Anesthesiology 2002; 96:1109–14

Effects of Clonidine on Postoperative Nausea and Vomiting in Breast Cancer Surgery

Eva Oddby-Muhrbeck, M.D., Staffan Eksborg, Ph.D.,† Henrik T. G. Bergendahl, M.D.,‡ Olle Muhrbeck, Ph.D., M.D.,§ Per Arne Lönnqvist, Ph.D., M.D.‖*

Background: **Postoperative nausea and vomiting (PONV) is still common, especially among female patients. Our hypothesis is that coinduction with clonidine reduces the incidence of PONV in adult patients undergoing breast cancer surgery.**

Methods: **Sixty-eight women premedicated with midazolam were randomly allocated to coinduction with intravenous clonidine (group C) or placebo (group P) in this prospective, double-blind study. Anesthesia was standardized (laryngeal mask airway, fentanyl, propofol, sevoflurane, nitrous oxide, and oxygen). Hemodynamic parameters and the requirements for propofol, sevoflurane, and the postoperative need for ketobemidone were noted. The primary endpoints studied were the number of PONV-free patients and patient satisfaction with respect to PONV.**

Results: **Patients in group C had a significantly reduced need for propofol ($P < 0.04$) and sevoflurane ($P < 0.01$) and a reduced early need for ketobemidone ($P < 0.04$). There were significantly more PONV-free patients in group C compared with group P (20 and 11 of 30, respectively; $P < 0.04$). The number needed to treat was 3.3 (95% confidence interval, 1.8, 16.9). Intraoperative blood pressure, postoperative heart rate, and postoperative blood pressure were all significantly lower in group C compared with group P, but were not considered to be of clinical importance. No negative side effects were recorded.**

Conclusion: **Coinduction with clonidine significantly increased the number of PONV-free patients after breast cancer surgery with general anesthesia.**

POSTOPERATIVE nausea and vomiting (PONV) is a frequent, undesired side effect of anesthesia and surgery.[1,2] Because of still unknown reasons, females experience PONV approximately two to three times more often compared with males.[1–3] Surgical procedures only performed in women, such as gynecologic operations, are known to cause a high incidence of PONV.[4] In accordance with other research groups, we previously identified breast surgery performed with general anesthesia to be associated with very high PONV rates (60–84%).[5–10]

The α_2-adrenergic agonist clonidine significantly reduces PONV in children after strabismus surgery, a surgical procedure known to be associated with a very high risk of PONV (40–80%).[11,12] Clonidine is a well-established drug associated with a low to moderate cost compared with newer antiemetics (*e.g.*, 5-HT_3 blockers) making it an interesting drug to study in the adult PONV setting. The primary aim of this study was to investigate if coinduction with clonidine compared with placebo could increase the number of PONV-free patients after breast cancer surgery performed with general anesthesia.

Materials and Methods

After obtaining approval from the local ethics committee (Karolinska Institutet, Stockholm, Sweden) and the Swedish drug regulatory agency, 68 female patients with American Society of Anesthesiologists physical status I or II who were scheduled for in-hospital breast cancer surgery gave written informed consent to participate in the study. The patients were prospectively randomized to receive either intravenous clonidine (group C: 2 μg/kg mixed with normal saline to a final volume of 10 ml) or intravenous placebo (group P: 10 ml of normal saline), given immediately before induction of anesthesia. Randomization was performed by the closed-envelope technique. The double-blind design of the study was assured by the fact that an anesthetist not further involved in the study prepared the syringes immediately before induction of anesthesia. The syringes were marked clonidine–placebo together with the name of the patient, and the anesthetist responsible for the anesthetic (the investigator, E. O-M.) was thus kept completely unaware of the content in the syringe. The randomization code was broken in connection to data analysis.

The primary endpoint parameters of the study were the number of PONV-free patients and patient satisfaction in the placebo and clonidine groups, respectively, as suggested by Rose and Watcha.[13] The number needed to treat (NNT) was calculated (see below). A number of other PONV-related factors, *i.e.*, PONV events and need for antiemetics, were also included as secondary endpoints.

Previous data generated at our hospital have shown that only approximately one third of women undergoing breast cancer surgery with general anesthesia are PONV-free during the first 24 h postoperatively.[5,6] The sample size of the study was based on the following power calculation: (1) an increase in the number of PONV-free patients from 35% in group P to 70% in group C; and (2) α and β values of 0.05 and 0.80, respectively. The estimated sample size was 30 in each group. Factors known to influence PONV (*e.g.*, previous PONV, tendency for motion sickness, smoking habits, and fertility–meno-

* Research Fellow, § Lecturer, Karolinska Institutet Danderyd Hospital, † Associate Professor, Karolinska Pharmacy, ‡ Research Fellow, ‖ Associate Professor, Karolinska Institutet.

Received from the Department of Anesthesia and Intensive Care, Karolinska Institutet Danderyd Hospital, Stockholm, Sweden. Submitted for publication June 7, 2001. Accepted for publication January 2, 2002. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Oddby-Muhrbeck: Department of Anesthesia and Intensive Care, Danderyd Hospital, 182 88 Stockholm, Sweden. Address electronic mail to: eva.oddby@ane.ds.sll.se.

pause) were recorded during the preoperative assessment. Anesthesia was administered according to a standardized protocol. All patients received premedication with intramuscular midazolam (3 mg for a body weight < 70 kg and 4 mg for a body weight > 70 kg) 15–20 min before arrival to the operating room. Immediately after intravenous cannulation, the patient was given the study drug or placebo over 10 min. Anesthesia was then induced with a single dose of fentanyl (1.5 μg/kg) and propofol (1.5–2.0 mg/kg) until loss of eyelash reflexes. A laryngeal mask airway was inserted without previous ventilation of the lungs. Breathing was assisted only when necessary to maintain end-tidal carbon dioxide within the range 5.0–6.5 kPa (37.5–48.75 mmHg). Anesthesia was subsequently maintained with sevoflurane in nitrous oxide (60%) and oxygen. The sevoflurane concentration was adjusted with the intention to keep heart rate and noninvasive blood pressure within 20% of preinduction values throughout the anesthesia period. A standardized volume of bupivacaine (20 ml; 2.5 mg/ml) was administered in the surgical wound at the end of the surgical procedure by the surgeon. Rectal paracetamol (1 g) was given immediately after surgery, and all patients were routinely prescribed further paracetamol (1 g every 8 h) during the first postoperative 24 h.

Baseline heart rate and blood pressure were recorded immediately before induction of anesthesia (preoperative values). During anesthesia, heart rate and blood pressure were measured at least every 5 min. For each individual patient, a mean value was determined from all heart rate and blood pressure measurements performed during anesthesia (intraoperative values). A recording of heart rate and blood pressure was also performed immediately before transfer of the patient to the recovery room (postoperative values).

PONV was assessed by specially trained nurses every 15–30 min in the recovery room and later once every hour in the surgical ward, except when patients were asleep. More than one PONV episode could be recorded in each patient. PONV was classified as nausea, retching, and vomiting. Patients experiencing nausea, retching, and vomiting were included in the vomiting category. Patients suffering both nausea and retching were included in the retching category.

Droperidol (1.25 mg administered intravenously; first choice) and ondansetron (4–8 mg administered intravenously; second choice) were used as rescue antiemetics and were administered when patients vomited twice or more within 30 min or when nausea was intense, with a duration of more than 30 min, and if patients explicitly asked for antiemetics.

Calculations to establish the NNT to avoid one patient having PONV, together with its corresponding 95% confidence interval, were performed according to Cook.[14]

Postoperative pain was assessed using a 100-mm visual analog scale. A score of more than 30 mm was treated with incremental doses of the opioid analog ketobemidone until the pain score was once again less than 30 mm.

Table 1. Patient Characteristics and Risk Factors for PONV

	Group C (n = 30)	Group P (n = 30)
Age (yr)	54.0 (33–82)	56.5 (42–83)
Weight (kg)	70.0 (53–86)	63.0 (50–102)
History of motion sickness	9	10
PONV after previous surgery	9	11
Smokers	6	6
Menopause	22	25

Data are given as median (range) and number of patients.
PONV = postoperative nausea and vomiting.

In the recovery room, sedation was assessed according to a five-point scale until the patients were completely awake (1 = awake; 2 = light drowsiness; 3 = heavy drowsiness; 4 = sleeping, easy to arouse; 5 = sleeping, difficult to arouse). To assess any possible delay in the recovery room discharge, the time when the patients actually left the recovery unit was noted.

Patients were interviewed regarding their overall evaluation of problems with both PONV and postoperative pain 24 h after surgery. Evaluations were made using a six-point scale (1 = no problem; 2 = a mild problem; 3 = a moderate problem; 4 = a definite problem; 5 = a severe problem; 6 = the worst possible problem). Patients who had experienced PONV were also asked to compare the problem of PONV with that of postoperative pain and to decide which had been the worst problem during the first 24 h postoperatively.

Statistical Analysis

Associations were established by the Spearman rank correlation test. Outcome of the two treatments were compared with the Fisher exact test. Data from two independent samples were compared by the Mann–Whitney U test. Statistical significance was accepted at $P \leq 0.05$.

Results

A total of 68 patients were included in the study. Thirty-four patients were randomly allocated to groups C and P, respectively. Groups C and P were comparable with respect to patient characteristics and factors known to influence PONV (table 1). Surgical procedures, duration of anesthesia and surgery, and blood loss were similar in both groups (table 2).

A primary intention-to-treat analysis was performed. Administration of clonidine was associated with a significantly higher overall number of PONV-free individuals compared with placebo (n = 23 and 13 of 34 in groups C and P, respectively), generating a P value < 0.03.

Because of protocol irregularities, four patients in each group were excluded: unexpected need for tracheal

Table 2. Surgical Procedures and Peroperative Observations

	Group C (n = 30)	Group P (n = 30)
Type of surgery		
Mastectomy	3	7
Mastectomy with axillary dissection	8	10
Partial mastectomy	7	7
Partial mastectomy with axillary dissection	12	6
Duration of surgery (min)	55 (20–115)	50 (28–120)
Duration of anesthesia (min)	74 (45–130)	78 (50–145)
Peroperative blood loss (ml)	78 (0–200)	40 (0–300)
Time spent in the recovery room (min)	190 (80–305)	185 (90–540)

Data are given as number of patients and median (range).

intubation (group C: n = 1; group P: n = 1), administration of prophylactic ondansetron (group C: n = 2), use of intravenous atropine or ephedrine (group C: n = 1; group P: n = 2) and intravenous sedation with dixyrazin, a neuroleptic drug belonging to the fentiazin group (group P: n = 1). When these patients were excluded, we found 20 and 11 of 30 patients were PONV-free in groups C and P, respectively ($P < 0.04$; fig. 1 and table 3). The results presented below are based on this per-protocol analysis.

In group C, more patients (n = 22 of 30) were PONV-free after leaving the recovery room compared with group P (n = 12 of 30; $P < 0.02$; table 3). Furthermore, in patients suffering from PONV, no statistically significant difference was observed regarding the number of PONV episodes per patient (group C: 2.2; group P: 3.1). Nine patients in group C and 13 in group P were given antiemetics (P = nonsignificant).

Patient satisfaction with respect to PONV during the 24-h study period was higher in group C compared with group P. According to the six-point patient satisfaction scale, group C evaluated the problem with PONV as 1.8, compared with 2.4 in group P ($P = 0.07$). Seventy-two percent of all patients experiencing PONV judged this problem to be worse when compared with the problem of postoperative pain. The NNT was 3.3 (95% confidence interval, 1.8–16.9). Time until discharge from the postoperative unit (median, 190 min [range, 80–305] *vs.* 185 min [range, 90–540]) did not differ between groups C and P, respectively.

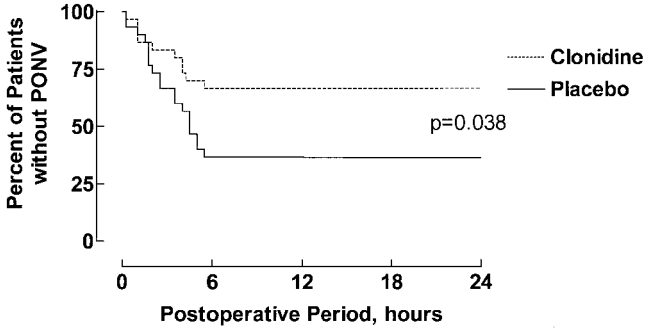

Fig. 1. Number of patients without postoperative nausea and vomiting (PONV) with respect to time. $P = 0.038$ (Fisher exact test).

Table 3. Number of Patients Experiencing Nausea and Vomiting in the Recovery Room, in the Surgical Unit, and Total During 24 h

	Group C (n = 30)	Group P (n = 30)	
Recovery room			
PONV-free	24	19	
Nausea	4	4	
Retching	0	0	
Vomiting	2	7	
Surgical unit			
PONV-free	22	12	$P < 0.02$
Nausea	2	4	
Retching	0	2	
Vomiting	6	12	
Entire 24-h period			
PONV-free	20	11	$P < 0.04$
Nausea	4	3	
Retching	0	2	
Vomiting	6	14	$P = 0.05$

PONV = postoperative nausea and vomiting.

No difference with regard to postoperative sedation could be observed between the two study groups (fig. 2). All patients in group C were assessed as fully awake 6 h after surgery, whereas three patients in group P still had varied degrees of sedation at this point of time.

No difference was found between the two groups regarding the total number of episodes with pain; visual analog scale scores were greater than 30 mm (group P: 68 episodes; group C: 50 episodes; P = nonsignificant) during the entire 24-h study period. Patient satisfaction with respect to pain during 24 h was also the same according to the six-point scale (2.5 and 2.4 in groups P and C, respectively).

The number of episodes with pain (visual analog scale scores > 30 mm) and amount of postoperative opioid administration did not correlate with the presence of PONV (data not shown).

The use of clonidine was associated with significant reductions of both the induction dose of propofol ($P < 0.04$) and the mean intraoperative end-tidal sevoflurane concentration ($P < 0.01$). The need for ketobemidone

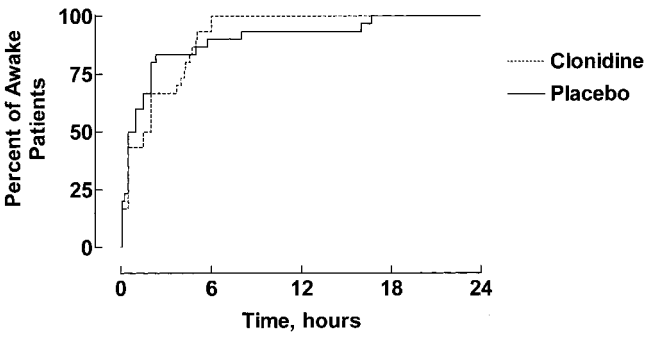

Fig. 2. Time until patients were awake.

Table 4. Amount of Anesthetics and Analgesics

	Group C (n = 30)	Group P (n = 30)	*P*
Propofol (mg)	100 (50–140)	120 (80–200)	$P < 0.04$
End-tidal sevoflurane concentration	1.10 (0.75–1.90)	1.25 (0.78–2.07)	$P < 0.01$
Intravenous ketobemidone, (mg) recovery room	2.75 (0–10)	5.0 (0–21)	$P < 0.04$
Intravenous ketobemidone (mg) (24 h postoperatively)	3.0 (0–18)	5.0 (0–24)	$P = 0.09$

Data are given as median (range).

was also reduced during the time in the recovery room ($P < 0.04$; table 4). Intraoperative blood pressure, postoperative heart rate, and postoperative blood pressure were all significantly lower in group C compared with group P but were not judged to be of clinical importance (table 5).

Discussion

The main finding of the current study was that coinduction with intravenous clonidine in general anesthesia in patients undergoing breast cancer surgery increases the number of PONV-free patients almost twice compared with placebo (67% *vs.* 37%; fig. 1). This improvement was achieved without any increase in postoperative sedation or other clinically important side effects of clonidine.

The α_2-adrenergic agonist clonidine has been found to offer a number of beneficial effects in general and regional anesthesia in both adults and pediatric patients.[11,15,16] However, one of the less investigated effects of clonidine is its action regarding PONV. Mikawa *et al.*[11] reported significantly reduced PONV rates after oral premedication with clonidine (4 μg/kg) in children undergoing strabismus surgery, a surgical intervention frequently accompanied by a very high PONV incidence.[12] Indications for a beneficial effect of clonidine regarding PONV in adults have previously been described.[17] However, to our knowledge, the current study is the first to explore the potential usefulness of clonidine in adult patients, using PONV as the primary endpoint of the study.

For unknown reasons, women experience PONV approximately two to three times more often than men after similar types of surgical interventions.[2,18] In previous studies, we identified women undergoing breast cancer surgery to be yet another high-risk group for PONV, with an incidence in the range of 60–70%.[5–7] General anesthesia remains the routine anesthetic for breast cancer surgery in most centers, although paravertebral somatic nerve blockade in combination with light sedation recently has been reported to moderately reduce the frequency of PONV after breast surgery.[19] Thus, these patients would certainly benefit from more effective protocols against PONV, and this patient population also is suitable for a scientific study, being a well-defined patient group with a high incidence of PONV.

In the current study, coinduction with clonidine caused a clinically as well as statistically significant increase in the number of PONV-free patients compared with placebo. These differences also remained when excluded patients were incorporated in an intention-to-treat analysis. The background for this effect is probably multifactorial. First, the significant reduction in sevoflurane requirements caused by clonidine (table 4) could partly explain this finding. Although resulting in reduced volatile agent exposure, this might not represent a true effect of anesthetic depth on the incidence of PONV. Because the anesthetic depth in the current study was evaluated mainly by cardiovascular reactions, the finding of reduced sevoflurane requirements may only be a reflection of the cardiovascular effects of clonidine. Second, a general reduction in sympathetic outflow caused by clonidine,[15] manifested as a significant reduction of intraoperative heart rate and postoperative heart rate and blood pressure (table 5), could also have attributed to the reduction of PONV since a high sympathetic tone and catecholamine release may trigger nausea and vomiting.[1,20] Third, the well-known analgesic effect of clonidine, illustrated in the current study by a signifi-

Table 5. Blood Pressure and Heart Rate

	Group C (n = 30)	Group P (n = 30)	*P*
Preoperative heart rate	70 (50–96)	66 (54–100)	
Intraoperative heart rate	61 (44–77)	60 (49–77)	
Postoperative heart rate	63 (50–100)	71 (54–100)	$P < 0.02$
Preoperative systolic blood pressure	140 (110–195)	141 (106–230)	
Intraoperative systolic blood pressure	102 (86–139)	110 (92–170)	$P < 0.01$
Postoperative systolic blood pressure	120 (80–160)	138 (90–230)	$P < 0.01$

Blood pressure is expressed in mmHg, and heart rate is expressed in beats/min. Data are given as median (range).

cantly reduced need for opioid administration in the recovery room (table 4), might have influenced the incidence of PONV. Opioids are known emetogens,[1,21] and a reduced exposure to such drugs in the recovery room would most likely result in reduced PONV rates. Fourth, it could be hypothesized that clonidine might have an intrinsic effect on α_2-adrenergic, imidazol,[17,22] or other receptor types in the central nervous system or elsewhere in the body. Still, unknown mechanisms of clonidine could possibly contribute to the antiemetic action seen in the setting of breast cancer surgery performed with general anesthesia. Further studies are necessary to gain better understanding regarding which of the aforementioned mechanisms that are most important with regard to the antiemetic effects of clonidine.

The choice of primary endpoints in PONV studies has been a subject of debate.[23,24] Current recommendations are to study not only the incidence of PONV episodes or other so-called surrogate endpoints, but to also include endpoints such as time until discharge from the recovery room, time of hospital stay, and overall patient satisfaction.[23] It has been argued that the number of patients that remain PONV-free represents a more useful endpoint in PONV studies.[13,25,26] However, time spent in the recovery room is often not related to the medical condition of the patient, but depends on a number of factors, some of which are of nonmedical type such as completion of paper and computer work by recovery room nurses, waiting for ward nurses to transfer the patient back to the ward, *etc.* These are not governed by recovery from anesthesia. This, combined with the fact that all patients were treated as in-hospital patients, made these parameters unsuitable to study. In these circumstances we opted to use both the number of PONV-free patients and overall patient satisfaction with respect to PONV as primary endpoints in the current study.

Regarding prevention and treatment of PONV, the issues of side effects and NNT are also of great importance. Apart from clinically insignificant reductions of heart rate and blood pressure, stressed by the fact that one patient in group C compared with two in group P needed atropine or ephedrine, no other side effects of clonidine were noted in the current study. It is of special interest that no increase in postoperative sedation was observed in patients given clonidine compared with placebo (fig. 2). This is in accordance with findings of previous publications[27] and is usually attributed to the reduced need for both induction agent and volatile anesthetics caused by perioperative clonidine administration.[15]

The pronounced effect of clonidine on PONV observed in the current study resulted in a NNT of 3. This figure compares well with the NNT figures (range, 3–31) reported in the systematic review by Tramèr *et al.*,[28] which was based on studies using ondansetron as PONV prophylaxis. In addition, the 95% confidence interval for the NNT value associated with coinduction with clonidine was found to be similar to those reported for ondansetron.[28]

The rather low NNT figure, the reduced need for both anesthetics and analgesics, as well as the low cost of clonidine compared to 5-HT_3 blockers, makes clonidine an attractive agent for clinical use. However, it should be kept in mind that the current study only investigated the effect of clonidine on PONV in a very specific patient category. Further studies are needed to show an effect in other postoperative situations.

In agreement with other PONV studies,[4,26] we found that as many as 72% of patients experiencing PONV considered this to be a more serious problem than postoperative pain. Patients are probably willing to accept a certain degree of pain, drowsiness, and delayed discharge rather than PONV.[4] The current widespread use of opioids for postoperative pain relief ought to be questioned. Anderson *et al.*[21] recently showed an almost linear relation between the dose of postoperative morphine and the incidence of vomiting after tonsillectomy. It appears to be in the best interest of our patients to use less emetogenic alternatives rather than opioids for postoperative analgesia, *e.g.*, local anesthesia, as regional blocks or as wound infiltration, paracetamol, and nonsteroidal antiinflammatory agents.[29]

In conclusion, coinduction with intravenous clonidine results in an increased number of patients free of PONV after breast cancer surgery performed with general anesthesia. This was accomplished without any increase in postoperative sedation or other side effects. These observations, combined with the low cost of clonidine and a low NNT, warrant further studies of this concept.

The authors thank Sten Lindahl, Ph.D., M.D. (Professor, Department of Anesthesia and Intensive Care, Karolinska Hospital, Karolinska Institutet, Stockholm, Sweden), for constructive criticism throughout this project.

References

1. Watcha MF, White PF: Postoperative nausea and vomiting: Its etiology, treatment, and prevention. ANESTHESIOLOGY 1992; 77:162–84
2. Palazzo MG, Strunin L: Anaesthesia and emesis. I: Etiology. Can Anaesth Soc J 1984; 31:178–87
3. Bellville JW: Postanesthetic nausea and vomiting. ANESTHESIOLOGY 1961; 22: 773–80
4. Tang J, Watcha MF, White PF: A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures. Anesth Analg 1996; 83:304–13
5. Oddby-Muhrbeck E, Jakobsson J, Andersson L, Askergren J: Postoperative nausea and vomiting: A comparison between intravenous and inhalation anaesthesia in breast surgery. Acta Anaesthesiol Scand 1994; 38:52–6
6. Oddby-Muhrbeck E, Jakobsson J, Enquist B: Implicit processing and therapeutic suggestion during balanced anaesthesia. Acta Anaesthesiol Scand 1995; 39:333–7
7. Enqvist B, Bjorklund C, Engman M, Jakobsson J: Preoperative hypnosis reduces postoperative vomiting after surgery of the breasts: A prospective, randomized and blinded study. Acta Anaesthesiol Scand 1997; 41:1028–32
8. Reihner E, Grunditz R, Giesecke K, Gustafsson LL: Postoperative nausea and vomiting after breast surgery: Efficacy of prophylactic ondansetron and droperidol in a randomized placebo-controlled study. Eur J Anaesthesiol 2000; 17: 197–203
9. Sadhasivam S, Saxena A, Kathirvel S, Kannan TR, Trikha A, Mohan V: The safety and efficacy of prophylactic ondansetron in patients undergoing modified radical mastectomy. Anesth Analg 1999; 89:1340–5

10. Gan TJ, Ginsberg B, Grant AP, Glass PS: Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. ANESTHESIOLOGY 1996; 85:1036–42

11. Mikawa K, Nishina K, Maekawa N, Asano M, Obara H: Oral clonidine premedication reduces vomiting in children after strabismus surgery. Can J Anaesth 1995; 42:977–81

12. Subramaniam B, Madan R, Sadhasivam S, Sennaraj B, Tamilselvan P, Rajeshwari S, Jagan D, Shende D: Dexamethasone is a cost-effective alternative to ondansetron in preventing PONV after paediatric strabismus repair. Br J Anaesth 2001; 86:84–9

13. Rose JB, Watcha MF: Postoperative nausea and vomiting in paediatric patients. Br J Anaesth 1999; 83:104–17

14. Cook RJ, Sackett DL: The number needed to treat: A clinically useful measure of treatment effect [published erratum appears in BMJ 1995; 310:1056]. BMJ 1995; 310:452–4

15. Maze M, Tranquilli W: Alpha-2 adrenoceptor agonists: Defining the role in clinical anesthesia. ANESTHESIOLOGY 1991; 74:581–605

16. Whitwam JG: Co-induction of anaesthesia: Day-case surgery. Eur J Anaesthesiol Suppl 1995; 12:25–34

17. Park J, Forrest J, Kolesar R, Bhola D, Beattie S, Chu C: Oral clonidine reduces postoperative PCA morphine requirements. Can J Anaesth 1996; 43: 900–6

18. Apfel CC, Greim CA, Haubitz I, Goepfert C, Usadel J, Sefrin P, Roewer N: A risk score to predict the probability of postoperative vomiting in adults. Acta Anaesthesiol Scand 1998; 42:495–501

19. Greengrass R, O'Brien F, Lyerly K, Hardman D, Gleason D, D'Ercole F, Steele S: Paravertebral block for breast cancer surgery. Can J Anaesth 1996; 43:858–61

20. Jenkins LC, Lahay D: Central mechanisms of vomiting related to catecholamine response: Anaesthetic implication. Can Anaesth Soc J 1971; 18:434–41

21. Anderson BJ, Ralph CJ, Stewart AW, Barber C, Holford NH: The dose-effect relationship for morphine and vomiting after day-stay tonsillectomy in children. Anaesth Intensive Care 2000; 28: 155–60

22. Regunathan S, Reis DJ: Imidazoline receptors and their endogenous ligands. Annu Rev Pharmacol Toxicol 1996; 36:511–44

23. Fisher DM: Surrogate outcomes: Meaningful not! (editorial). ANESTHESIOLOGY 1999; 90:355–6

24. White PF, Watcha MF: Postoperative nausea and vomiting: Prophylaxis versus treatment (editorial). Anesth Analg 1999; 89:1337–9

25. Watcha MF: The cost-effective management of postoperative nausea and vomiting (editorial). ANESTHESIOLOGY 2000; 92:931–3

26. Hill RP, Lubarsky DA, Phillips-Bute B, Fortney JT, Creed MR, Glass PS, Gan TJ: Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. ANESTHESIOLOGY 2000; 92:958–67

27. Bellaiche S, Bonnet F, Sperandio M, Lerouge P, Cannet G, Roujas F: Clonidine does not delay recovery from anaesthesia. Br J Anaesth 1991; 66:353–7

28. Tramer MR, Reynolds DJ, Moore RA, McQuay HJ: Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: A quantitative systematic review of randomized placebo-controlled trials. ANESTHESIOLOGY 1997; 87:1277–89

29. Dahl V, Raeder JC: Non-opioid postoperative analgesia. Acta Anaesthesiol Scand 2000; 44:1191–203