] found no association between delayed postoperative gastric emptying and PONV in patients undergoing laparoscopic cholecystectomy, suggesting that gastric emptying may be not a predictor of PONV. Another study by Burlacu and colleagues suggested that gastric decompression might have no advantage for this group of patients. Even it may result in a trend towards a more frequent incidence of PONV. They removed the gastric tube in ICU at the same time as tracheal extubation.[17] The presence of the gastric tube may stimulate mechanoreceptors in the pharyngeal area followed by an increase of the afferent input to the "vomiting" center.[31] In our study, in order to omit the potential for observer bias and reduce the patient bias in group N, NG tube was removed postoperatively in ICU about thirty minutes before tracheal extubation to avoid any pharyngeal stimulation-induced vomiting. Since patients typically remain ventilated for at least 6 hours postoperatively, we believed that early removal of the NG tube at the end of surgery might have obviated any benefit in terms of reducing PONV. Despite these considerations, our study has shown that during anesthesia and mechanical ventilation in ICU,

gastric decompression does not reduce the incidence of PONV after surgery; so it is not recommend for routine use in FTCA.

In conclusion, in this randomized, double blind study, we have demonstrated that prophylactic granisetron or metoclopramide before tracheal extubation effectively reduces PONV after FTCA. Given a considerable background incidence of PONV in cardiac surgical procedures and the economics, we suggest metoclopramide as a routine prophylactic antiemetic in FTCA.

References

1. Macario A, Weinger M, Carney S, Kim A. **Which clinical anesthesia outcomes are important to avoid? The perspective of patients.** *Anesth Analg* 1999; 89**:** 652-658.
2. Fisher DM. **The "big little problem" of postoperative nausea and vomiting: do we know the answer yet?** *Anesthesiology* 1997; 87**:** 1271-1273.
3. Mace L. **An audit of post-operative nausea and vomiting, following cardiac surgery: scope of the problem.** *Nurs Crit Care* 2003; 8**:** 187-196.
4. Grebenik CR, Allman C. **Nausea and vomiting after cardiac surgery.** *Br J Anaesth* 1996; 77**:** 356-359.
5. Woodward DK, Sherry KM, Harrison D. **Antiemetic prophylaxis in cardiac surgery: comparison of metoclopramide and ondansetron.** *Br J Anaesth* 1999; 83**:** 933-935.
6. Halvorsen P, Raeder J, White PF, Almdahl SM, Nordstrand K, Saatvedt K *et al*. **The effect of dexamethasone on side effects after coronary revascularization procedures.** *Anesth Analg* 2003; 96**:** 1578-83, table.
7. Carpenter DO. **Neural mechanisms of emesis.** *Can J Physiol Pharmacol* 1990; 68**:** 230-236.
8. Sanger GJ, Andrews PL. **Treatment of nausea and vomiting: gaps in our knowledge.** *Auton Neurosci* 2006; 129**:** 3-16.
9. Kenny GN. **Risk factors for postoperative nausea and vomiting.** *Anaesthesia* 1994; 49 Suppl**:** 6-10.
10. Schumann R, Polaner DM. **Massive subcutaneous emphysema and sudden airway compromise after postoperative vomiting.** *Anesth Analg* 1999; 89**:** 796-797.
11. Col C, Soran A, Col M. **Can postoperative abdominal wound dehiscence be predicted?** *Tokai J Exp Clin Med* 1998; 23**:** 123-127.
12. Kogan A, Eidelman LA, Raanani E, Orlov B, Shenkin O, Vidne BA. **Nausea and vomiting after fast-track cardiac anaesthesia.** *Br J Anaesth* 2003; 91**:** 214-217.
13. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I *et al*. **A factorial trial of six interventions for the prevention of postoperative nausea and vomiting.** *N Engl J Med* 2004; 350**:** 2441-2451.
14. Ku CM, Ong BC. **Postoperative nausea and vomiting: a review of current literature.** *Singapore Med J* 2003; 44**:** 366-374.
15. Purhonen S, Niskanen M, Wustefeld M, Mustonen P, Hynynen M. **Supplemental oxygen for prevention of nausea and vomiting after breast surgery.** *Br J Anaesth* 2003; 91**:** 284-287.
16. Kovac AL. **Prophylaxis of postoperative nausea and vomiting: controversies in the use of serotonin 5-hydroxytryptamine subtype 3 receptor antagonists.** *J Clin Anesth* 2006; 18**:** 304-318.
17. Burlacu CL, Healy D, Buggy DJ, Twomey C, Veerasingam D, Tierney A *et al*. **Continuous gastric decompression for postoperative nausea and vomiting after coronary revascularization surgery.** *Anesth Analg* 2005; 100**:** 321-326.
18. Jones JE, Tabaee A, Glasgold R, Gomillion MC. **Efficacy of gastric aspiration in reducing posttonsillectomy vomiting.** *Arch Otolaryngol Head Neck Surg* 2001; 127**:** 980-984.
19. Silbert BS, Santamaria JD, O'Brien JL, Blyth CM, Kelly WJ, Molnar RR. **Early extubation following coronary artery bypass surgery: a prospective randomized controlled trial. The Fast Track Cardiac Care Team.** *Chest* 1998; 113**:** 1481-1488.
20. Saghaei M. **Random allocation software for parallel group randomized trials.** *BMC Med Res Methodol* 2004; 4**:** 26.
21. Consales G, Chelazzi C, Rinaldi S, De Gaudio AR. **Bispectral Index compared to Ramsay score for sedation monitoring in intensive care units.** *Minerva Anestesiol* 2006; 72**:** 329-336.
22. Kaplan M, Kut MS, Yurtseven N, Cimen S, Demirtas MM. **Accelerated recovery after cardiac operations.** *Heart Surg Forum* 2002; 5**:** 381-387.

23. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. **A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers.** *Anesthesiology* 1999; 91**:** 693-700.
24. Apfel CC, Greim CA, Haubitz I, Grundt D, Goepfert C, Sefrin P *et al*. **The discriminating power of a risk score for postoperative vomiting in adults undergoing various types of surgery.** *Acta Anaesthesiol Scand* 1998; 42**:** 502-509.
25. Oddby-Muhrbeck E, Eksborg S, Helander A, Bjellerup P, Lindahl S, Lonnqvist P. **Blood-borne factors possibly associated with post-operative nausea and vomiting: an explorative study in women after breast cancer surgery.** *Acta Anaesthesiol Scand* 2005; 49**:** 1346-1354.
26. Gan TJ. **Risk factors for postoperative nausea and vomiting.** *Anesth Analg* 2006; 102**:** 1884-1898.
27. Pusch F, Berger A, Wildling E, Tiefenthaler W, Krafft P. **The effects of systolic arterial blood pressure variations on postoperative nausea and vomiting.** *Anesth Analg* 2002; 94**:** 1652-5, table.
28. Gan TJ, Mythen MG, Glass PS. **Intraoperative gut hypoperfusion may be a risk factor for postoperative nausea and vomiting.** *Br J Anaesth* 1997; 78**:** 476.
29. Sanjay OP, Tauro DI. **Midazolam: an effective antiemetic after cardiac surgery--a clinical trial.** *Anesth Analg* 2004; 99**:** 339-43, table.
30. Wattwil M, Thorn SE, Lovqvist A, Wattwil L, Klockhoff H, Larsson LG *et al*. **Perioperative gastric emptying is not a predictor of early postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.** *Anesth Analg* 2002; 95**:** 476-9, table.
31. Lerman J. **Surgical and patient factors involved in postoperative nausea and vomiting.** *Br J Anaesth* 1992; 69**:** 24S-32S.