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Postoperative Symptoms After Gynaecological Surgery

How They Are Influenced by Prophylactic Antiemetics and Sensory Stimulation (P6-Acupressure)

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Destiny is not a matter of chance, it is a matter of choice;
it is not a thing to be waited for, it is a thing to be achieved.

William Jennings Bryan

To Hazim, Yazan, Wasan and Hammoudi

To my Parents, brothers and sisters

With love

CONTENTS

ABSTRACT

Symptoms after surgery and anaesthesia influence the patient´s ability to resume daily activities. If postoperative symptoms are controlled rehabilitation may be accelerated. The aims of this dissertation were to identify disturbing symptoms reported by patients after gynaecological surgery, to investigate what effect prohylactic treatment with antiemetics has on these symptoms and whether or not sensory simulation of the P6-acupressure has an effect on postoperative nausea and vomiting (PONV) and motion sickness.

Methods: Total 1138 women participated in three clinical trials (Studies I, II, III) and one experimental study (Study IV). A questionnaire investigating postoperative symptoms was constructed and validated. The questionnaire was used in a prospective, consecutive, double-blind, randomised, multicentre, and controlled study to identify incidence, and intensity of postoperative symptoms and the effect of common antiemetics (droperidol and granisetron) (Study III). The patients were followed for 24 h. In two studies (I, II) P6-acupressure was compared (prospective, double-blind, ransomised, controlled) with placebo acupressure and a reference group where the effect on PONV was followed over 24 h. The effect of P6-acupressure and placebo acupressure on motion sickness induced by a nauseogenic motion challenge was studied (Study III).

Results: A high incidence and severity of postoperative symptoms were found after gynaecological surgery in a group with a high risk (>30%) for PONV. Sixty-four per cent (107/165) of the patients experienced disturbing symptoms after surgery and 46 % (76/165) scored their symptoms as moderate to very severe. Fourty-eight per cent (79/165) had two or more symptoms. A higher incidence of symptoms were reported in the groups with prophylactic treatment, granisetron 74% (123/165) and droperidol 80% (133/165) compared to the control group 41% (69/165) ($P < 0.05$). The relative risk reduction for PONV with granisetron or droperidol prophylaxis is 27% respective 22%. The relative risk increase for headache is 63% after granisetron, and 44% for difficulty with accommodation after droperidol. Less PONV was seen after P6-acupressure, 33% (44/135) compared to reference group 46% (63/136) ($p = 0.019$), number needed to treat (NNT) was 7 [95% confidence interval (CI) 4- 6]. When comparing laparoscopic and vaginal surgery (subgroup analysis) the main effect was in the vaginal group (day-case surgery), 36% (27/75) in the reference group to 27% (23/86) in the placebo group and to 20% (17/84) in the P6-acupressure group, ($P = 0.017$), NNT for the vaginal group was 6 [95% CI 3-18]. P6-acupressure increased time to nausea after a laboratory motion challenge and reduced the total number of symptoms reported ($p < 0.009$).

Conclusions: There is no clinical efficacy in the form of reduced postoperative symptoms after prophylactic antiemetics (droperidol and granisetron) in females with a high risk (>30%) for PONV undergoing gynaecological surgery. P6-acupressure reduces the incidence of PONV after gynaecological surgery in females with a high (>30%) risk for PONV. The effect seems to be most prominent after vaginal surgery. P6-acupressure increased tolerance to experimental nausogenic stimuli and reduced the total number of symptoms reported in females with a history of motion sickness.

Keywords: Acupuncture, P6-acupressure, antiemetics, PONV, gynaecological surgery, motion sickness, eccentric rotation, coriolis effect, antiemetic prophylaxis, granisetron, droperidol.

ABBREVIATIONS

ANS	Autonomic Nervous System
AP	Area Postrema
CCKA	Cholecystokinin A
CTZ	Chemoreceptor Trigger Zone
D_2	Dopamine receptor-subtype-2
5-HT_3	5-HydroxyTryptamine receptor-subtype-3
5-HT	5-HydroxyTryptamine (serotonin)
GABA	Gamma-Amino-Butyric Acid
MANE	Morrow Assessment of Nausea and Emesis
NK1	Neurokinin 1
NTS	Nucleus of the Solitary Tract
PONV	Postoperative Nausea and Vomiting
POV	Postoperative Vomiting
TAES	Transcutaneous Acupoint Electrical Stimulation

DEFINITION OF TERMS

(in alphabetic order)

Absolute Risk Increase (ARI). The absolute arithmetic differences in rates of bad outcomes between experimental and control patients in a trial. Calculated as [EER (Experimental Event Rate) - CER (Control Event Rate)].

Confidence Interval (CI). Quantifies the uncertainty in measurement. It is usually reported as 95% CI, which is the range of values within which we can be 95% sure that the true value for the whole population lies. For example for an NNT of 7 with a 95% CI of 4-33, we would have 95% confidence that the true NNT value lies between 4 and 33 (Sachett et al 2000).

The *Likelihood of being Helped versus Harmed (LHH)* is generated by the ratio of 1/NNT and 1/NNH. For example with granisetron the NNT for PONV was 7 and NNH for headache was 6. LHH = (1/NNT) vs. (1/NNH) = (1/7) vs. (1/6) = 0.14 vs 0.17.

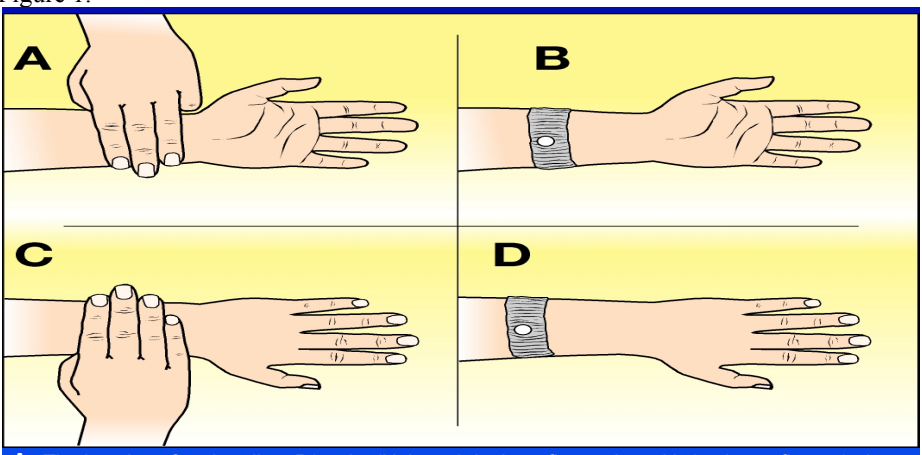
Number Needed to Treat (NNT) describes the number of patients needed to be treated to achieve one additional good outcome. This is calculated as 1/Absolute Risk Reduction (ARR).

Number Needed to Harm (NNH). The number of patients needed to receive the experimental treatment to cause one additional patient to be harmed, compared with patients who received the control treatment calculated as 1/ARR

Nausea. A subjective unpleasant sensation, which can only be evaluated by the individual, not by the observer. The feeling is best described as the desire to vomit without expulsive muscular movement of the stomach. When nausea becomes severe, secretion of saliva is increased and is associated with vasomotor disturbances and sweating (Knapp and Beecher 1956).

The *P6 point (Nei-Guan*). A point located on the pericardial meridian, which is found three fingers´ breadth (approximately 5 cm) proximal to the proximal flexor palmar crease, about 1 cm deep, between the tendons of flexor carpi radialis and palmaris longus. It is supposed to have an effect on postoperative nausea and vomiting (Figure 1) (A barefoot doctor´s manual 1990).

Figure 1.



A *The location of pericardium P6 point (Neiguan):* Is three fingers breadth (patient´s fingers) about 5 cm proximal to the proximal flexor palmar crease, about 1 cm deep between the tendons of flexor carpi radialis and palmaris longus .
B *Active acupressure*: An elastic wristband with a pressure stud, a small button the size of a pea (7mm) *Seaband* (SeaBand®, UK Ltd., Leicestershire, England) was placed bilaterally before anaesthesia over the P6 point.
C *The location of a non-acupoint*. A point on the dorsal side of the forearms, four fingers breadth (patient`s fingers) proximal to the flexor palmar crease was used for stimulation.
D *Pressure on a non-acupoint: Seabands* were placed bilaterally before anaesthesia over *the non-acupoints described under C.*

Relative Risk Increase (RRI) is the proportional increase in rates of bad outcomes between experimental and control patients in the trial, calculated as [EER (Experimental Event Rate) - CER (Control Event Rate)] /CER.

Retching is defined as laboured spasmodic and rhythmical contractions of the respiratory muscles including the diaphragm, chest wall and abdominal wall muscles without the expulsion of gastric contents or opening of the mouth (Watcha & White 1992). The feature that distinguishes retching from vomiting is the production of even the smallest amount of stomach contents. When no stomach contents are expelled, the expulsive efforts are classified as retching. Retching is usually indicative of an empty stomach and is generally as unpleasant for the patient as vomiting (Knapp and Beecher 1956).

Vomiting is the forceful expulsion of gastric contents through the mouth and is brought about by a powerful contraction of the abdominal muscles and the diaphragm and opening of the gastric cardia (Watcha & White 1992, Kovac et al 2000). Retching and vomiting may also be grouped together under the common term “emetic episode” (Knapp and Beecher 1956).

Torsades de pointes is a form of polymorphic ventricular tachycardia that is preceded by a prolongation of the QT interval. Although this condition is found in many clinical settings, it is mostly induced by drugs and drug interactions that prompt a long QT syndrome. Clinical symptoms of torsades de pointes include dizziness, syncope, irregular heartbeat, and sudden death (Monahan et al 1990).

ORGINAL PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I Alkaissi A, Stålnert M, Kalman S
Effect and placebo effect of acupressure (P6) on nausea and vomiting after outpatient-gynaecological surgery. Acta Anaesthesiol Scand 1999; 43: 270-274.

II Alkaissi A, Evertsson K, Johnsson V, Ofenbartl L, Kalman S
P6 acupressure may relieve nausea and vomiting after gynecological surgery: an effectiveness study in 410 women. Can J Anesth 2002; 49 (10): 1034-1039.

III Alkaissi A, Gunnarsson H, Evertsson K, Johnsson V, Ofenbartl L, Kalman S
Disturbing postoperative symptoms are not reduced by prophylactic antiemetric treatment in patients at high risk for post-operative nausea and vomiting. Uncorrected proof. Accepted for publication in Acta Anaesthesiol Scand 5 February 2004

IV. Alkaissi A, Ledin T, Ödkvist L, Kalman S
P6 acupressure increases tolerance to nausogenic motion stimulation in women with high risk for postoperative nausea and vomiting. Submitted for publication, 2004

INTRODUCTION

Anaesthetic and surgical procedures influence the incidence of postoperative symptoms (Chung 1996, Philip 1992). The most frequently observed symptoms postoperatively were incisional pain, headache, drowsiness, dizziness and nausea and/or vomiting (Philip 1992, Chung 1996). Dissatisfaction with anaesthesia is related to the number of postoperative symptoms experienced (Gan et al 1997) and patients with no postoperative symptoms have a faster return to normal daily life than those with symptoms (Chung 1996). When investigating postoperative recovery one or two symptoms are often focused upon. These are often those for which we have a treatment, as for example, nausea and /or vomiting and pain. The effect of a treatment on one specific symptom is often reported and less emphasis is placed on the patient's own judgement on whether or not this symptom is the most disturbing. Improvement in care is possible if the patient's view of postoperative problems can be identified (Gan et al 1997).

Despite advances in surgical and anaesthetic techniques and new anaesthetic agents, the incidence of PONV after anaesthesia is still between 20% and 30% (Kovac 2000, Watcha 2002). PONV could lead to delayed postoperative recovery by causing dehydration, electrolyte imbalance, aspiration and suture dehiscence (Kovac 2000, Chung 1995) and in ambulatory surgery to overnight admission (Gan et al 2003). Prophylactic antiemetic treatment could be used but should be based on both risk-benefit and cost-benefit analysis (Watcha and Smith 1994).

It has been suggested that from the patients´ perspective, total avoidance of PONV would be preferable (Eberhart et al 2002). But patient satisfaction with antiemetic prophylaxis does not appear to be superior when compared with immediate rescue treatment (Scuderi et al 1999). To give antiemetic prophylaxis to all patients cannot be justify as some patients will receive the drug without actually needing it and there are increased costs and more drug related adverse effects with prophylaxis (Scuderi et al 1999). But antiemetic prophylaxis could be cost-effective when administered to patients who are at high risk for PONV (Watcha and Smith 1994). Several antiemetics have been investigated. Traditional anti-emetics include dopamine receptor antagonists, droperidol (Dridol®) (Henzi et al 2000) and newer 5-HT_3 receptor antagonists as granisetron (Kytril®) has been studied in different surgical settings and proven effective in preventing PONV (Wilson et al 1996).

In the past patients were intuitively classified by reference to their past medical history of PONV or the type of surgery. To do this with more accuracy, risk scores have been developed (Palazzo and Evans 1993, Koivuranta et al 1997 a, Apfel et al 1999). Numerous risk factors have been described but only a few seem to be unequivocally proven (Fisher 1997). The Apfel risk score for postoperative vomiting (POV) under inhalational anaesthesia is based on gender, young age, non-smoking, history of motion sickness or PONV and length of anaesthesia. He suggests that prophylaxis should be given if the individual risk for POV > 30%, a statement that has been approved by others (Eberhart et al 2000 a).

The efficacy of currently available antiemetics remains poor (Harmon et al 1999). Concern over side-effects and high cost of the newer drugs has led to renewed interest in non-pharmacological methods of treatment. The P6 (Nei-Guan) meridian point in acupuncture has been used to treat vomiting in traditional Chinese medical practice (The Academy of Traditional Chinese Medicine1975). Acupressure, a non-invasive variation of acupuncture, at

the P6 point has been reported to be effective in reducing PONV (Barsoum et al 1990, Ho et al 1996). Acupressure using wristbands is an easy way of giving acupressure and may be used by the patient at home (Harmon et al 1999). Acupressure also decreases nausea during pregnancy (Dundee et al 1988 a), cytotoxic therapy (Dundee et al 1987), motion sickness (Bertulucci et al 1995) and after epidural morphine (Ho et al 1996).

Over 50% of patients discharged from day-case surgery experienced PONV at home and found it more or equally debilitating than the after-effect of the surgery itself (Lee and Hirsch 1992). Movement was identified as the precipitating cause of nausea by 66% of patients (Kamath et al 1990). These patients had higher scores for history of motion sickness. A disparity between input from the visual and vestibular systems is a potent stimulus. Input from the vestibular system may therefore play a part in PONV when the patient is moved postoperatively from the recovery room to the hospital ward, or following day case surgery where early ambulation is required (Naylor and Inall 1994). Nitrous oxide (N_2O) (Thomsen 1965) and opioids (Naylor and Inall 1994) increase susceptibly to motion-induced nausea. Motion sickness can be created in a controlled laboratory situation (Bruce et al 1990). P6-acupressure has been reported to reduce symptoms of motion sickness (Bertulucci et al).
The aims of this dissertation were to identify disturbing symptoms reported after gynaecological surgery, to investigate the effect of propylactic treatment with antiemetics on postoperative symptoms, to investigate if sensory stimulation of the P6-acupressure has an effect on PONV and motion sickness.

BACKGROUND

Physiology of postoperative nausea and vomiting

The vomiting centre is located in the reticular formation of the medulla, close to the area postrema (AP) (Fig. 2) (Naylor and Inall 1994). It is activated by stimuli from the periphery (gastrointestinal tract, mediastinum, renal pelvis, peritoneum, genitalia) and from the central nervous system (CNS), e.g. (visual centre, labyrinth, vestibular apparatus), and chemoreceptor trigger zone (CTZ) (Watcha and White 1992, Kovac 2000).

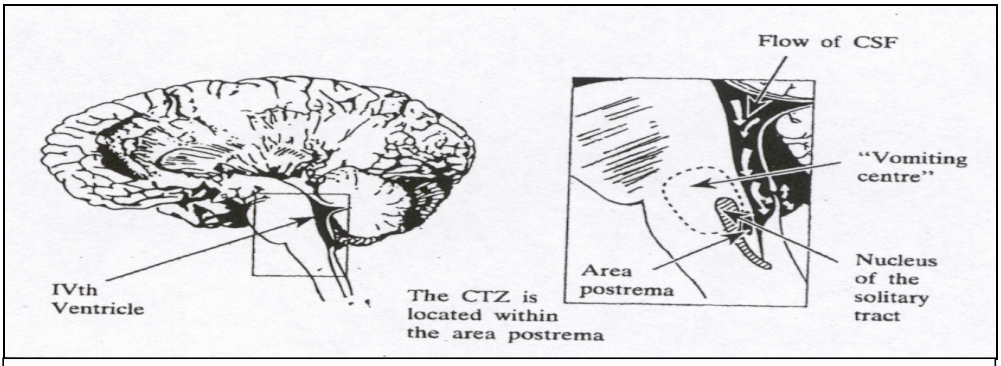


Figure 2. The anatomical location of the area postrema and the region of the vomiting centre (Naylor and Inall 1994). Published with permission from Blackwell publishing.

The CTZ is situated within the area postrema of the brain stem, dorsal in the medulla oblongata, outside the blood-brain-barrier, and it can react to toxic agents in the circulating blood and in cerebrospinal fluid (Andrews 1992). The CTZ has high concentration of enkephaline, dopamine, and opioid receptors. The nucleus of the solitary tract (NTS) contains high concentrations of enkephaline, histamine, muscarinic, and cholinergic receptors. The area postrema is rich in opioid, dopamine and 5-hydroxytryptamine (serotonin) (5-HT) receptors. Antagonism of these receptor sites is the mechanism of action of many of the drugs used to treat PONV (Watcha and White 1992, Kovac 2000) (Figure 3). Neurokinin 1 (NK1) receptors and cholecystokinin A (CCKA) receptors have been identified in the nucleus tractus solitarius and the area postrema, as well as in the peripheral nervous system (Gillis et al 1980, Maubach and Jones 1997).

Stimuli from the gastrointestinal tract activate the vomiting centre mainly through the afferent part of the vagus nerve (Naylor and Inall 1994). The vagus nerve is the main nerve for detection and mediation of emetic stimuli from the gastrointestinal tract. Two different kinds of vagal afferents are involved, mechanoreceptors in the muscular wall and chemoreceptors in the mucosa of the small intestine (Andrews 1988). Surgical manipulation of the gut may influence the mechanoreceptors and probably also irritates the mucosa of the small intestine. Enterochromaffin cells of the mucosa in the small intestine can release 5-HT (Hindle 1994). Release of 5-HT can be induced by stimulating nerve fibres including the vagus or by applying pressure to the mucosa by diffusion of nitrous oxide (Cokson 1986), manipulation of the gastrointestinal tract (Bullbring and Grema 1959), by opioids, adrenaline and ischaemia (Andrews 1992), resulting in an initiation of the vomiting reflex. Mechanism of action for cholinesterase inhibitors and atropine is probably secondary to release of 5-HT due to distension of the gut (King et al 1988, Salmenpära et al 1992).

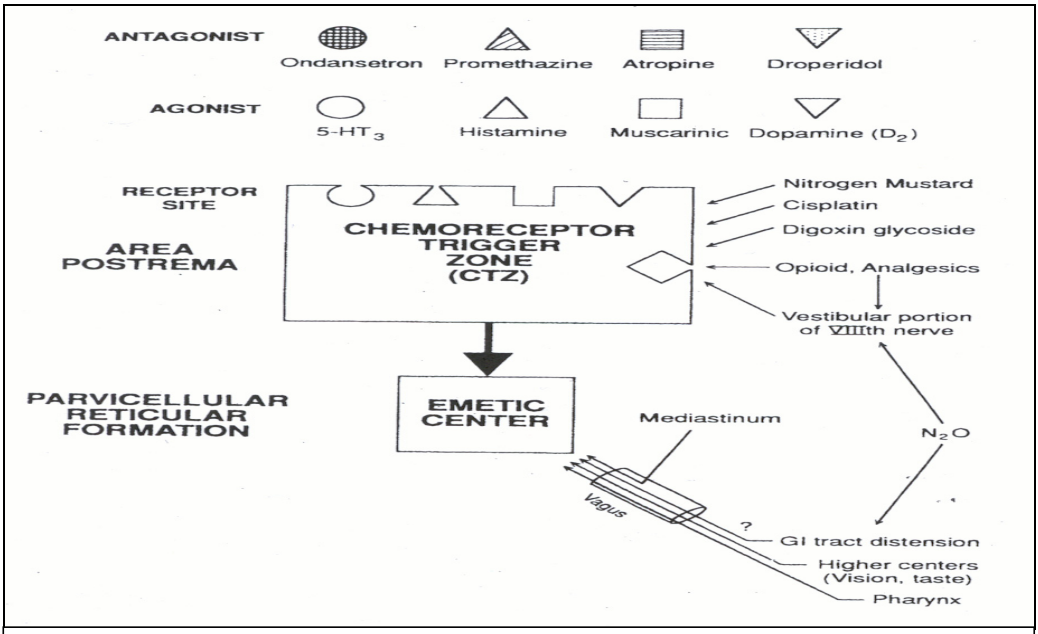


Figure 3. The chemoreceptor trigger zone and the emetic centre with the agonist and antagonist sites of action of various anaesthetic–related agents and stimuli (Watcha and White 1992). Published with permission from the publisher Lippincott Williams & Wilkins.

The vestibular labyrinth provides the pathway for the induction of motion sickness (Koch 1993). Histamine and acetylcholine play a role in triggering these impulses (Thompson 1999).

Signs associated with nausea are mediated by the autonomic nervous system (ANS) e.g. salivation, tachycardia, pupil dilatation, cutaneous vasoconstriction, cold sweats and pallor (Andrews 1999). It is known that low blood pressure and tachycardia can induce emesis (Andrews 1992). ANS is supposed to play a major role in emesis both as a consequence of activation by gastrointestinal distension and of low blood pressure (Abrahamsson 1972). The mechanisms by which low blood pressure induces emesis is unclear but one possibility could be that hypotension induces a sympathetic discharge that releases adrenaline from the adrenal medulla which then may trigger emesis by an action on the AP (Andrews 1992). Another possible mechanism involves activation of vagal afferent mechanoreceptors with unmyelinated axons located in the ventricles of the heart (Abrahamsson 1972). The precise physiological function of these afferents is unclear, but they can trigger emesis and may be responsible for the nausea and vomiting associated with vaso-vagal fainting, and infero-posterior myocardial infarction (Andrews 1992).

Risk factors for PONV in adults

(see Table 1)

The identification of individuals at high risk for PONV can help to identify patients with a high probability of benefiting from prophylactic antiemetic therapy (Gan et al 2002).

Table 1. Suggested risk factors for PONV in adults

Patient-specific	**Anaesthetic**
♦ Female-sex	♦ Volatile anaesthetics
♦ Non-smoking status	♦ Nitrous oxide (N_2O)
♦ History of PONV/motion sickness	♦ Intraoperative opioids
♦ High body mass index	♦ Antagonism of neuromuscular blockade
Surgical	♦ Mask ventilation and experience of anaesthesiologist
♦ Type and site of surgery	♦ Nasogastric decompression
♦ Long duration of surgery	
Postoperative	
♦ Pain	
♦ Hypotension	
♦ Early ambulation	
♦ Postopertive opioids	

The female-sex has been associated with a high incidence of PONV (Burtles and Peckett 1957, Bellville et al 1960, Larsson and Lundberg 1995). Almost all PONV risk scores use female-sex as one of the most important predictive factors (Koivuranta et al 1997 a, Cohen et al 1994, Palazzo and Evans 1993, Apfel et al 1998, 1999). Hormonal variations associated with the menstrual cycle have been suggested as a risk factor (Watcha and White 1992, Beattie et al 1991) but have not been univocally supported by other studies (Eberhart et al 2000 a). Non-smokers suffer more frequently from PONV than smokers (Cohen et al 1994, Apfel 1998, 1999, 1997, Chimbria and Sweeney 2000). Apfel et al (1997) suggested that this might be due to the effect of smoking on the dopaminergic system. Dopamine is known to play a central role in the pathophysiology of vomiting (Flake et al 2004). Smoking is also known to induce P450 isoenzymes and as a result, an increased metabolism of anaesthetic agents (Chimbria and Sweeney 2000). The patient´s history of motion sickness and/or PONV has been demonstrated to be a strong risk factor (Palazzo and Evans 1993, Koivuranta et al 1997 a, Apfel et al 1998, Sinclair et al 1999, Apfel et al 1999, Kamath et al 1990). Body mass index has no impact on PONV (Kranke et al 2001 a).

The incidence of PONV is higher after surgery lasting longer than 3 hours (Naylor and Inall 1994). A panel including major PONV researchers presented a consensus guideline for managing postoperative nausea and vomiting in 2003 (Gan et al 2003). The panel did not reach full agreement about the association between type of surgery and increased PONV risk, but there seems to be a relationship in the day-case setting (Sinclair et al 1999) but not with in-patients (Apfel et al 1998, 1999). Some studies suggest a lower incidence of PONV after regional anaesthesia compared to general anaesthesia (Sinclair et al 1999). Use of volatile anaesthetic is known to be associated with a higher incidence of PONV than total intravenous anaesthesia (TIVA) (Sneyd et al 1998, Apfel et al 2002 a). Inhalational anaesthesia appears to be the main cause of PONV in the early phase of postoperative recovery (Apfel et al 2002 a). Three meta-analyses have shown that the omission of N_2O reduces the risk for postoperative emesis (Divatia et al 1996, Tramèr et al 1996, Hartung 1996). The mechanism behind N_2O-induced PONV has been suggested to be bowel distention (Giuffre and Gross 1986),

increased cerebrospinal opioid peptides (Finck et al 1995), stimulation of the sympathetic nervous system with catecholamine release and changes in middle ear pressure (Watcha and White 1992).

Perioperative opioids increase the risk for PONV (Koivuranta et al 1997 a, Apfel et al 1999, 2002 b). Pain and opioids have been reported to increase the incidence of PONV (Chia et al 2002). Different opioids have been compared during propophol anaesthesia (Dershwitz et al 2002) and as a part of balanced anaesthesia. The results are not univocal but most studies show no significant differences in incidence of PONV when using different opioids (Jakobsson et al 1991, Langevin et al 1999). The mechanisms of action of opioids are complex. They can directly simulate the CTZ, decrease gastrointestinal (GI) motility, prolong emptying time (De Ponti et al 1990) and so predispose the patient to PONV. Opioids also sensitise the otic and vestibular areas to motion (Naylor and Inall 1994). The use of muscle relaxants alone is not associated with PONV. However, reversal agents, especially anticholinesterase agents such as neostigmine, may contribute if given in high doses > 2.5 mg (Tramèr and Fuchs-Buder 1999, Lovstadt et al 2001). Face-mask ventilation can cause gastric distension and the latter can elicit the vomiting reflex. The degree of gastric distension could be supposed to be dependent on the experience of the anaesthesiologist. A higher incidence of PONV after mask ventilation by an unexperienced anaesthesiologist has been reported (Hovorka et al 1990). A later study could not confirm this result (Hetchler et al 1999). The incidence of PONV is not decreased by peroperative gastric evacuation with a nasogastric tube (Cheatham et al 1995, Wattwill et al 2002).

Scores for the assessment of clinical risk for PONV

Various risk scores for PONV have been developed and compared with each other (Palazzo and Evans 1993, Koivuranta et al 1997 a, Apfel et al 1998, Sinclair et al 1999, Apfel et al 1999, Apfel et al 2002 b, Pierre et al 2002). A summary of risk factors studied by different authors can be seen in (Table 2).

Table 2. Factors used for establishing a PONV risk score. [(+) = Presence of factor, (-)= absence of factor].

	Burtles 1957	Bellville 1960	Palazzo 1993	Cohen 1994	Toner 1996	Koivuranta 1997 a	Apfel 1998	Apfel 1999	Sinclair 1999	Stadler 2003
Female sex	+	+	+	+	+	+	+	+	+	+
Non-smoking	-	-	-	+	-	+	+	+	+	+
Motion sickness/ previous history of PONV	+	-	+		+	+	+	+	+	-
Postoperative opioids	-	-	+	-	+	-	-	+	-	-
Duration of surgery > 60 min	-	-	-	-	-	+	-	-	-	-
Young age	-	-	-	+	-	-	+	-	+	-
Good physical status	-	-	-	+	-	-	-	-	-	-
Long duration of anaesthesia	-	-	-	+	-	-	+	-	+	-
Type of surgery	-	-	-	-		-	-	-	+	+
Type of anaesthesia	-	-	-	-	-	-	-	-	+	-
General anaesthesia	-	-	-	-	-	-	-	-	-	+
Interaction between male sex & previous history of PONV	-	-	+	-	+	-	-	-	-	-
History of migraine	-	-	-	-	-	-	-	-	-	+

Risk agreement at the individual level is poor (Thomas et al 2002). A high incidence of a single factor could be misleading if not corrected for other coexisting factors wherefore several risk factors are needed to estimate the probability of PONV (Apfel and Roewer 2003). Apfel et al (2001) demonstrated that the inclusion of more than five predictors did not lead to a clinically relevant improvement and that currently available simplified risk scores (with four or five predictors) are useful both as a method to estimate individual risk for PONV and as a method for comparing groups of patients in antiemetic trials.

A simplified risk score (Table 3) has been validated in in-patients (Apfel et al 2002 b, Pierre et al 2002). It is easy to use and can be used for a risk dependent antiemetic strategy in clinical practice (Pierre et al 2002, Apfel et al 2002 b, Apfel and Roewer 2003, Gan et al 2003).

Table 3. Simplified risk score for PONV counting occurrence of the following 4 factors female-sex, history of PONV and/or motion sickness, non-smoking, postoperative opioids (Apfel et al 1999).

Risk factors for PONV	Incidence of PONV %
♦ 0 factor	♦ 10%
♦ 1 factor	♦ 20%
♦ 2 factors	♦ 40%
♦ 3 factors	♦ 60%
♦ 4 factors	♦ 80%

Management of PONV

Currently discussed anti-emetic methods

- Dopamine (D_2) receptor antagonist.
  Butyrophenones (droperidol, haloperidol).
  Phenothiazines (promethazine, prochlorperazine).
  Benzamides (metoclopramide).
- Histamine (H_1) receptor antagonist.
  Diphenhydramine, promethazine.
- Muscarinic cholinergic receptor antagonist.
  Anticholinergic (atropine, scopolamine).
- 5-HT_3 receptor antagonist.
  Ondansetron, granisetron, tropisetron, dolasetron, ramosetron.
- Neurokinin-1 receptor antagonist.
  (CP-122, 721, GR 205171).
- Alpha-adrenergic agonists.
  Clonidine, ephedrine.
- Corticosteroids.
  Dexamethasone, betamethasone.
- Benzodiazepines.
  Midazolam.
- Supplemental oxygen.
- Hydration.
- Slow deep breathing.
- Sensory stimulation.

Drugs commonly used and their side-effects are seen in Table 4.

Table 4. Some currently available anti-emetics and their side-effects

Pharmacological groups	**Side-effects of the pharmacological groups**
1. Dopamine (D_2) receptor antagonist	1. Sedation, dizziness, drowsiness, restlessness, dystonia, parkinsonia, hypotension, extrapyramidal symptoms, vertigo, akathisia, neuroleptic malignant syndrome, visual-disturbances, nightmares, urinary retention, and arrhythmias.
2. Histamine (H_1) receptor antagonist	2. Sedation, drowsiness, dizziness, dry mouth, visual disturbance, and urinary retention.
3. Muscarinic cholinergic receptor antagonist	3. Dry mouth, difficulty with accomodation, dizziness, agitation, and drowsiness.
4. 5-HT_3 receptor antagonist	4. Headache, increased liver enzymes, constipation, warm sensation in the epigastrium, flushing, dizziness, hypersensitivity, and serotonin syndrome.

Dopamine (D_2) receptor antagonist

Butyrophenones (droperidol)

The most commonly used dopamine receptor antagonists include the butyrophenones (droperidol). The long duration of action (up to 24 h) after administration probably depends on strong binding affinity to the emetic receptors (CTZ and area postrema), even though the half-life is 3h (Kovac 2000, Henzi et al 2000). Droperidol is the best-documented antiemetic drug when given with morphine in adults, having a NNT of 3 (Tramèr and Walder 1999) and the only antiemetic effective in preventing PONV caused by opioids administered with PCA (Tramèr and Walder 1999).

Reported side-effects of droperidol can be seen in Table 4 (Henzi et al 2000). Recently the US Food and Drugs Administration (FDA) issued a warning on the pro-arrhythmic effects of droperidol (FDA 2001). They stated that droperidol might cause life-threatening events associated with QT prolongation and torsades de pointes. The FDA decision has met strong criticism, as the arrhythmias and electrophysiological changes associated with droperidol appear to be rare. It is interesting to note that there has not been a single case report in a peer-reviewed journal in which droperidol in doses used for the management of PONV has been associated with QT prolongation, arrhythmias, or cardiac arrest (Gan et al 2002). Sedation and drowsiness are dose dependent (Henzi et al 2000).

Droperidol has a similar effect in reducing PONV as ondansetron (Peixoto et al 2000), perphenazine (Desilva et al 1995), tropisetron (Jokela et al 1999) and dexamethasone (Wang et al 1999). Droperidol and ondansetron are more effective than metoclopramide (Domino et al 1999). Some studies have found that ondansetron was more effective than droperidol in reducing the severity of vomiting and the incidence of late nausea (Koivuranta et al 1997 b). In general, combination therapy is superior to monotherapy for PONV-prophylaxis (Eberhart et al 2000 b). The 5-HT_3 antagonists, which have better anti-vomiting than anti-nausea effect can be used in combination with droperidol, which has greater anti-nausea effect and is protective against headache (Tramèr 2001 part I) but some uncertainty remains concerning the efficacy of the combination (Eberhart et al 2000 b).

We chose a dose of 20μg/kg droperidol because in previous dose-finding studies this dose gave the greatest reduction in PONV (Pandit 1989, Domino et al 1999, Jokela et al 1999, Henzi et al 2000). There is a dose-response relationship for the anti-vomiting but the dose-response relationship concerning the anti-nausea effect is not well defined (Pandit 1989). With droperidol 0.30 mg the NNT was 5. Increasing the dose did not improve the early anti-nausea efficacy. However, to maintain this effect long-term repeated low doses are required for example 0.5 mg every 12^{th} h. (Henzi et al 2000). For anti-vomiting 0.30 mg, and 0.75 mg i.v. are not effective. With increasing doses, droperidol´s anti-vomiting effect improved considerably, but beyond 2.5 mg no further increase was seen (Henzi et al 2000). Droperidol is most effective when administered at the end of surgery (Henzi et al 2000, Gan et al 2003).

5-HT_3 receptor antagonists

Ondansetron, granisetron, tropisetron, dolasetron and ramosetron

Members of this group exert their effect by binding to the serotonin 5-HT_3 receptor in the CTZ and at vagal afferents in the gastrointestinal tract. They have been used as prophylaxis and treatment of nausea and vomiting due to chemotherapy and radiation therapy (Dicato and Freeman 1992) and PONV (Lee et al 2002). There is no evidence of any difference in the efficacy and safety profiles of 5-HT_3 receptor antagonists in the prophylaxis of PONV (Gan et al 2003). These drugs are most effective when given at the end of surgery (Henzi 2000). The known side-effects can be seen in Table 4 (Russel and Kenny 1992).

Granisetron is a selective antagonist of 5-HT_3 receptors and is thought to elicit its antiemetic effect by blocking 5-HT_3 receptors at both peripheral and central sites (Sanger et al 1989). The onset of the antiemetic action of granisetron occurs within approximately 30 min after a single intravenous administration, with a duration of action of more than 24 h (Furue et al 1990). Granisetron is reportedly more potent and has a longer lasting therapeutic effect than ondansetron (Andrews 1992). These findings may be due to the higher specificity and affinity of granisetron for 5-HT_3 receptors (Andrews 1992).

Oxygen, hydration, and oral intake

High inspired concentration of oxygen has been suggested to decrease PONV but results from studies have been conflicting (Coll et al 2001, Purhonen et al 2003). In patients undergoing ambulatory surgery, A 20 ml/kg bolus of an isotonic solution was associated with significantly less nausea, thirst, dizziness, and drowsiness on the first postoperative day, compared to patients who received a bolus of 2 ml/kg (Yogendran et al 1995). It has been speculated that this is caused by better perfusion of the gastrointestinal tract, thereby reducing the release of serotonin from the gut (Gan et al 1997). The use of colloids for intra-operative fluid resuscitation was associated with less PONV, compared with crystalloid administration (Moretti et al 2003). Postoperative oral intake does not seem to influence the incidence of PONV (Jin et al 1998).

Slow deep breathing

Parasympathetic nervous system (PNS) activity can be influenced by breathing at a frequency of 4-8 breaths per minute (Naylor and Inall 1994). Instructions were given to patient to inhale over 4 seconds and exhale over 4 seconds which led to a breathing frequency of 8 per min. Breathing at this frequency appears to stimulate reflexes that control the autonomic nervous system (ANS), particularly the baroreflex system. It reduces vagal activity and thereby maintains normal gastric activity (Lehrer et al 1997). It also decreased symptoms of vection-induced motion sickness (Jorkest et al 1999).

Sensory stimulation

Many types of sensory stimulation have been investigated. Lee and Done (1999) performed a systematic review of 24 randomised trials of acupuncture, transcutaneous electrical nerve stimulation, acupoint stimulation, and acupressure. The main findings were that non-pharmacological techniques had an effect similar to commonly used antiemetic drugs (metoclopramide, cyclizine, droperidol and prochlorperazine). So non-pharmacologic techniques could be recommended in adults as an alternative to no treatment or as first-line antiemetic to prevent early PONV (Lee and Done 1999). Vickers (1996) concluded after analysing 21 controlled trials of P6-acupuncture that acupuncture decreased emetic symptoms. Gan et al reported similar effects of P6-electroacupuncture and prophylactic ondansetron (Gan et al 2001). A combination of ondansetron and P6-electroacupuncture was even better (White et al 2002, Coloma et al 2002).

Acupuncture and acupressure

History

P6, a Chinese meridian point, is specifically effective for the treatment of nausea and vomiting. Acupressure is related to acupuncture and uses the same acupoint to relieve nausea. The Chinese have been using this technique for centuries. Acupuncture and acupressure are based on the belief that an individual´s well-being depends on the balance of energy in the body as well as the overall energy level. It is hypothesised that energy flows in the body along paths referred as meridians and that it is possible to restore the balance of energy by manipulating these meridians by for example acupressure and acupuncture (Vincent and Richardsson 1986).

Acupressure mechanism

A neural mechanism has been suggested based on the ability of local anaesthetic to block the antiemetic action of P6-acupressure (Dundee and Ghaly 1991). Both manual acupuncture and electro-acupuncture analgesia may be blocked by the opioid antagonist naloxone (Pomeranz and Chiu 1976). Clement-Jones et al (1980) reported that B-endorphin-like immunoreactivity in CSF increased during low-frequency electro-acupuncture, whereas met-enkephaline concentrations did not change. In contrast, met-enkephaline levels but not B- endorphin, increased in CSF after high-frequency electro-acupressure (Clement-Jones et al 1979). Acustimulation also increases parasympathetic activity and decreases motion sickness (Andersson 1993).

Acupuncture and acupressure efficacy

Preoperative intradermal acupuncture reduced the incidence of post-operative nausea and vomiting (Kotani et al 2001). This antiemetic effect can be explained, in part, by better analgesia and less need for opioid analgetics (Wang et al 1997). A direct antiemetic effects is also plausible as P6-acupuncture decreases PONV in patients undergoing minor gynaecologic surgery in whom pain was unlikely to be a major trigger for PONV (Dundee et al 1989).

Control of symptoms that influence the incidence of PONV

Pain control

Visceral pain is a major cause of PONV (Naylor and Inall 1994, Chia et al 2002). Pain triggers PONV for a variety of reasons including an increase in catecholamines that directly affects the CTZ. An increased peripheral release of 5-HT caused by tissue trauma also directly affects the CTZ (Marley 1996). Adequate postoperative pain control may thus reduce the incidence and severity of PONV (Andersen and Krohg 1976). A multimodal approach to

postoperative pain is generally recommended. The preoperative oral administration of the opioid oxycodone reduced the total dose of opioid needed and the incidence of PONV (Reuben et al 1999).

Avoid hypotension and variation in blood pressure

A marked decrease in systolic blood pressure (>35%) during the induction of general anaesthesia was associated with greater PONV (Pusch et al 2002). If compensatory mechanisms are insufficient for fast restoration of adequate cardiovascular function, a temporary decrease in splanchnic perfusion may result (Piriou et al 1999). One consequence is the release of 5-HT from the intestine which could induce PONV (Greif et al 1999). A fall in systolic blood pressure during induction of anaesthesia may also reduce the blood flow to the brain stem and influence the CTZ. This may intensify such adverse effects of anaesthetics as dizziness, disturbances of the vestibular system, nausea and vomiting (Nakagawa et al 1993). The patient´s blood pressure in the PACU is another important aspect. If there is a significant reduction in blood pressure, or if the patient attempts to ambulate causing orthostatic hypotension, the patient may experience nausea, become dizzy, or have syncopal episodes further contributing to PONV (Rothenberg et al 1991).

AIM

Postoperative symptoms are distressing for the patient and influence satisfaction with care and postoperative recovery. Postoperative nausea and vomiting have been extensively studied in recent years but still there is no consensus about whether to use prophylaxis or timely treatment, or about what treatment to choose. We suggest that this is partly because surrogate end-points have been focused upon, i.e. nausea and/or vomiting and not actual increased well-being and general symptom relief experienced by the patient. Non-pharamcological treatments could compare favourably.

General Aims

- To identify disturbing symptoms reported after gynaecological surgery.
- To investigate the effect of prophylactic treatment with antiemetics on postoperative symptoms.
- To investigate if sensory stimulation of the P6-acupressure has an effect on postoperative nausea and vomiting.
- To investigate if P6-acupressure favourably effects motion sickness.

The specific objectives of dissertation

1. To evaluate patient experience of type, incidence and intensity of postoperative symptoms following various gynaecological procedures in modern day practice using a postoperative questionnaire (III).
2. To evaluate a questionnaire regarding postoperative symptoms (III).
3. To investigate how prophylactic antiemetic treatment, with two different well-studied and effective antiemetics (granisetron Kytril® and droperidol Dridol®), affects disturbing postoperative symptoms in a group of women at high-risk for PONV after gynaecological surgery (III).
4. To investigate the effect and placebo effect of acupressure in prevention of postoperative nausea and vomiting (PONV) after minor day-case gynaecological surgery (1).
5. To investigate the effect of P6-acupressure on PONV after gynaecological surgery in the everyday clinical setting (effectiveness study) (II).
6. To investigate whether P6 acupressure increases time to nausea induced by a laboratory motion challenge and whether a previous history and severity of motion sickness matters (IV).
7. To investigate the effect of P6-acupressure on symptoms induced by a laboratory motion challenge (IV).

PATIENTS AND METHODS

The total number of patients and volunteers in the studies reported here (I-IV) was 1138 women. They participated in three clinical trials and one experimental trial. The total number of drop-outs was 52. These can be seen under the heading “Drop-outs” in Table 5. The Specific cause for each individual can be seen in the method section in articles I-III. They were all patients and were replaced by randomising another 52 patients at the end of the study period. Sixty-one women participated in the development of the postoperative questionnaire. Patients and methods in Studies I-IV are described in detail in Table 5.

Table 5. Patient characteristics, study design and methods in Studies I-IV.

	Study I	Study II	Study III	Study IV
Study population Demographic data	**60 women.** Age 18 to 62 years (median 30), weight 49 to 93 kg (median 65) with American Society of Anaesthesiologists physical status (ASA) I, II or III.	**410 women.** Age 18 to 65 years (median 40), weight 41 to 110 kg (median 68) with ASA I, II or III. Apfel risk score for POV was calculated for every patient (Apfel 1998).	**495 women.** Age 18 to 75 years (median 42), weight 42 to 145 kg (median 67) with ASA I, II or III with high risk for postoperative vomiting (POV) (Apfel 1998).	**60 women (volunteers).** Age 18-40 years (mean 29, SD ± 6 years), weight 47 to 100 kg (median 63), with a history of motion sickness were included.
Study design	♦ A prospective, consecutive double-blind, randomised, placebo, and controlled clinical trial.	♦ A prospective, consecutive, multicentre, double-blind, randomised, placebo, and controlled clinical trial.	♦ A prospective, consecutive, multicentre, double-blind and controlled clinical trial. ♦ A group of patients with >30% risk for (POV).	♦ A prospective, double-blind, randomised, placebo, and controlled experimental trial. ♦Groups stratified to 10 women with high susceptibility and 10 with low susceptibility to motion sickness.
Inclusion and exclusion criteria	♦ Patients undergoing minor gynaecological surgery Exclusion criteria ♦ Previous problems with the wrists. ♦ Anatomical or neurological abnormalities of the upper limbs. ♦ Nausea and vomiting within 24 hours of the operation. ♦ A history of diabetes mellitus. ♦ Over 110 kg body weight. ♦ Previous experience of acupressure.	♦ Patients undergoing minor gynaecological surgery or laparoscopy. Exclusion criteria were the same as in (Study I).	♦ Women undergoing minor gynaecological surgery, hysterectomy, prolapse or laparoscopy. ♦Women with POV risk score calculated according to Apfel > 30%. Exclusion criteria ♦ Nausea and vomiting the last 24 hours before the operation. ♦ Antiemetics within 24 h before surgery. ♦ Breast-feeding.	♦ Women with a previous history of motion sickness. Exclusion criteria ♦ Previous experience of acupressure bands. ♦ Previous experience of chair rotation. ♦ Known history of visual problems, gastro-intestinal, oculomotor, vestibular or central nervous system disorders.
Prophylactic antiemetic intervention	♦ P6-acupressure (n=20). ♦ Placebo acupressure (n=20). ♦ Reference group (n=20).	♦ P6-acupressure (n=135). ♦ Placebo acupressure (n=139). ♦ Reference group (n=136).	♦ Droperidol 1.25 mg (n=165). ♦ Granisetron 3 mg (n=165). ♦ Control group (n=165).	♦ P6-acupressure (n= 20). ♦ Placebo acupressure (n= 20). ♦ Reference group (n= 20).

	Study I	Study II	Study III	Study IV
Study period	Until noon the day after surgery.	Until 8 p.m. the day after surgery.	Until 8 p.m. the day after surgery.	Until 30 min after rotation stopped.
Primary outcome	Complete response (no nausea, no vomiting, no need for rescue antiemetic).	Complete response (see Study I).	Patients' overall rating of intensity, incidence, and number of disturbing postoperative symptoms.	Time to moderate nausea (3 or more on a Lickert type scale 0-6) provoked by an eccentrically rotating chair.
Secondary outcome	♦ Nausea only. ♦ Vomiting only. ♦ Need for rescue antiemetics. ♦ Nausea 24 h after surgery.	♦ Nausea only. ♦ Vomiting only. ♦ Nausea and vomiting. ♦ Rescue medication.	♦ Number needed to treat (NNT). ♦ Number needed to harm (NNH). ♦ Complete response. ♦ Nausea only. ♦ Vomiting only. ♦ Nausea and vomiting. ♦ Rescue medication.	♦ The number and types of symptoms reported. ♦ Nausea.
Timing of intervention	20 min. before induction of anaesthesia.	20 min. before induction of anaesthesia.	Immediately before induction of anaesthesia.	10 min. before a nausogenic challenge.
Randomisation	By drawing a sealed envelope with instructions, which was opened when the patients arrived in the operating theatre.	Randomisation was the same as in (Study I).	According to a randomisation list, which was generated by the pharmacy. Block randomisation was used with 9 patients in each group.	By drawing a sealed envelope with instructions, which was opened on arrival of the women at the laboratory.
Blinding	The lower arms were covered with a dressing.	Blinding was the same as in (Study I).	All study drugs were diluted by a pharmacist to a fixed volume of 3 ml and marked with a coded label A or B. The control group was not blinded to the anaesthetist but to all others.	The areas stimulated were covered with a dressing during the trial period. Neither the observer nor the women knew if P6 or placebo stimulation was given.
Premedication and anaesthesia	♦ Premedication: paracetamol 1 g. ♦ Hydration with 10 ml / kg of glucose 2.5%. ♦ Thiopentone 3-5 mg / kg. ♦ Alfentanil 0.5 mg. ♦ Tracheal intubation succinylcholine. ♦ For maintenance, 66% N_20 in oxygen and isoflurane.	♦ Premed. and hydration as in Study I ♦ Induction propofol 2 mg / kg or thiopentone 3-5 mg / kg. ♦ Intraoperative analgesia alfentanil 0.5 mg or fentanyl 0.2 mg. ♦ Tracheal intubation esmeron or succinylcholine ♦ For maintenance 66% N_20 in oxygen and isoflurane, desflurane or sevoflurane. ♦ Reversal of muscle relaxation glycopyrrolate 0.5mg / neostigmine 2.5 mg.	♦ Premedication: paracetamol 1g and diazepam 5 mg. ♦Anaesthesia was the same as in (Study II).	Not used.

	Study I	Study II	Study III	Study IV
Assessment of nausea and vomiting in the PACU	♦ Visual analogue scale horizontal, 100 mm. Endpoints were assigned "no nausea" to the left and "worst possible nausea" to the right. ♦ At 30, 60 and 120 min. ♦ Vomiting was noted by the nurses, as was the need for antiemetics. ♦ Retching was classified together with vomiting.	♦ Nausea was estimated using a 7- point Lickert-type scale in which 0= no nausea, 1= very mild, 2= mild, 3= moderate, 4= severe, 5= very severe and, 6= worst possible nausea. ♦ The nurses recorded the frequency of vomiting at 30, 60, and 120 minutes.	♦ Nausea was estimated using the same scale as in Study II. ♦ At arrival and every hour until discharge from the PACU.	♦ Nausea was estimated using a 7-point Lickert-type scale. ♦ After rotation was stopped the women were asked to assess their degree of nausea at 2-minute intervals for 30 minutes.
Assessment of nausea and vomiting after discharge from PACU	♦ Assessment forms were sent with the patients, who were asked to record their level of nausea using a VAS-scale at 6 p.m., when going to bed, at breakfast time, and at noon the day after surgery. ♦ They were also asked to note vomiting, pain, and satisfaction with the treatment that they had been given.	♦ Assessment forms were sent with the patients, who were asked to record their level of nausea using a 7-point Lickert-type scale, at 8:00 p.m., and 8:00 a.m. and 8:00 p.m. on the day after surgery ♦ They were also asked to note vomiting, pain, and satisfaction with the treatment that they had been given.	♦ When leaving the PACU all patients received the Post-operative symptom questionnaire (Appendix1) where common symptoms reported after surgery were asked for. ♦ Nausea/vomiting were recorded at 8:00 p.m. on the day of surgery and at 8:00 p.m. on the first day after surgery as well as the other postoperative symptoms.	Not applicable.
Rescue medication	♦ Antiemetic was given at the discretion of the PACU nurse. ♦ Metoclopramide 10 mg i.v. as the first option, then ♦ Droperidol 1.25 mg was given i.v. if needed.	If the nausea was more than 2 on the Lickert-type scale or the patient vomited twice she was given: ♦ Dixyrazine 2.5 mg. This was repeated once, if not effective. ♦ Metoclopramide 10 mg i.v. was given. If this was not effective ♦ Ondansetron 4 mg i.v. was given.	The same indications as in (Study II) ♦Dixyrazine 5 mg intravenously first optionn, then ♦ Droperidol 1.25 mg, then ♦Granisetron 1 mg.	Not indicated.
Assessment of pain and analgesia given	♦ A visual analogue scale (VAS), 100 mm horizontal. ♦ Paracetamol 1g. ♦ Additional analgesia if VAS ≥ 40 ♦ Morphine in doses of 2 mg i.v. ♦Paracetamol for pain relief up to 4 times / 24 hours after discharge.	♦ Assessment of pain and analgesia as in (Study 1).	♦ Assessment of pain and analgesia as in (Study 1).	Not applicable

	Study I	Study II	Study III	Study IV
Drop-outs	♦ 10 patients were lost to follow up. They were replaced at the end of the study. ♦ The drop-outs were evenly distributed between the groups. For more details see Study I.	♦ 30 patients were lost to follow up. They were replaced by entering another 30 at the end of the study. ♦ Withdrawals were evenly distributed among the groups. For more details see Study II.	♦ 12 patients were lost to follow up . They were replaced by entering another 12 at the end of the study. ♦ Withdrawals were evenly distributed among the groups. For more details see Study III.	*None*
Statistical analysis	♦ Demographic data are given as median (range). ♦ Kruskal-Wallis test was used to test for differences between demographic data. ♦ Comparison of treatment effects was performed with Fishers exact test. ♦ A P-value of < 0.05 was considered to be significant.	♦The presentation of continuous data is as mean (± SD) or occasionally as median and range. ♦ Students t- test for comparison of continuous data. ♦ Outcome data were analysed using logistic regression. ♦ The Apfel risk score was included as an auxiliary explanatory variable. Likewise, the type of operation (vaginal or laparoscopic) was introduced as an explanatory variable when both types of operation were included in the same regression analysis. ♦A P-value below 0.05 was considered to be significant.	♦ Values are given as mean ± SD, median and range, or number. ♦ Symptoms are analysed and described in two ways first focusing on intensity of disturbing symptoms, based on Question 7 in the questionnaire and then in a dichotomous fashion, i.e. is there a symptom, yes or no? ♦ A logistic ordinal regression analysis was used to describe differences in intensity profiles for postoperative symptoms based on Question 7 for the three groups. Number of symptoms was counted. ♦ The incidence of PONV and other specified symptoms was analysed with Fishers exact test. ♦ The number needed to treat (NNT) and number needed to harm (NNH) was used to compare the relative efficacy of a treatment. ♦ A p-value below 0.05 was regarded as significant.	♦ The presentation of continuous data is as mean (± SD). ♦ The analysis of variance (ANOVA) was used to analyse differences between the three groups concerning time to nausea of moderate nature that is 3 on 0-6 scale. ♦ If a difference was found, post hoc analysis with Tukey HSD was used to find where the difference was. ♦ The number of symptoms was analysed with χ^2 test to identify any differences between the groups. ♦ Repeated measures ANOVA was used to identify differences between the three groups concerning MANE assessment (0-6 Lickert-type scale) after chair rotation. ♦ The differences between observations in a before-after rotation concerning MAP, pulse rate were tested with a paired t-test. ♦ A p-value below 0.05 was regarded as significant.

	Study I	Study II	Study III	Study IV
Power analysis	Not calculated	♦ The sample sizes were chosen to provide at least a 90% chance of detecting a 50% reduction in postoperative nausea and vomiting from the reference group to the acupressure group. ♦ This assumed an incidence of nausea and vomiting in the reference group of 30% or more and we used a single tailed z-test at the 5% level of significance. ♦ On the assumption that the placebo incidence of nausea and vomiting was midway between the other two, the chance of detecting the difference between the placebo group and the reference group is roughly half as large (46% at least). ♦ The chance of finding a significant difference between the acupressure group and the placebo group is even less (40% at least). As we are actually using a more effective way of testing group differences than the z-test, the power should be somewhat larger than stated above. We were in need of 135 patients in every group.	♦ A 50% reduction in PONV was considered of clinical interest. Accepting a significance of 0.05 and a power 0.80, the estimated sample size necessary to demonstrate such a difference was in the order of 154 persons with > 30 % risk for POV to draw meaningful conclusions.	♦ A power analysis of the present material (post hoc) showed that we would need 95 patients in each group to demonstrate a significant difference in motion sickness between P6-acupressure and placebo acupressure. We have refrained from this because of the high cost of a study with 190 volunteers.

Procedures

In Studies I and II

A letter about the study was sent to the patient before admission. Patients were informed verbally on the day of operation and consent was asked for. In the anaesthetic room the patients were randomised to one of three study groups. The Sea-Bands® were positioned on both wrists in both active and placebo group 20 min before the start of the anaesthesia by a nurse who was not involved in anaesthetising or caring for the patient postoperatively, and the patients were asked to wear the bands continuously for 24 hours. If the bands caused discomfort, they could be removed for 30 minutes in each 2-hour period. An assessment form was taken home by the patient and was later returned together with the Sea- Bands® by mail to the hospital. The reference group was observed in the same way as the two treatment groups.

In Study III

A letter about the study was sent to the patients before admission. Patients were also informed verbally on the day of surgery and consent was obtained. A risk score for PONV was established after the patient history and examination was completed. If the risk for vomiting according to Apfel was >30% (Apfel et al 1998) the patients were asked to participate in the study. The patients that accepted to take part in the study were randomised to one of three groups (n=165 for each group), see prophylactic antiemetic intervention (Table 5). Drugs were blinded and given the name A or B. An anaesthetic nurse who was not later involved in the assessment of treatment effect administered the drug intravenously immediately before induction of anaesthesia. Postoperative symptom questionnaires were sent with the patients when they left the PACU. The questionnaire was later returned by mail to the hospital.

In Study IV.

A letter about the study was sent to the women at home and consent was asked for. They were requested to refrain from eating or drinking two hours preceding the motion challenge. All women were instructed to strictly abstain from alcohol and tobacco for at least 24 hours prior to the experiment. On arrival at the laboratory (between 10.00 a.m. to 04:00 p.m.), women were randomised to one of three groups, each group included two equal subgroups according to high or low susceptibility to motion sickness. Blood pressure and pulse rate were measured. Sea- Bands® were fitted ten minutes before the start of the rotation stimulus and remained in place throughout the trial period. The observer who asked the patients about nausea and the experimenter who administered chair rotation were not aware of which treatment the patient received. The control group was observed in the same way as the two treatment groups. The woman was placed in the chair and rotation started. Rotation was stopped when the woman reported nausea as moderate or a value of 3 on a 0-6 scale. Subjective symptoms were obtained by asking the woman to report any discomfort she felt during the chair rotation period immediately after the chair rotation stopped and then every 4th min until the 30 min study period was over. Blood pressure and pulse rate were monitored.

Apparatus and nauseogenic provocation. The experimental nauseogenic stimulation used in the present study has been used in earlier studies and is likely to recreate the subject's susceptibility to "real life" motion sickness (Bruce et al 1990). The nauseogenic motion challenge was induced by a combination of head movements (chin to chest, head flexion) whilst the subject was blindfolded and seated in a chair on an eccentrically rotating about a vertical axis. It has been well established that nodding head movements concomitant with body rotation around the vertical axis is an intense stimulation of the vestibular

receptors of the inner ear (the Coriolis effect), thereby inducing motion sickness (Johnson et al 1951). It has also been proposed that vestibulosympathetic reflexes contribute to autonomic responses of a prone individual during head-down neck flexion (Ray and Hume 1998). Chair rotation took place in complete darkness to exclude visual cues to the true orientation of the subject. The woman was positioned in the chair with a headrest, which was designed to assist the woman to place her head in a predetermined position. The headrest also served to guide the forward and downward movements of the head. The chair rotation speed was 60°/s for all groups. The motor driven chair was stopped when the women reported nausea as moderate or a value of 3 on a 0-6 scale.

Predicting risk for PONV

We used a risk score for *postoperative vomiting (POV)* (Apfel et al 1998) in Studies II and III. The score is based on patient-related risk factors and length of anaesthesia (being female, young, non-smoking, having a history of motion sickness or PONV and length duration of anaesthesia). The probability of POV was estimated from the equation: $POV = 1/ (1+e^{-z})$, where z= 1.28 x (gender) -0.029 (age) -0.74 x (smoking) +0.63 x (history of PV or motion sickness) + 0.26 x (duration) -0.92 (Study II). And in Study III from a simplified table (Apfel et al 1998)

Assessment of postoperative symptoms using a questionnaire

No available questionnaire was sufficient for the purposes of our study so we developed one. We were interested in what symptoms the patients experienced postoperatively and to get an estimate of their incidence and severity. To discover what had been reported previously we ran a search on MedLine of studies reporting postoperative symptoms between 1992 and 2002 using the following terms: postoperative symptoms, post-discharge symptoms, postoperative pain, PONV, dizziness, drowsiness, fatigue, and sleep disturbances. Articles reporting more than two symptoms (of any kind) and with an observation time of at least 24 hours were scrutinised (Table 6). This was used as a base when developing the questionnaire. The questionnaire was divided into two similar sets of nine questions, one set for each day. The questions were both open-and closed-ended. The closed-ended questions had options on a scale (no, very mild, mild, moderate, bad, severe, very severe). The open-ended questions required written responses from the patient. The patients were first asked if they had experienced a number of symptoms commonly reported after surgery (nausea/ vomiting, incision pain, headache, abdominal pain, difficulties with accommodation, drowsiness and fatigue). Then, in the open-ended questions, patients were asked to report whether they experienced any other symptoms. Thereafter the patients were asked to report disturbing symptoms and to grade which of these were most disturbing (could be more than one). Patients were asked to grade the intensity of their overall suffering and the degree of pain. Symptoms of very mild intensity were ignored in the primary outcome, as using a questionnaire to obtain post-anaesthetic complaints increases both the number of patients responding positively and the number of complaints reported by each patient (Philip 1992, Rawal et al 1997, Fahy et al 1969). The patients were classified as having disturbing symptoms if they rated them as moderate to very severe in intensity. The quality of sleep the night after surgery was asked for (good, slightly disturbed or poor).

Table 6. Type and incidence of postoperative symptoms given in % reported in articles found in MedLine, published between 1992-2002. Articles giving at least 2 symptoms and with an observation time of 24 hours are reported. ng=not given.

	Present study	**Bauer et al 2001**	**Hunter et al 1998**	**Beauregard et al 1998**		**Rawal, et al 1997**	**Chung 1996**	**Chung 1995**	**Roberts et al 1995**	**Ratcliffe et al 1994**			**Philip, 1992**	
The patient population/ response (n)	165/165	700/589	635/553	103/84		1100/1035	1017/778	500/414	193/106	74/65			3722/1511	
Age (y) (range)	18-75	adults	adults	17-59		5-88	19-66	16-85	15-55	23-52			adults	
Type of anaesthesia:General=G, regional=R, local=L, spinal=S	G	G	G	G/R/L		G/R/L/	G/S	G/S	G	G			G/R	
Type of surgery. Gynaecological=gyn or mixed	gyn	mixed	mixed	mixed		mixed	mixed	mixed	gyn	gyn			mixed	
Intensity of symptoms. Graded scale=G, dichotomous scale=D	D	G	D	D		D	D	D	D	G			D	
Method of surveillance. Mail=M, Interview=I, telephone=Ph	M	M&I	M	M		M	Ph	Ph	M	M			M	
Postoperative period studied (hr)	24	48	24	24	48	48	24	24	24	12	24	48	24	48
Pain in the area of surgery	84	57	40	95	83	35	26	30	63	ng	ng	ng	31	ng
Sleep disturbances	48	ng	ng	47	34	50	ng	ng	ng	ng	ng	ng	ng	ng
Abdominal pain	70	ng	ng	ng	ng	ng	ng	ng	ng	92	89	72	ng	ng
PONV, n= nausea, v= vomiting	54	24	9	27	12	n 21/v 8	5	12	30	13	3	4	n 73/v 92	n 19/v 5
Fatigue	92	ng	ng	54	43	20	ng	ng	ng	ng	ng	ng	19	ng
Drowsiness	88	79	ng	45	26	ng	11	13	47	55	27	12	56	33
Headache	27	ng	19	27	13	ng	11	12	30	7	12	12	61	24
Pain in thorax, arms, shoulder, back	12	ng	ng	ng	ng	ng	ng	ng	ng	44	44	30	27	45
Dizziness	1	ng	ng	22	16	ng	9	10	ng	29	13	7	65	25
Difficulty in urination	1	ng	ng	ng	ng	6	ng	ng	ng	ng	ng	ng	ng	ng
Mental problems	2	21	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng
Feeling of cold	1	24	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng
Shivering	0	15	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng
Difficulty with accommodation and eyes	36	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng
Thirst	0	53	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng
Hoarseness	0		ng	40	18	ng	ng	15	ng	ng	ng	ng	ng	ng
Expectorate, sore throat	1	32	ng	47	30	ng	ng	25	23	38	26	12	37	42
Tingling	0	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng	ng
Fever	0	ng	ng	ng	ng	ng	5	3	ng	ng	ng	ng	ng	ng
Number of different symptoms	**14**	**9**	**3**	**9**		**5**	**6**	**8**	**5**	**7**			**8**	

In pre-testing and final layout of the questionnaire 10 professionals were involved (2 doctors, 3 anaesthetic nurses, 4 PACU nurses, and a statistician). They were asked to judge whether or not the questions were appropriate and reasonable. After some changes the questionnaire was considered valid. The questionnaire was pretested on 43 patients similar to the sample we planed to study. All patients answered a question about the appropriateness of the questions at the end of the questionnaire. This is important as the willingness of patients to complete a questionnaire is related to whether or not the questionnaire is perceived to measure what they wish to relate (Thomas 1992). Reliability was investigated with a test-retest in 18 patients. The same postoperative patient filled in the questionnaire at 06:00 p.m. and 08:00 p.m. on the day of operation. The questionnaire used is shown in Appendix 1 in Swedish. An English translation is found in Article III.

Explanation of some statistical methods

We had Question 7 as a gateway to the material (Appendix 1): "How much discomfort did you suffer after the operation apart from pain? Try to give an overall rating for the whole period". The patients scored between "no discomfort"= 0, to "very severe discomfort" = 6, on a Lickert-type scale 0-6. From this question we can approach the information about how disturbing the symptom was. Ordinal logistic regression was used. Then we used the next question "what symptom on average was most disturbing?" (Could be more than one). We have also described the symptoms in a dichotomous fashion and counted all symptoms that were reported in Question 8.

Assessment of patient satisfaction

Patients estimated their satisfaction with their PONV treatment using a Lickert-type scale 0-6, in which 0 = very much dissatisfied, and 6 = very much satisfied in studies I, II.

Ethical considerations

The studies presented in this dissertation were performed in accordance with the Declaration of Helsinki and were approved by the Research Ethics Committee of the Faculty of Health Science, Linköping University, Sweden.

To randomise to treatment was an ethical dilemma as the patient was not allowed to decide over her treatment. Nevertheless, all patients were given both verbal and written information before considering participation in the studies. It was made clear that participation was voluntary, could be terminated at any time and that confidentiality was guaranteed. For that reason, the ethical dilemma was deemed to be small (Studies I, II, III, IV).

When predicting risk for vomiting for the patients in the control group there were some with more than 30% risk of POV, yet they did not receive any form of prophylactic antiemetic. However the benefits of antiemetic prophylaxis are much debated and have not been shown scientifically. That is why the ethical dilemma was deemed to be small (Study III). All the patients received antiemetics when required regardless of which group the patients were randomised to (Studies I, II, III).

The patients´ integrity may be threatened when performing continuous data collection. The results were presented in a way that ensured that it was not possible to identify any of the individuals. The study protocol concentrates on the patients' health and well-being. It is important to know the incidence, intensity and type of postoperative symptoms so that the right symptom can be adressed. Knowing which pharmacological and non-pharmacological

preventive treatments for PONV are beneficial and which are not will enable us to decrease the suffering for patients and the cost for society. The above made the ethical dilemma small in comparison with the expected benefits for the patients (Studies I, II, III).

To burden the patient with questions concerning postoperative symptoms takes time and strength. However, patients feel that they receive more attention and this could be regarded as positive. Furthermore, identification of other postoperative symptoms as seen from the patients´ perspective, and not just the symptoms that we expect could lead to improvement in postoperative care for other patients in the future (Studies I, II, III).

We knew that volunteers would experience discomfort. This was an ethical dilemma. The experiment could be stopped at any time at the request of the volunteer. Motion sickness causes problems especially for women, as does PONV. We considered it therefore important to study this symptom in an experimental study which could yield important information leading to symptom relief for patients in the future. We therefore considered the ethical problem to be small. To study females is important since women suffer more side-effects of pharmacological treatment than do men (Study IV).

RESULTS

Symptoms

After gynaecological surgery under general anaesthesia

(Study III)

One hundred and sixty-five women scheduled for elective gynaecological surgery at three hospitals formed the control group. Demographics are seen in Table 7. Procedures were transabdominal (n= 30), laparascopic (n= 37) and vaginal (n= 98).

Table 7. Demographic data of the patients and details of anaesthesia and postoperative care. Values are given as mean ± SD unless otherwise stated.

Control group	*Whole group (n=165)*	*Abdominal (n=30)*	*Laparoscopy (n=37)*	*Vaginal (n=98)*
Risk factors				
Age (y)	46 ± 15	53 ± 10	42 ± 9	44 ± 16
BMI (body mass index)	25 ± 5	25 ± 5	26 ± 4	25 ± 5
History of motion sickness (n)	69	15	20	34
History of previous PONV (n)	71	12	18	41
Smoker (n)	31	4	5	22
Apfel risk score	43 ± 10	42 ± 8	44 ± 10	42 (± 10
Anaesthesia				
Thiopentone (n)	30	13	8	9
Propofol (n)	135	17	30	88
Fentanyl (n)	89	29	37	23
Alfentanil (n)	75	1	0	74
Intubation (n)	94	30	37	27
Duration of operation (min)	49 ± 50	107 ± 51	55 ± 43	29 ± 34
Duration of anaesthesia (min)	68 ± 62	140 ± 62	75 ± 45	42 ± 46
Postoperatively				
Antiemetic treatment (n)	51	21	14	16
Morphine (mg) median (range)	4 (0-24)	8 (0-22)	4 (0-21)	2 (0-24)
Morphine (n)	73	28	20	25
Time to discharge (min)	133 ± 65	182 ± 64	135 ± 68	117 ± 56

Sixty-four % (107/165) of the patients experienced disturbing symptoms after surgery (Table 8).

Tabel 8. *Number of symptoms experienced* by the patients after gynaecological surgery, n=107/165. Values given for the whole group and according to type of surgery.

Number of symptoms	Whole (n=165)	Abdominal (n=30)	Laparoscopic (n= 37)	Vaginal (n= 98)
0	58	4	7	47
1	28	5	6	17
2	34	9	8	17
3	23	7	8	8
4	14	3	4	7
5	5	2	2	1
6	1	0	1	0
7	1	0	0	1
8	1	0	1	0
Number of patients with symptoms	107	26	30	51

Fourt-six % (76/165) scored their symptoms as *moderate to very severe* (that is 3 or more on a 0-6 scale) (Table 9). The corresponding figure for the abdominal group was 73 % (22/30), for the laparoscopic group 70 % (26/37), and for the vaginal group 29 % (28/98) (Table 9). There was a high accumulative *incidence* of moderate to very severe symptoms (Fig. 4). Noteworthy is the high incidence of symptoms after laparoscopic surgery and the great diversity of symptoms found (Fig 4).

Table 9. *Number of disturbing symptoms of moderate to very severe nature* experienced by the patients after gynaecological surgery, n=76/165. Values given for the whole group and according to type of surgery.

Number of symptoms	Whole group (n=165)	Abdominal (n=30)	Laparoscopic (n=37)	Vaginal (n=98)
0	65	8	11	70
1	7	4	1	2
2	24	7	7	10
3	19	3	8	8
4	16	6	4	6
5	5	1	3	1
6	3	1	1	1
7	1	0	1	0
8	1	0	1	0
Number of patients with symptoms	76	22	26	28

Fourty-eight % (79/165) had *two or more symptoms* of disturbing nature (Table 8). The corresponding number for the abdominal group was 70 % (21/30), for the laparoscopic group 65 % (24/37), and for the vaginal group 35 % (34/98) (Table 8). The number of symptoms experienced for the whole group as well as according to surgery may be seen in Table 8.

The *number of moderate to severe* disturbing symptoms experienced by the whole group as well as according to surgery is seen in Table 9. The incidence of symptoms declined with time but a substantial number of patients still had pain at the site of operation, abdominal pain and fatigue on the first day after surgery (Fig. 5).

Figure 4. Accumulative incidence of disturbing symptoms of moderate to very severe nature up to 24 hr after gynaecological surgery in the control group of Study III. Values are given according to type of surgery

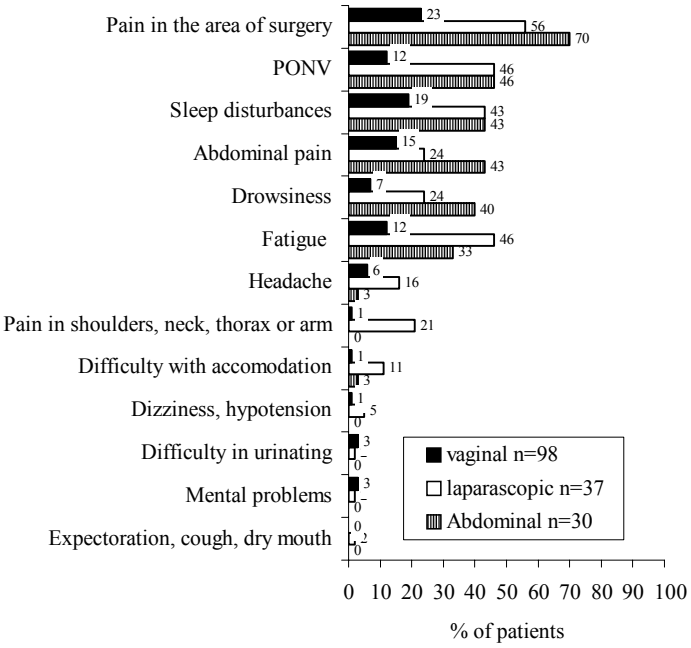
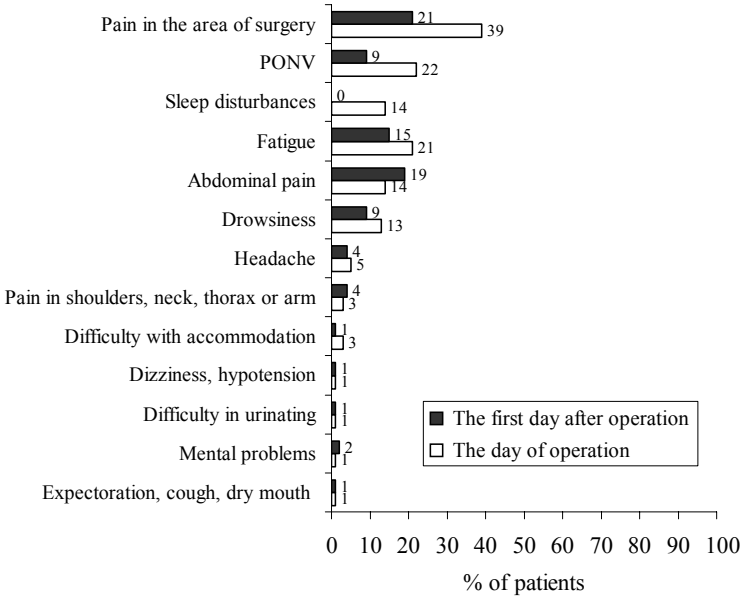


Figure 5. Disturbing symptoms of moderate to very severe nature on the day of surgery and the first day after surgery in the control group of Study III



After prophylactic treatment with granisetron or droperidol

The intensity of disturbing postoperative symptoms differed depending on whether droperidol, granisetron or no prophylaxis had been given, P = 0.005. Differences between the groups differed at different intensity levels and it is not possible to describe any of the groups as faring better (Table 10).

Table 10. Intensity of disturbing symptoms. Intensity of discomfort as graded by the patients on a Lickert-type scale. There is a difference between the groups analysed with ordinal logistic regression, P = 0.005. Numbers of patients are given.

How much discomfort did you suffer after operation apart from pain?	Control group (n=165)	Granisetron (n=165)	Droperidol (n=165)	Total (n=495)	P-value
No	45	38	24	107	0.02
Very mild	32	34	48	114	0.28
Mild	20	37	30	87	0.24
Moderate	42	29	39	110	0.09
Bad	16	18	16	50	0.13
Severe	8	7	2	17	0.02
Very severe	2	2	6	10	0.15

Table 11. Number of symptoms (see Figures 6 and 7) in the three groups (0-24 h), given in a dichotomous fashion (yes or no) and after grading the symptoms as moderate to very severe (a value of 3 or more on a scale 0-6) (Study III).

	Droperidol		Granisetron		Control	
Number of symptoms	Dichotomous (n=165)	Moderate to severe (n=165)	Dichotomous (n=165)	Moderate to severe (n=165)	Dichotomous (n=165)	Moderate to severe (n=165)
0	32	89	42	96	58	89
1	33	5	31	10	28	7
2	36	20	39	24	34	24
3	29	22	28	18	19	19
4	16	14	15	9	16	16
5	12	11	7	6	5	5
6	5	3	2	1	3	3
7	1	1	0	0	1	1
8	1	0	1	1	1	1
Number with symptoms	133[1]	76	123[2]	69	107[1, 2]	76

[1]= P <0.05 when droperidol group is compared with control group
[2]= P <0.05 when granisetron group is compared with control group

Symptoms were diverse and the accumulative incidence of symptoms given in a dichotomous fashion (yes or no) 0-24 h (Study III) was high (Fig. 6). Total number of symptoms reported was lower in the control group (P <0.05) than in the two treatments groups (Table 11). The number of moderate to very severe symptoms was similar (Table 11). Accumulative incidences of symptoms experienced by patients are seen in (Fig. 7). The incidence of disturbing symptoms declined with time but a substantial number of patients still had pain and fatigue on the first day after surgery.

Figure 6. Accumulative incidence of symptoms reported in a dichotomous fashion (yes or no) 0-24 h (Study III)

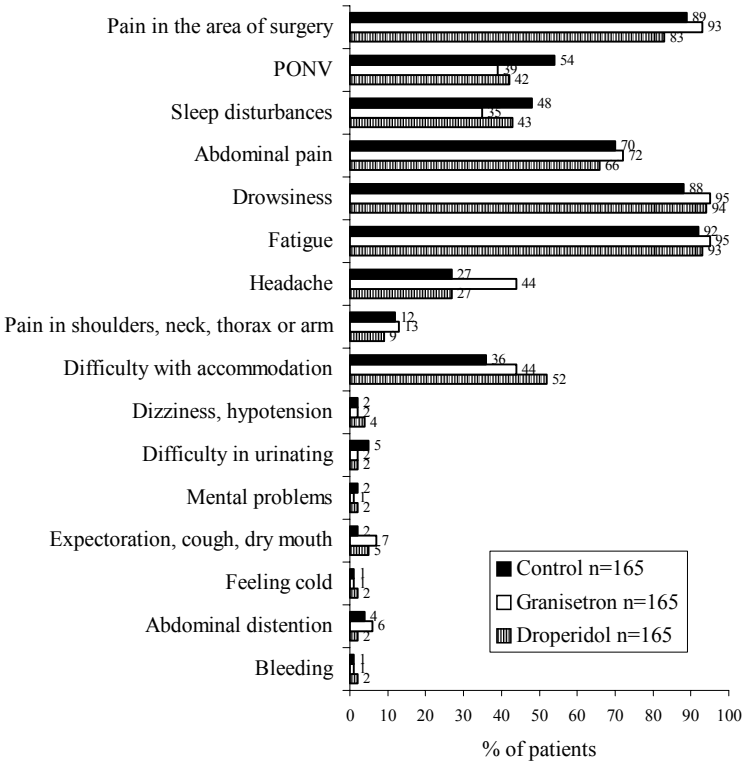
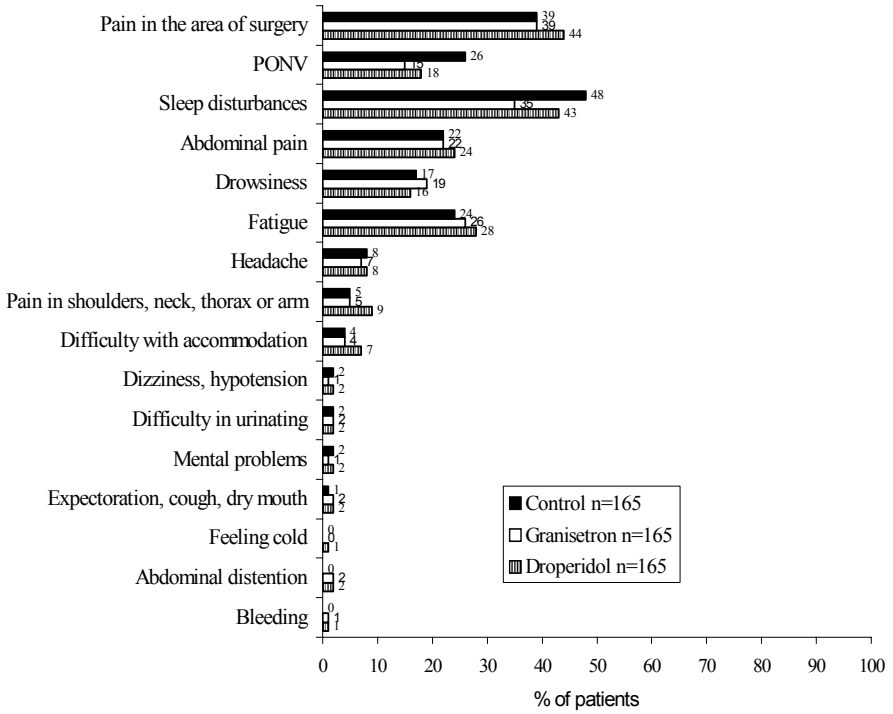


Figure 7. Accumulative incidence of moderate to very severe disturbing symptoms (0-24 h) (Study III)

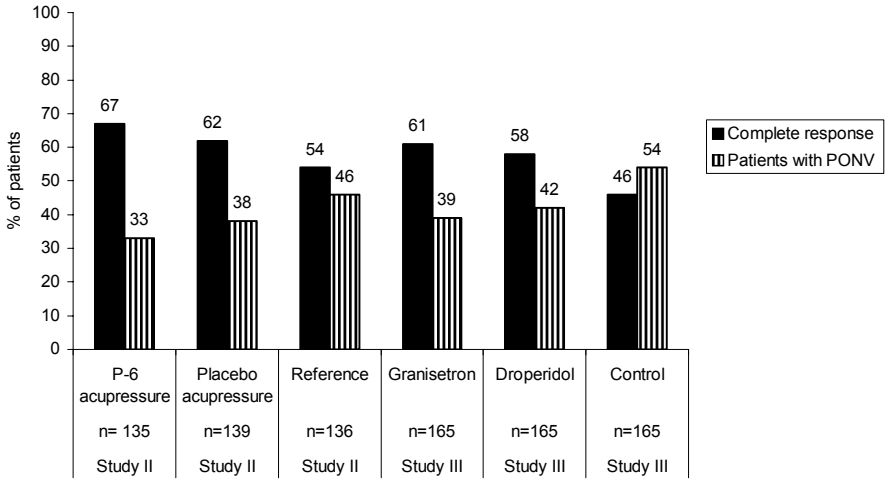


After prophylactic treatment with P6- and placebo acupressure, granisetron and droperidol

(Studies II and III)

Less PONV was seen after P6-acupressure (33%) than in the reference group (46%) (P = 0.019), the NNT was 7 [95% CI 4-68]. P6-acupressure (33%) did not differ significantly from pressure on a non-acupoint (38%) (P = 0.165) (Study II). The incidence of PONV was significantly lower in the granisetron (39%), NNT = 7 [95% CI 4-33] and droperidol (42%) NNT= 8 [95% CI 4-77] groups compared to the control group (54%) ($p < 0.05$) (Fig. 8) (Table 15). We have had an inconsistency in terms between Study II and III. We called the group observed reference group in study II but used the term control group in Study III. Both groups were observed and had no treatment.

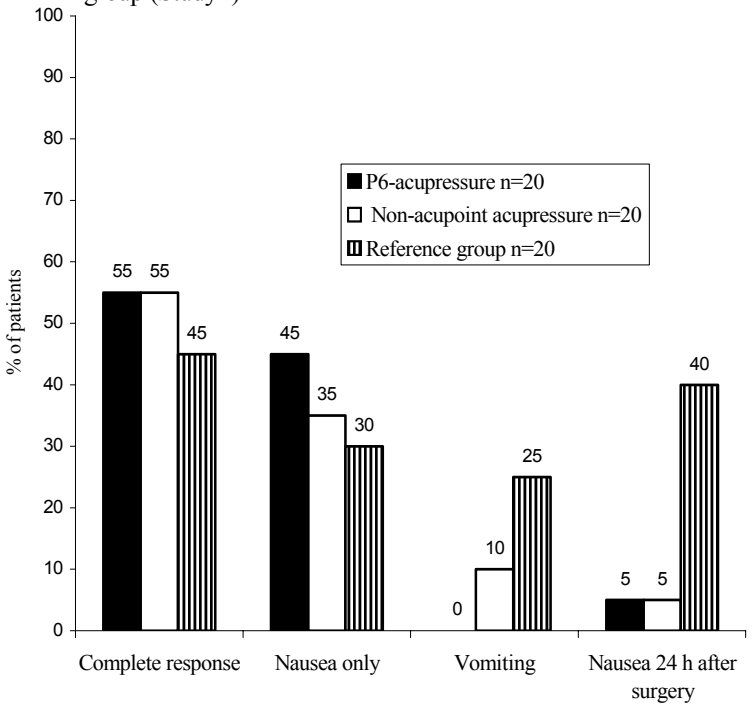
Figure 8. Effect of P-6 acupressure, placebo-acupressure (Study II), granisetron and droperidol (Study III) on the incidence of PONV



P6-acupressure and placebo acupressure

In a group with low incidence of PONV complete response (no nausea, no vomiting, no rescue medication) was similar between the groups, as was the incidence of nausea (only) (Study I). Less vomiting was seen after P6-acupressure (0%) than in the control group (25%) ($P < 0.05$). Regarding nausea 24 h after surgery, when the patient was at home, there was a significant difference between the incidence of nausea in the control group 40% as compared to the placebo group 5% ($P < 0.05$) and acupressure group 5% ($P < 0.05$) (Fig. 9).

Figure 9. Complete response, nausea only, vomiting and nausea after 24 h at home after P6-acupressure, non-acupoint stimulation and in the reference group (Study I)



Subgroup analysis after vaginal and laparoscopic surgery

(Study II)

Effects of acupressure were also evaluated for cases of laparoscopic and vaginal surgery separately. The incidences of PONV in patients undergoing laparoscopic surgery were 59, 57 and 55% in the reference, the placebo and the acupressure groups respectively. The differences between treatment groups are far from significant (p = 0.231) (Table 12). On the other hand, in patients having vaginal surgery the incidence of PONV was greater in the reference group 36 compared to 27 in the placebo group and to 20% in the acupressure group. The difference between 36% and 20% is significant (P = 0.017) the NNT is 6 [95% CI 3-18] (Table 13).

Table 12. Outcome in the three groups after laparoscopic surgery.
Figures are in number (%) of patients

	P6-acupressure n= 51 (100)	Placebo n= 53 (100)	Reference n= 61 (100)
Complete response	23 (45)	23 (43)	25 (41)
Nausea (only)	15 (29)	14 (26)	19 (31)
Vomiting (only)	0	0	2 (3)
Patients with PONV	28 (55)	30 (57)	36 (59)
Rescue medication	4 (8)	6 (11)	4 (7)

None of the differences are significant

Table 13. Outcome in the three groups, after vaginal surgery.
Figures are in number (%) of patients.

	P6-acupressure n= 84 (100)	Placebo n= 86 (100)	Reference n= 75 (100)
Complete response	67 (80)*	63 (73)	48 (64)*
Nausea (only)	17 (20)*	16 (19)	24 (32)*
Vomiting (only)	1 (1)	0	2 (3)
Patients with PONV	17 (20) *	23 (27)	27 (36) *
Rescue medication	2 (2)	3 (3)	1 (1)

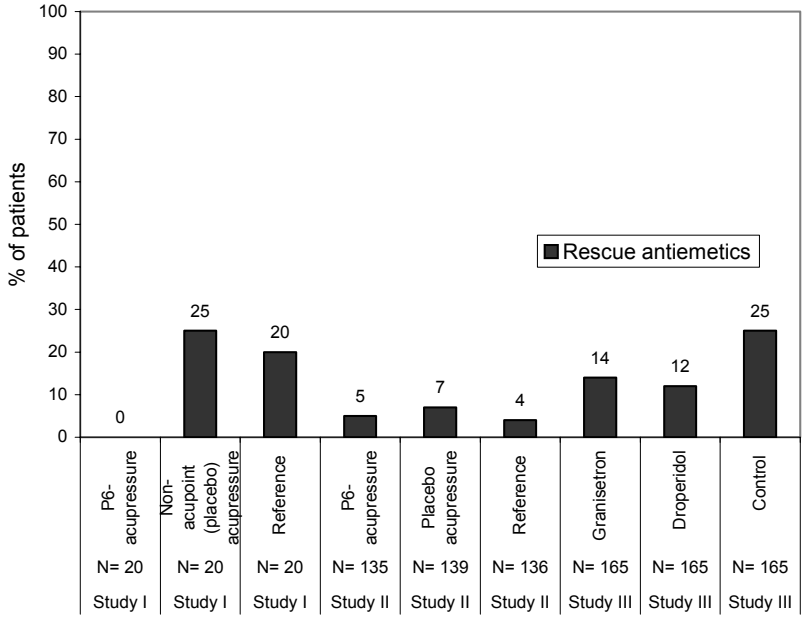
* $P < 0.05$ when P6-acupressure group is compared with reference group

Requirement of rescue antiemetics

(Studies I, II, III)

The need for rescue antiemetics was less after P6-acupressure (0%), vs placebo acupressure (25%) ($P < 0.05$) in Study I but no difference between the three groups regarding requirement of rescue antiemetics was seen in Study II. Requirement of rescue antiemetics was significantly lower in the granisetron (14%) and droperidol (12%) groups (Study III) compared to the control (25%) ($P < 0.05$) (Figure 10).

Figure 10. Requirement of rescue antiemetics in the different groups of Studies I, II, and III



Patient satisfaction

(Study II).

The patients were satisfied with the antiemetic treatment in all three groups (P6-acupressure, placebo-acupressure and reference group). The percentage of the patients who would like the same treatment again was 79 in the P6-acupressure group, 83 in the placebo-acupressure group, and 88% in the reference group.

Adverse events

Acupressure band

Number and type of adverse events reported are seen in (Table 14).

Table 14. A total of 72 adverse events with Sea-Bands® were reported in P6-acupressure and placebo acupressure groups (Studies I, II, IV).

Adverse events	Study I (n= 40)	Study II (n= 274)	Study IV (n= 40)
♦ The bands felt uncomfortable, produced a red indentation or caused itching	4	15	1
♦ Headache and dizziness	0	1	0
♦ Wrists hurt and the tightness of the band caused swelling or deep marks or blistering at the site of the button	4	45	2

Granisetron and droperidol

The NNT and NNH in the control group and after prophylaxis with granisetron and droperidol are seen in (Table 15). The most common symptoms reported after surgery (> 10% incidence) are nausea/ vomiting, incision pain, headache, abdominal pain, difficulties with accommodation, drowsiness and fatigue.

After prophylaxis with granisetron the number needed to harm (NNH) (0-24 h) for one extra patient to have headache was 6 [95% CI 4-15] and for difficulty with accomodation 12 [95% CI 5- ∞]. After prophylaxis with droperidol NNH were 50 [95% CI 9 - ∞] for headache and 6 [95% CI 4-18] for difficulty with accomodation (Table 15).

We could tell our patients that prophylactic antiemetic treatment is as likely to help you as to harm you. To calculate the likelihood of being helped versus harmed (LHH) the ratio of 1/NNT and 1/ NNH is used. LHH for droperidol (Table 16) and for granisetron (Table 17) are shown at next side.

Table 15. Number needed to treat (NNT) and number needed to harm (NNH) (0-24 h) after prophylactic antiemtic treatment with granisetron and droperidol in patients at high risk for PONV. Formula for computing NNT = 1/ARR, NNH = 1/ARD, RRR = (CER-EER) /CER, ARR = CER- EER

	Intervention	Control Event Rate (CER)	Experimental Event Rate (EER)	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	NNT Confidence Intervals (CI)
PONV	Granisetron Droperidol	54% 54%	39% 42%	27% 22%	15% 12%	7 (4-33) 8 (4-77)
Sleep disturbances	Granisetron Droperidol	48% 48%	35% 43%	27% 10%	13% 5%	8 (4-41) 20 (6- ∞)
				Relative risk increase (RRI)	Absolute risk increase (ARI)	NNH (CI)
Difficulty with accommodation	Granisetron Droperidol	36% 36%	44% 52%	22% 44%	8% 16%	12 (5- ∞) 6 (4-18)
Headache	Granisetron Droperidol	27% 27%	44% 25%	63% 7%	17% 2%	6 (4-15) 50 (9- ∞)
Drowsiness	Granisetron Droperidol	88% 88%	95% 94%	8% 7%	7% 6%	14 (8-97) 17 (8- ∞)
Abdominal pain	Granisetron Droperidol	70% 70%	72% 66%	3% 6%	2% 4%	50 (8- ∞) 25 (7- ∞)
Fatigue	Granisetron Droperidol	92% 92%	95 % 93%	3% 1%	3% 1%	33 (12- ∞) 100 (15- ∞)
Pain in the area of surgery	Granisetron Droperidol	84% 84%	93% 83%	11% 1%	9% 1%	11 (6-46) 100 11- ∞)
Pain in shoulders, neck, thorax, arm	Granisetron Droperidol	12% 12%	13% 9%	8% 25%	1% 3%	100 (12- ∞) 33 (10- ∞)

Table 16. When treated with prophylactic droperidol. LHH= (1/NNT) vs. (1/NNH) regarding PONV vs. other postoperative symptoms.

PONV/ Postoperative symptoms	1/NNT vs. 1/NNH	LHH
PONV/ sleeping disturbances	1/8 vs. 1/20	0.13 vs. 0.05
PONV/ difficulty with accommodation	1/8 vs. 1/6	0.13 vs. 0.17
PONV/ headache	1/8 vs 1/50	0.13 vs. 0.02
PONV/ drowsiness	1/8 vs. 1/17	0.13 vs. 0.06
PONV/ abdominal pain	1/8 vs. 1/25	0.13 vs. 0.04
PONV/ fatigue	1/8 vs. 1/100	0.13 vs. 0.01
PONV/ pain in the area of surgery	1/8 vs. 1/100	0.13 vs.0.01
PONV/ pain in shoulders, neck, thorax or arm	1/8 vs. 1/33	0.13 vs. 0.03

Table 17. When treated with prophylactic granisetron. LHH= (1/NNT) vs. (1/NNH) regarding PONV vs. the other postoperative symptom.

PONV/ Postoperative symptoms	1/NNT vs. 1/NNH	LHH
PONV/ sleeping disturbances	1/7 vs. 1/8	0.14 vs 0.13
PONV/ difficulty with accommodation	1/7 vs. 1/12	0.14 vs.0.08
PONV/ headache	1/7 vs. 1/6	0.14 vs. 0.17
PONV/ drowsiness	1/7 vs. 1/14	0.14 vs. 0.07
PONV/ abdominal pain	1/7 vs 1/50	0.14 vs. 0.02
PONV/ fatigue	1/7 vs. 1/33	0.14 vs. 0.03
PONV/ pain in the area of surgery	1/7 vs 1/ 11	0.14 vs. 0.09
PONV/ pain in shoulders, neck, thorax or arm	1/7 vs 1/100	0.14 vs. 0.01

The incidence of PONV was significantly lower in the granisetron and droperidol groups compared to the control ($p < 0.05$) (Table 18).

Table 18. Postoperative nausea and vomiting (0-24 h). Number of patients (%) (Study III).

	Droperidol (n=165)	Granisetron (n=165)	Control (n=165)
Complete response	95 (58) [1]	101 (61) [2]	76 (46) [1,2]
Nausea (only)	26 (16) [1]	28 (17) [2]	41 (25) [1,2]
Vomiting (only)	7 (4)	6 (4)	4 (2)
Vomiting with nausea	37 (22)	30 (18)	44 (27)
Patients with PONV	70 (42) [1]	64 (39) [2]	89 (54) [1,2]

[1] = P <0.05 when droperidol is compared to control group
[2] = P <0.05 when granisetron is compared to control group

The Questionnaire

(Study III)

The questionnaire revealed a wide range of symptoms and was judged by the patients to give us adequate information about their symptoms. It was easy to complete within a short period of time. All patients answered a question about the appropriateness of the questions at the end of the questionnaire. The questionnaire was described as appropriate and giving a correct picture of their experience by 98% of the patients. The test-retest correlation coefficient was between 0.77 and 0.95.

Correlation between the Apfel risk score for POV and the observed PONV and POV

The control groups in Studies II and III were used in order to obtain the real incidence of PONV and POV, (n= 301) in our clinical situation. The Apfel risk score for every patient had been calculated to be > 30%. Seventeen % (51/301) of patients in the control group vomited after operation and 44% (135/301) experienced both nausea and vomiting compared to calculated Apfel risk score, 57% for vomiting and 60% for nausea.

P6- and placebo acupressure and experimental motion sickness

(Study IV)

The mean time to moderate nausea differed between the three groups (P6-acupressure, placebo acupressure and reference) [$F(2.57) = 5.4649$, $P = 0.006$]. Further analysis indicated

that the women in the P6-acupressure group had a significantly longer time to nausea compared to the control group ($P < 0.005$). P6-acupressure = 352 (259 - 445), control = 151 (121- 181) and non-acupoint acupressure = 280 (161- 340), values given as mean (95% CI). Susceptibility to motion sickness had no effect on the mean time to nausea [$F(1.56) = 2.6789$, $P = 0.107$].

The number of cumulative symptoms experienced by the test persons after chair rotation stopped differed between the three groups ($P < 0.05$). The women in the P6-acupressure group had significantly fewer symptoms (compared to the control group, $P < 0.009$). The intensity of nausea declined with time in a similar fashion in all groups. There were no differences between the groups concerning MAP or pulse rate.

DISCUSSION

Postoperative symptoms

A high accumulative incidence of symptoms was found. The intensity was high, there were several symptoms per patient and some symptoms persisted for at least 24 hours. This has been reported before and is actually still the case despite improvements in anaesthetic agents, surgical techniques and care (Table 6). It seems that the patient's view of postoperative problems has not been in focus and used when developing care (Van Wijk et al 1990). Patients who listed more postoperative symptoms also report a lower functional level (Tong et al 1997). Incision pain was associated with the largest decrease in postoperative function, but headache, drowsiness, dizziness, and sore throat were also significant (Chung 1996, Marshall and Chung 1999). Some less frequent symptoms such as pain in the shoulders, neck, thorax or arm, difficulty in urinating, mental problems, expectorate, cough, and dry mouth have received little attention, although they may have a significant impact on a patient´s well-being (Marshall and Chung 1999).

Recent reports fail to show a lower incidence of postoperative pain than previous studies (Marks & Sacher 1973, Lynch et al 1997, Rawal et al 1997, Study III). About 30- 40% of discharged outpatients suffer from moderate to severe pain during the first 24-48 h (Rawal et al 1997). A predictive factor for severe postoperative pain is the length of anaesthesia (Chung et al 1997). Severe pain can be an important cause of nausea, and treatment of pain may relieve nausea, but the association remains unresolved, as only a few studies have shown a correlation (Andersen and Krohg 1976, Watcha and White 1992, Chia et al 2002). But the treatment of pain could influence PONV as morphine acts directly on the chemoreceptor trigger zone inducing nausea and vomiting, and have gastrointestinal effects (gastric relaxation, increased retrograde pressure activity in duodenum and vomiting) (De Ponti et al 1990). So pain must be treated while closely observing the side-effects of the drugs used. We used paracetamol as pain prophylaxis. Paracetamol has very few side-effects in clinical doses (Peduto et al 1998).

Ninty-two per cent of patients were bothered by fatigue 24 h after surgery in the control group (Study III) (Table 6). This is in accordance with other studies which identifies postoperative fatigue as the most important reason for delay in return to regular activity (Salmon and Hall 1997). Fatigue could be detected in patients as long as one to three months after a surgical procedure (Jakeways et al 1994). Postoperative fatigue is a direct consequence of the surgical stress response, the physiological and metabolic disturbance that is associated with major surgery, and impaired muscle function caused by immobilisation and impaired nutrition (Christensen 1993). It has been reported that fatigue correlates with anxiety and depression after surgery and that the patients who were most fatigued after surgery, where those who were most depressed preoperatively (Aarons 1996). The measurement of anxiety, depression and fatigue early in the postoperative period can predict the duration of convalescence (Rosenberg-Adamsen et al 1996). Anxiolytic and antidepressant drugs might be useful in the postoperative period to reduce fatigue (Salmon 1997) and their mood enhancing properties has been suggested to explain the positive effect of glucocorticoids in the postoperative period.

Drowsiness occurs with an incidence between 53 and 96% (Table 6, Fig 4) (Fahy et al 1969, Heneghan et al 1981, Study III). The mechanisms are unclear. Perioperative dehydration has been suggested since giving adequate hydration can reduce the incidence of

drowsiness for up to 24h postoperatively (Campell et al 1990, Yogendran et al 1993). We had a strict hydration routine, 10 ml/kg body weight.

Sleep disturbances could be one of the causes of fatigue (Rosenberg-Adamsen et al 1996) and has been found regardless of anaesthetic technique (Rosenberg et al 1995). Factors that may contribute are the surgical stress response (magnitude of trauma, hormones, cytokines, fever) (Friess et al 1994), environmental factors (noise, light), pain and opioids (Rosenberg et al 1995). The contribution of pain has been studied following ambulatory surgery. Twenty per cent of the patients had difficulty in sleeping due to severe pain while 30% woke up at night due to pain (Rawal et al 1997). Even when pain was well controlled postoperatively patients suffered profound sleep disturbances (Rosenberg et al 1995).

In Study I, the control event rate for PONV was 9/20 (45%), in Study II, 63/136 (46%) and in study III, 89/165 (54%). PONV was more common post-discharge (54%, 0-24 h) than in the recovery room (37%, 0-4 h) (Study III). This is in accordance with previous studies (Philip 1992). The aetiology of post-discharge PONV may not only include factors commonly associated with PONV but also motion sickness, premature ambulation, and pain medication (Carroll et al 1995). In our studies laparoscopic gynaecological surgery under general anaesthesia was associated with a high incidence of PONV, 59% (36/61) (Table 12, Study II). Similar incidences have been reported after laparoscopic gynaecological surgery (Jacobsson et al 1999). A panel trying to reach consensus on how to treat PONV could not reach full agreement about the association between type of surgery and PONV risk (Gan et al 2003).

Prophylactic treatment with droperidol or granisetron reduced the incidence of PONV after gynaecological surgery compared to the control group but did not decrease the total incidence of disturbing postoperative symptoms (Table 11, Study III). This is the surprising main result of Study III. So the reduction in PONV did not translate into greater benefit for the patient even though we studied a group at high risk for POV and it has been reported that to avoid PONV has high priority for the patient (Macario et al 1999). Similar results for other prophylactic PONV regimens have been described (Scuderi et al 1999, Fisher 1999). Is then the incidence of PONV an adequate surrogate end-point (Fisher 1994) that is an end-point possible to convert to a clinically meaningful outcome? Should we look at other outcomes such as stay in the recovery room, incidence of unplanned re-admission and patient satisfaction? The optimal strategy to prevent PONV or to treat established symptoms is far from obvious (Tramèr 2001 part II). Systematic reviews suggest that prophylaxis does not work very well, and that there is a finite risk of adverse drug reactions with most antiemetic interventions (Tramèr 2001 part II). Most anaesthetists agree that routine antiemetic prophylaxis for all surgical patients is not indicated (Scuderi et al 1999, Gan et al 2003), but also agree that some patients would benefit from prophylaxis rather than a strategy of waiting for symptoms to become established before treatment (Rose and Watcha 1999). Thus identification of patients who are at increased risk is imperative. Recommendations for PONV prophylaxis and treatment must consider the following factors: the patients risk for PONV, potential morbidity associated with PONV, including suture dehiscence (Col et al 1998), oesophageal rupture (Temes et al 1999), haematoma formation, and aspiration pneumonitis (Nanji 1992), potential adverse events associated with various antiemetics, efficacy of antiemetics and cost of antiemetic therapy (Gan et al 2003). Patients at low risk for PONV are unlikely to benefit from prophylaxis and should not be exposed to the potential side-effects of antiemetics (Gan et al 2003).

We used the Apfel risk score for POV (Apfel et al 1998) to predict those patients who would probably vomit postoperatively. The inclusion criterion for patients to Study III was a risk score >30%. It is easy to convert the Apfel score for POV (Apfel et al 1998) used in our patients to the simplified risk score for PONV (Apfel et al 1999) see Table 19. The simplified risk score for PONV included female sex, history of motion sickness or PONV, non-smoking status, and the use of postoperative opioids.

Table 19. Simplified risk score for PONV (Apfel 1999) for patients in Study III.

Number of factors = corresponding risk in % for PONV	Droperidol (n=165)	Granisetron (n=165)	Control (n=165)
1 = 20%	8	8	9
2 = 40%	61	45	42
3 = 60%	70	79	68
4 = 80%	26	33	46
Patients with 2 or more risk factors for PONV	157	157	156

The women in this study had on average 2.8 risk factors for PONV. Corresponding mean was 2.7 for the droperidol group, 2.8 for the granisetron group, and 2.9 for the control group. This is equal to approximately 40-60% risk for PONV. The patient´s risk can be estimated using risk scores but the prediction for an individual will only be correct in approximately 70% of patients (Apfel and Roewer 2003).

Drugs that prevent nausea and vomiting may have a different efficacy profile. Droperidol for instance prevents nausea better than vomiting (Henzi et al 2000), while 5-HT_3 receptor antagonists prevent vomiting better than nausea (Tramèr 2001 part I). In our study granisetron and droperidol had a similar effect in reducing “nausea only”, but there was no effect on “vomiting only” (Table 18, Study III). Moreover, the anti-nausea effect of droperidol was more profound during the early phase of recovery (0-6h) than during the later course of recovery. Droperidol seems to be effective for the prevention of early PONV but may not be equally effective in late post-discharge PONV (Gupta et al 2003).

We found that the the droperidol group had significantly less abdominal pain 30% (50/165) than in the granisetron group 45% (74/165) (0-4 h) after surgery. In the early postoperative period patients in the droperidol group reported less headache (4%) compared to patients in the granisetron group (15%) and the control group (12%). It has been reported that patients who are treated with droperidol, experience less headache postoperatively (Eberhart et al 1999, Henzi et al 2000) and droperidol has been used to treat headache (Miner et al 2001). Previous studies have suggested that droperidol has a synergistic analgesic effect with opioids (Isosu et al 1995). The mechanism is not clear, but droperidol acts at many sites such as dopamine, norepinephrine, serotonin and GABA receptors at the post-synaptic membrane. These receptors interact with each other and modify analgesic effect (Elkadi and Sharif 1998). Dopamine can inhibit the release of immunoreactive β-endorphin from the hypothalamus neurones (Vermes et al 1985). Interruption of dopaminergic transmission by blocking dopamine receptors with droperidol increased opioid peptide levels in the myenteric plexus. The biosynthesis of endogenous opioids is increased by droperidol (Vargas et al 1987).

Concerns regarding the side-effects associated with traditional antiemetics (Watcha and White 1992) and the large cost of newer drugs (Tang et al 1996) have increased interest in the use of non-pharmacologic techniques such as acupuncture (Dundee et al 1986), electroacupuncture

(Ho 1990), transcutaneous electrical nerve stimulation (TENS) (Fassoulaki et al 1993), acupoint stimulation (Yang et al 1993), and acupressure (Stein et al 1997, Alkaissi et al 1999, 2002). There is clear evidence that acupuncture is effective against postoperative nausea and vomiting (The NIH Consensus Development Panel on Acupuncture 1998). The mechanism of action is still unclear though basic research has demonstrated changes in release of opioids and other peptides in the central and peripheral nervous system and in neuroendocrine function (NIH consensus 1998). But still the practice of acupuncture is based on a model of energy balance (NIH consensus 1998).

Our preliminary study on patients having vaginal surgery suggested that placebo acupressure decreased nausea after 24 h but vomiting and rescue antiemetics could only be reduced by P6-acupressure (Study I). This was in patients that had vaginal surgery. When we looked at patients after similar surgery in Study II we found that NNT to prevent PONV with P6-acupressure (0-24 h) was about 6. A meta-analysis has showed that NNT with P6-acupressure to prevent early (6 h) PONV was about 5 (Lee and Done 1999). Our results after laparoscopy (Study II) are not in accordance with those reported by others after laparoscopic surgery (Harmon et al 1999). Sensitivity analyses may help to identify subgroups of patients who are most likely to profit from treatment (Tramèr 2001 part 1).

We noted that P6-acupressure seemed to be efficient in preventing PONV in patients undergoing day-case vaginal surgery. These patients have to walk on the way home and we could see that the incidence of PONV was higher post-discharge than in the recovery room. This led us to the hypothesis that it was through an effect on motion-induced sickness that P6-acupressure had its effect. When tested in an experimental situation we found an increased tolerance to motion-induced nausea in subjects with P6-acupressure and fewer symptoms post stimulation. Studies on experimental motion sickness (with a nauseogenic stimuli that is actually motion) and P6-acupressure are summarised in Table 20. Our study is the only one that could demonstrate an effect. The two negative studies have compared P6-acupressure to placebo stimulation and have not had a control group. We suggest that omitting the control group is one of the reasons for the negative result as there is a placebo effect with adequate placebo sensory stimulation and there was not enough power in these studies to demonstrate an effect. In our study we could demonstrate an effect compared to the control but not to the placebo group.

The design of studies has differed. Bruce used repeated exposure to rotation (Bruce et al 1990). It is well documented that repeated exposure to a particular nauseogenic motion stimulus eventually leads to a gradual reduction and eventual disappearance of the symptoms of motion sickness caused by that stimulation (Reason and Brand 1975**)**. Warwick-Evans used a short stimulation time and had no predefined nausea end-point (Warwick-Evans et al 1991). Several studies have used the optokinetic drum (Hu et al 1995, Stern et al 2001). These report mainly good results with P6-acupressure. What is surprising with these studies is that no effect of placebo acustimulation was seen which suggests a flaw in placebo design. What is more, the optokinetic drum does not produce actual motion and so does not produce a reproducible motion stimulus that corresponds to the motion stimuli usually encountered in real life

Tabel 20. Summary of studies (including present Study IV) of P6-acupressure´s effect on nausea caused by an experimental motion challenge. Only studies with experimental motion sickness caused by eccentric motion stimuli are included.

Variables	*Bruce et al 1990*	*Warwick-Evans et al 1991*	*The present study (Study IV)*
Age (years)	18-42.	18-25.	18-40.
Sex	Male.	Male.	Female.
Number per group	19.	18.	20.
Objective	♦ To assess the effectiveness of Sea-Bands® acupressure to increase time to nausea compared with placebo and hyoscine (0.6mg).	♦ To evaluate whether the procedure was equally effective for subjects with low or high susceptibility to motion sickness.	♦ Time to nausea induced by a laboratory motion challenge. ♦Whether previous history and severity of motion sickness matter. ♦ Effect on reported symptoms.
Fasting	Yes.	Not mentioned.	2 hours before motion challenge.
Withdrawal	None.	Not mentioned.	None.
Type of P6 stim.	Sea-Bands®.	Sea-Bands®.	Sea-Bands®.
Uni- or bilateral	Bilateral.	Bilateral.	Bilateral.
Start of stimulation	15 min before rotation.	5 minutes before rotation.	15 min before rotation.
Duration of rotation	Incipient vomiting or 31 min.	10 minutes.	Until moderate nausea, that is 3 (0-6 scale)
Previous history of motion sickness	Motion sickness Questionnaire (Reason and Brand 1975).	Two equal groups, high or low risk (Reason ad Brand 1975).	Yes, high and low susceptibility.
Nauseogenic stimulus	Chin- to- chest head flexion, blindfolded, and seated on a chair rotating eccentrically about a vertical axis in a darkened room.	Rotated in a chair about a vertical axis, 8 revolutions per minute, while tilting the head and trunk 45 degrees to the left or right once every 4 s.	Chin- to-chest- head flexion, blindfolded, and seated on a chair rotating eccentrically about a vertical axis, in a darkened room. 60°/s.
Randomised	Yes.	Yes.	Yes.
Double-blind	Not mentioned.	Yes.	Yes.
Design	3 groups, each subject four exposures with at least a week between. ♦ Hyoscine + placebo band. ♦ Placebo drug (vitamin C) + placebo band. ♦ Placebo drug + active band.	♦Placebo controlled experiment with two levels of each independent variable ♦ A matched pairs design with each subject being tested in just one condition.	3 groups, Each subject one experimental session. ♦ P6-acupressure. ♦ Non –acupoint acupressure. ♦ Control, no stimulation. ♦ Three equal groups according to high or low susceptibility to motion sickness.

Variables	*Bruce et al 1990*	*Warwick-Evans et al 1991*	*The presentstudy (study IV)*
Scale of nausea	Using scoring procedure developed by Graybiel et al (1968). Specified scoring code:1-5 stages: Stage 1 = no symptoms to 5 = severe nausea and likely to vomit if motion continues	Motion sickness was assessed using the scoring procedure developed by Graybiel et al (1968).	♦ A Lickert-type scale (0-6) was used. ♦Reporting any discomfort they felt during and after the rotation was stopped for 30 minutes.
Primary outcome	♦ Time to the different symptom stages.	♦ Graybiel scoring procedure. Signs and symptoms of motion sickness.	♦ Time to moderate nausea (3 or more on a Lickert-type scale 0-6) ♦ Number and types of symptoms reported by the woman.
Effect	♦ There was a significant increase in tolerance with hyoscine but not with the Sea-Bands® or placebo. The significant treatment effects were seen at stages 4 and 5.	♦ The highly susceptible subjects showed significantly more signs and symptoms of motion sickness than the low susceptibility subject.	♦ P6-acupressure increased tolerance to nausea compared with the control group. ♦ Fewer symptoms were reported in P6-acupressure compared with the control group. ♦There were no difference in high and low susceptibility groups.
Conclusion	♦ Sea-Bands® was not effective.	♦ Sea-Bands® was not effective.	♦ P6-acupressure increased tolerance to nauseogenic stimuli compared to control but not to placebo ($p < 0.05$) . ♦ The mean time in seconds 95% (CI), P6-acupressure = 352 (259- 445). Placebo = 280 (161-340). Control = 155 (121-181). ♦ P6-acupressure reduced the total number of symptoms reported after stimulation.

Methods

We used a three-group design to be able to estimate control event rate i.e. the incidence without intervention of PONV and disturbing postoperative symptoms in our daily practice. This is important when discussing the benefits of prophylactic treatment (Tramèr 2001, part II). The three-group design also gives us a real estimate of the placebo effect (Montogomry et al 1997). Study I was carried out in one hospital and Studies II and III in three hospitals (multicentre studies). The obvious reason for this is the need to collect a sufficient sample size.

The use of placebo treatment in research is controversial. It has been stated that placebo may be used for comparison only if there is no effective treatment with which the study drug can be compared (Lee and Done 1999, Vickers 1996). As there is no evidence that treatment of established PONV is less efficacious than prevention the use of placebo may be justified in our studies (Tramèr et al 1997). Informed consent and adequate rescue antiemetic treatment are of course necessary to ensure ethical legitimacy (Tramèr et al 1998). We used active stimulation (the Sea-Bands®) of a point that is not an accupoint. The Sea-Bands® were covered so that their position should not be obvious to care providers, but we cannot rule out the possibility that the stimulation at the non-acupoint chosen on the dorsal side of the forearm could have stimulated a meridian connected to the P6-acupoint. Blinding was used to eliminate bias (Day and Altman 2000).

Questionnaire

We had a high response rate (96%) and the questionnaire was deemed by the patients to give us adequate information about their symptoms. There was a high incidence and diversity of symptoms reported by the patients, indicating that the questionnaire was effective. Fahy et al (1969) and Philip (1992) observed an increase in both the number of patients responding positively to questions and the number of complaints reported by each patient. The extent and completeness of the response to a questionnaire are important for external validity (Wu et al 2002). Factors that contributed to a high response rate were surveillance early in the postoperative period rather than late and asking about specific complications rather than only those volunteered by the patients (Fahy et al 1969).

It has been suggested that patients who do not answer a questionnaire may differ from responders with regard to severity of symptoms (Sheikh and Mattingly 1981). Non-responders were few in this study, but of course there is no “safe level” of response rate (Sheikh and Mattingly 1981). The strategy used to obtain a high response rate was the use of a stamped, addressed envelope and in the absence of a reply a follow-up phone call one week after surgery (Baker 1985).

Recall bias could be a problem (Litwin and McGuigan 1999). In the present study assessment of postoperative symptoms was made close to the time of surgery, i.e. the evening of the day of surgery and the evening the day after surgery. A possible confounder is that the patients answered in the context of a clinical situation when patients are not so willing to report disturbing symptoms (Jones 1996). In this study, however, many disturbing symptoms were reported, which indicates that this possible confounder was not of major importance. The questionnaire ended with a question where patients were asked if they thought that their answers gave a correct picture of their symptoms and well-being. Ninety-eight per cent of the patients answered “yes”. An open question at the end gave the patients the chance to elaborate.

A questionnaire has some advantages as it can be given to large number of people simultaneously and can be sent by mail. Subjects are also more likely to feel that they can

remain anonymous and thus may be more willing to express controversial opinions. The questionnaire was pre-tested to test the clarity, instructions and completeness of the questions and usefulness in the clinical situation (Brink & Wood 2001). The subjects and technique used were close to those planned for in the main study. We have used both closed and open questions. More information could have been gained with open questions, but it has been described that some patients prefer closed questions (Cormack 1996). Closed questions were deliberately chosen because it was important that the questionnaire should be quick and easy to complete to encourage a high response rate (Cormack 1996).

Patient satisfaction depends on the agreement between what is expected and what occurs to the patient (La Monica 1986). The results of 20 studies offer some reassuring evidence that 80-100 % of patients were satisfied or very satisfied with their anaesthesia care (Fung and Cohen 1998). We used the Lickert response format to measure patient satisfaction in Studies I and II. All patients in the three groups were highly satisfied with the treatment of PONV. Unfortunately, it is unclear what these global ratings mean. Cross-sectional surveys using single-item questions and yes/no or Lickert response format (Avis et al 1995) have yielded uniformly high scores (> 80% satisfied or very satisfied). Psychological artifacts in the health-care environment (trust, relief, friendliness) threaten the validity of all satisfaction measures (Pascoe 1983). A valid and reliable patient satisfaction measurement requires a multi-item questionnaire composed of items representing valid determinants of patient satisfaction specific to anaesthesia care (Fung and Cohen 1998).

We analysed the material in two ways in Study III. First using the overall grading of how disturbing the symptoms were (that is Question 7, analysed with logistic regression analysis) and then, as is more common, in a dichotomous fashion “do we have a symptom or not”. The first way says something about how disturbing the symptom was. In our study there was a difference between treatments, but the difference was not uniform at different intensity levels, which meant that we could not state that one group fared better than another. This is obvious when focusing on patients having moderate to severe complaints. But if we analyse the material in a dichotomous way we actually find more symptoms in the treated groups. To analyse the result in a dichotomous fashion enables us to calculated NNT and NNH.

End point measured

A wide variety of endpoints have been used for PONV. In some studies the incidence of nausea and vomiting is reported separately, others include additional information about the severity of emesis. Nausea may occur without vomiting, and vice versa. When evaluating the symptoms, it is important to separate the two phenomena as vomiting is a relatively clear physiological end point, and nausea is not (Morrow 1984). To use the number of patients who remain completely free of nausea, retching and/or vomiting has been suggested (Morrow 1992). But is this endpoint on actually marker of a better outcome or not? There is no standard means of measuring postoperative nausea intensity, and lack of universal agreement about what degree of symptomatology constitutes clinically significant nausea which leads to lack of comparability between studies (Apfel et al 1998).

The definition of *complete response of PONV* (no nausea, no vomiting, no need for rescue medication) was constant throughout Studies I-III (Korttila 1992). It could be discussed whether or not a phenomenon or a symptom should be measured in a dichotomous or graded fashion. Nausea and vomiting is not an all or nothing event, e.g., a patient does not have to be completely free from PONV to benefit from antiemetic prophylaxis. If the individual patient has suffered from very severe PONV in the past, even a reduction in the severity of PONV can

be a success (Eberhart et al 2000 b). However, separating patients into those with and without PONV is the "least common denominator" that all antiemetic trials can be reduced to (Korttila 1992). Patient ratings of antiemetic efficacy are based on changes in self-reported nausea (Bonneterre et al 1991). Conversely, personnel assessment of antiemetic efficacy is based primarily upon reduction of number of vomiting episodes. An ideal scale should be able to deal with both objective signs and subjective symptoms.

In Study I the patients used a *VAS scale* (1-100 mm) to assess the intensity of nausea. Patients have often difficulties with accommodation and so also with focusing on the VAS scale after surgery and anaesthesia. The VAS has proved to be simple, reliable, and valid, as well as having ratio scale properties (Katz and Melzack 1999) and may also be used for nausea. The VAS requires the ability to transform a complex subjective experience to a visual-spatial display (Boogaerts et al 2000). Even in clinical daily practice, the PACU nurses often use an 11-point numeric scale instead of a VAS when assessing pain. Older patients have difficulties in understanding the VAS scale and there is a significant correlation between age and incorrect response to the VAS (Kremer et al 1981). The studies included in this dissertation are based on a rather young population. Morrow has described, a Lickert-type scale, which is called MANE (Morrow Assessment of Nausea and Emesis*)* (Morrow 1984) when assessing symptom such as nausea. This scale (0-6) was used in 1060 patients (Studies II, III, IV) and we use it in daily clinical practice on the PACU at our hospital. Symptom severity is rated on the scale (0-6) to answer the question "how would you describe your nausea at its worst" from 0= none, 1= very mild, 2= mild, 3= moderate, 4= severe, 5= very severe and, 6= intolerable. MANE has been clinically validated and a test-retest reliability coefficient has been determined (Morrow 1984). We find the scale easy for patients to understand and easy for the nurses to use.

When using rescue medication as an end-point it is important to have a precise indication for intervention (Korttila 1992). In our studies, if the patient reported nausea that was described as tolerable (up to 2 on the 7- point scale) no antiemetic was given. If nausea was described as disturbing (between 3-6 on the same scale) or if the patient vomited twice, she was given an antiemetic. Examples of indications for rescue medication used in other studies include: patient suffering from intractable vomiting (Ho et al 1996); patient feeling that nausea was intolerable in the absence of vomiting (Harmon et al 1999), if there were more than two emetic episodes (Frytak et al 1979); and if nausea persisted for 10 minutes or had at least two emetic episodes (Bonder and white 1991). There is no consensus about criteria for rescue treatment in antiemetic studies but the criteria used must be defined. A value of 4 on the VAS has been shown to be a threshold triggering anaesthesiologists or nurses to administer rescue medication (Boogaerts et al 2000).

An antiemetic drug from a different pharmacological group should be used as rescue treatment if prophylactic medication fails to prevent PONV (Scuderi et al 1999, Kovac 2000, Apfel and Roewer 2003). In the present studies dixyrazine was the first alternative for rescue medication. There were very few patients that were given a second dose of granisetron or droperidol (Study III). A total of 6 patients had the same drug once again. The side-effects of the rescue routine are most probably small. Doses required for rescue treatment of established PONV may be half or even a quarter of those required for prophylaxis. One advantage of rescue as apposed to prophylactic treatment is that much lower doses are needed, for example ondasteron where only 1 mg instead of 4 mg is required (Tramèr et al 1997). All antiemetics apart from dexamethasone (because of slow onset of action) may be used as rescue treatment. When PONV occurs more than 6 h after surgery, a repeated dose of 5-HT_3 antagonist or droperidol

may be considered (Gan et al 2002). The optimal dose and interval for re-administration of these two antiemetics remain unknown.

Pharmacological treatment of PONV

A systematic review suggested that PONV prophylaxis with mono-therapy does not work very well (Tramèr 2001, part 1). The multifactorial nature of PONV and its neuronal signal transduction suggests that for successful prophylaxis or treatment, more than one form of therapy may be needed (Royston and Cox 2003). Antiemetic drugs have several mechanisms of action, so it seems reasonable to combine drugs to obtain greater efficacy. The use of prophylaxis has been questioned as there is a finite risk for side effects with most antiemetic interventions, and that treatment is more cost-effective than prophylaxis (Tramèr 2001, part II).

Our aim was to investigate how commonly used established prophylactic antiemetic treatment affects the number and intensity of symptoms experienced by patients postoperatively. 5-HT_3 receptor antagonists have been advocated for the control of PONV. A common argument is the apparently lower incidence of side-effects compared to older anti-emetic drugs such as droperidol (Henzi et al 2000). Droperidol has been widely used and reported to be as effective as the 5-HT_3 receptor antagonists.

We gave 3 mg granisetron i.v. prior anaesthesia which with today´s knowledge, was a rather high dose. When we designed our study it was thought that the optimal dose of granisetron for profylaxis was 40 μg/kg and many studies used granisetron 3 mg (Fujii 1997 b, 1998 a, Mikawa et al 1995, Naguib et al 1996). A considerable proportion of trials of granisetron have been conducted at one centre (1997 b, 1998 a). It has been demonstrated that the dose-response curve for granisetron may be significantly altered if results from one dominating centre are excluded (Kranke et al 2001 b). When the results of Fuiji et al are compared with other centres they are seen to have an extremely low variability. Fujii has also showed almost all other antiemetic drugs including droperidol to be ineffective in comparison (Fujii 1997 a, 1997 c, 1998 a, 1998 b) and that granisetron was effective. We are concerned about these reports upon which we based our decision to use 3 mg. However the antiemetic effect of granisetron as PONV profylaxis is not dose-dependent in the dose range investigated (Kranke et al 2001 b). We doubt that the outcome of our Study III would have been different if we had used a smaller dose of granisetron as we actually gave the dose prior to anaesthesia and some of the side-effects should have had time to wear off during anaesthesia. It is now recommended that 5-HT_3 antagonists should be given shortly before the end of anaesthesia (Henzi et al 2000, Gan et al 2002), to enable the pharmacological effect to last longer into the postoperative period.

The antiemetic prophylaxis is most effective when given at the end of surgery (Sun et al 1997). We gave the prophylactic treatment (granisetron and droperidol) before the start of anaesthesia. We were guided by previous studies where prophylaxis antiemetics were given before the induction of anaesthesia (Nagib et al 1996, Wilson et al 1996).

P6-acupressure

Invasive sensory stimulation such as acupuncture and non-invasive sensory stimulation such as acupressure or acustimulation seem to be similar in efficacy (Dundee et al 1989). Acupressure with Sea-Bands® applies a constant pressure, which obviates the need for repeated stimulation (Barsoum et al 1990). Our study gives no insight to whether it is better to stimulate both or one forearm as we always used bilateral stimulation (Studies I, II, IV). Bilateral (Ho et al 1996, Stein et al 1997), dominant (Dundee and Milligan 1988 b) and right forearm stimulation have

been investigated (Harmon et al 1999) and effect of unilateral stimulation has been reported (Lee and Done 1999, Vickers 1996).

P6-acupuncture should be administered prior to induction of anaesthesia (Dundee and Milligan 1988 b). This is in agreement with an oncology study were P6-acupressure was effective as an antiemetic only when it was given prior to chemotherapy (Dundee and Milligan 1988 b). In the present study acupressure bands were applied before induction of anaesthesia. It has also been suggested that the patient has to be awake to benefit from P6-acupressure (Vickers 1996). When P6-acupressure was used to prevent PONV in a wake patient, many trials have shown a decrease in PONV (Dundee 1986, Barsoum et al 1990, Dundee and Ghaly 1991). P6-acupressure reduced intraoperative nausea during cesarean section under regional anaesthesia (Stein et al 1997). The antiemetic effect of P6-acupuncture has been shown to be dependent on an intact nervous system as this is blocked by local anaesthesia at the P6 point (Dundee and Ghaly 1991).

Placebo stimulation with acupressure, acupuncture and acustimulation has proven effective in studies on morning sickness during pregnancy (Bayreuther et al 1994) but placebo stimulation has consistently proved less effective than P6-stimulation (Dundee et al 1986, Bayreuther et al 1994). We do not know if duration of treatment matters. The duration of stimulation has varied widely between different studies and the longest stimulation time that we have encountered in the literature was 7 days (Barsuom 1990). Our patients in Studies I and II wore the bands continuously (if possible) for 24 hours. The incidence of adverse events when using Sea- Bands® is quite high (Table 14) and seems to depend on the size of the band. By manufacturing various band sizes some of these problems could be eliminated.

The cost-effectiveness of antiemetics

The cost-effectiveness of antiemetic therapy depends on the effectiveness and cost of the drug, frequency and severity of PONV, and whether the antiemetic is used as prophylactic or rescue medication (Hill et al 2000). Prophylactic antiemetic therapy was cost-effective for operations associated with high frequency of emesis, on the other hand treatment of established symptoms was more cost effective when the frequency of emesis was low (Watcha and Smith 1994). In Study III the cost of prophylactic granisteron per effectively treated patient was 100 US$ more than the cost of prophylactic droperidol treatment. Similar results have been reported previously and as far as prophylaxis is concerned one could argue that an equally effective but cheaper agent such as droperidol should be recommended (Tang et al 1996). Acupressure bands ”Sea-Bands®” are commercially available at a cost of 120 Swedish crowns (SKr) (US$ 12). Acupressure bands can be used repeatedly.

When discussing the cost of prophylaxis one must take into consideration the cost of events that occur on the PACU. In our study the total cost of rescue medication in the droperidol group was 621 SKr (US$ 62), in granisetron group 852 SKr (US$ 85), and in the control group 992 SKr (US$ 99) (Study III). The cost of prophylactic granisteron per effectively treated patient was SKr 1124 (US$ 112) and for droperidol SKr 84 (US$8). A delayed discharge of 24 minutes could add $15 to the cost of care per patient (Carroll et al 1994). Each episode of emesis delays the patient’s discharge from the recovery room by approximately 20 min (Carroll et al 1994) and the cost of treating vomiting was three times more than the cost of treating nausea (Carroll et al 1994). This reasoning regarding prophylaxis / treatment costs depends on whether or not reduction / increasing cost of care is converted into taking care of more patients or diminishing staff costs.

Motion sickness

The severity of nausea evoked by Coriolis stimulation is proportional to the effective value of the sensation caused by the Coriolis stimulus (Isu et al 1996). Visual information has also been well documented as a major factor in motion sickness (Lackner and Grabiel 1979). It is now fairly widely accepted that motion sickness is caused by conflicting inputs between the visual and vestibular systems, or between the two vestibular systems, and comparison of inputs with the individual´s expectations derived from previous experience (Eyeson –Annan et al 1996). Tachygastria is seen in patients with nausea and vomiting (Stern et al 1987) and usually occurs prior to feeling nausea (Hu et al 1989). Tachygastria is a reliable physiological marker of motion sickness. Postoperatively it is known that ambulation and wheeling the bed provokes nausea and vomiting.

To obtain stable experimental conditions for the motion sickness study (Study IV) the women were requested to refrain from eating or drinking two hours preceding the rotation challenge (Lindseth and Lindseth 1995). There has been controversy regarding the effect of a meal on motion sickness. Ingestion of a meal reduces drug-induced dysrhythmia of the stomach (Kim 1985) and produces an increase in afferent and efferent vagal traffic between the CNS and the gastrointestinal system (Miolan & Roman 1978) with an increase in gastric motility (Jones 1985). But still motion sickness developed sooner in the fed than in the fasted state (Uijtdehaage et al 1992) and a decrease in food intake reduces motion sickness (Kozarsky 1998).

Clinical implications

The measurement of patient perspective has become an important component of treatment evaluation in many areas of medicine. There is evidence that the patient's view of their recovery from a surgical procedure differs from their clinician's judgement. Thus there is a need to expand the outcome measures used. Using a postoperative symptom questionnaire, which was deemed adequate by the patients, gave a high response rate and showed a wide range of postoperative symptoms. Analysis shows where improvements can be made. Prevention of PONV is not unanimously accepted as a "true end-point". Assessment of overall well-being may be one way of obtaining a more holistic view of the impact of nausea, vomiting and antiemetic treatment on the situation of the individual patient. The objective in caring for patients is to achieve well-being and not just to reduce the incidence or severity of specific symptoms. We studied a group at high risk for PONV and could not demonstrate an improved outcome after PONV profylaxis. We suggest that timely treatment and not prophylaxis is the strategy of choice.

Nurses could inform the patient about the likelihood of being helped and the risk of being harmed (LHH). This could increase patient understanding and thereby reduce the risk for misunderstanding and unrealistic expectations. PONV is an important concern for patients undergoing surgery. By identifying patients at risk, a systematic evidence-based approach can be incorporated into the anaesthetic plan to prevent PONV. If the patient has not responded to prophylactic therapy, an antiemetic agent from a different class (i.e.different mechanism of action) should be administered. Pain control, adequate hydration, slow deep breathing, avoiding sudden movement, not forcing fluid intake, and maintaining blood pressure are important in the care of the patient.

P6-acupressure is an easy form of sensory stimulation and may also have higher patient acceptability than invasive P6-stimulation**.** P6-acupressure treatment is useful against post-discharge nausea and vomiting. P6-acupressure increases tolerance to motion-induced nausea.

What further studies are needed?

- How are postoperative symptoms influenced by prophylactic acupressure?
- What is the optimal timing of acustimulation (i.e. pre-vs. postoperative) and is bilateral more effective than unilateral stimulation?
- What do patients regard as being good postoperative care?
- What is the effect of combining pharmacological and non-pharmacological techniques in patients at high risk for PONV?

CONCLUSION

♦ A high incidence and severity of postoperative symptoms was found after gynaecological surgery. Almost half of the patients had two or more symptoms. Laparoscopic gynaecological surgery had a surprisingly high incidence and diversity of symptoms. Multimodal improvements in perioperative care are called for (Study III).

♦ The intensity of symptoms or the total number of disturbing symptoms did not decrease after prophylactic antiemetic treatment in a group of patients at high risk for PONV undergoing gynaecological surgery, but the profile of disturbing symptoms changed. The relevance of postoperative symptoms in terms of patients´ well- being needs to be addressed (Study III).

♦ The questionnaire, which was deemed adequate by the patients, gave a high response rate and showed a wide range of postoperative symptoms (Study III).

♦ The efficacy of prophylactic antiemetics could be questioned as patients reported disturbing symptoms to a similar degree in all groups. The patients who were given PONV prophylaxis experienced significantly more symptoms in total than patients who were not treated. It seems reasonable to state that the use of prophylactic antiemetic treatment in the present study was less cost-effective than timely treatment of symptoms and that droperidol is more efficient than granisetron (Study III).

♦ Acupressure is a non-invasive, simple method that can be used with good results in patients having vaginal surgery. It is acceptable to patients and is economical if the stimulation bands are reused (Studies I, II).

♦ P6-acupressure increased tolerance to experimental nauseogenic stimuli and reduced the total number of symptoms reported after stimulation compared to a control group in females with a history of motion sickness (Study IV).

♦ The P6-acupressure bands may be an alternative to drug treatment of postoperative nausea and vomiting and for nausea induced by motion sickness (Studies I, II, IV).

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APPENDIX 1

The Swedish Postoperative symptoms Questionnaire

OBEHAG/SMÄRTA
Att besvaras operationsdagen
Vi vill få reda på hur ont Du haft idag efter operationen, dvs hur stor operationssmärta Du känt. Vi vill också få reda på hur stora besvär Du känt till följd av illamående, huvudvärk och magvärk, m m. Besvara de två första sidorna (sid. 1 och 2) i detta formulär på operationsdagens kväll, helst någon gång mellan klockan 20 och 21. De flesta av frågorna kan Du besvara genom att sätta kryss i rutor.

Här kommer först några frågor om hur Du känner Dig just nu, när Du fyller i formuläret. (Sätt kryss för det svar Du tycker stämmer bäst.)

	Nej	Ja, lite	Ja
1) Om operationssmärta:			
Har Du fortfarande ont efter operationen?	☐	☐	☐
2) Om besvär:			
Är Du illamående?	☐	☐	☐
Har Du kväljningar?	☐	☐	☐
Har Du huvudvärk?	☐	☐	☐
Har Du magvärk?	☐	☐	☐
Är Du trött?	☐	☐	☐
Är Du dåsig?	☐	☐	☐
Har Du dimsyn?	☐	☐	☐

Känner Du av andra besvär? I så fall vilka
……

3) Hur ont hade Du idag efter operationen när Du kände av operationssmärtan som mest? (Sätt kryss för det svar Du tycker stämmer bäst.)

Ingen smärta ☐	Obetydlig smärta ☐	Mild smärta ☐	Måttlig smärta ☐
Rätt svår smärta ☐	Svår smärta ☐	Mycket svår smärta ☐	

4) Hur stora besvär kände Du idag efter operationen när besvären var som störst? Tänk inte på smärtan efter operationen, utan på hur obehagliga besvären var när de var som värst.

Inga besvär ☐	Obetydliga besvär ☐	Milda besvär ☐	Måttliga besvär ☐
Rätt svåra besvär ☐	Svåra besvär ☐	Mycket svåra besvär ☐	

5) Vad har varit särskilt besvärande? (Sätt kryss i en eller flera rutor.)

Illamående/kräkning ☐ Huvudvärk ☐ Magvärk ☐ Dimsyn ☐
Dåsighet ☐ Andra besvär, nämligen …….

6) Beskriv hur ont Du har haft idag efter operationen. Tänk då inte på hur det var när det var som värst, utan försök ge en sammanfattande beskrivning av hur Du upplevt smärtan efter operationen idag.

Ingen smärta ☐ Obetydlig smärta ☐ Mild smärta ☐ Måttlig smärta ☐
Rätt svår smärta ☐ Svår smärta ☐ Mycket svår smärta ☐

7) Försök beskriva hur mycket besvär Du haft idag efter operationen. Tänk då inte på smärtan, utan försök ge en sammanfattande beskrivning av de besvär Du haft.

Inga besvär ☐ Obetydliga besvär ☐ Milda besvär ☐ Måttliga besvär ☐
Rätt svåra besvär ☐ Svåra besvär ☐ Mycket svåra besvär ☐

8) Vilka besvär tycker Du har varit särskilt obehagliga när Du tänker sammanfattande på hela dagen efter operationen? (Sätt kryss i en eller flera rutor.)

Illamående/kräkning ☐ Huvudvärk ☐ Magvärk ☐ Dimsyn ☐
Dåsighet ☐ Andra besvär, nämligen …….

9) Har Du kräkts idag efter operationen?

Nej ☐ Ja, en gång ☐ Ja, flera gånger ☐

Hur mycket är klockan när Du fyllt i dessa sidor? …….

Den första dagen efter operationen -samma frågor som de ovan nämnda men med början:
Hur sov Du natten efter operationen?

Bra ☐ varken bra eller dåligt ☐ Dåligt ☐

Frågeformuläret avslutas med följande fråga:
Tror Du att vi kommer att få en någorlunda riktig uppfattning om hur Du haft det med smärta och obehag utifrån Dina svar på detta formulär?

Ja ☐ nej ☐
Om svaret är nej är vi tacksamma för en kommentar om hur Du tror att det besvarade formuläret ger oss en missupptattning om hur Du verkligen känt det. ……