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Disturbing post-operative symptoms are not reduced by prophylactic antiemetic treatment in patients at high risk of post-operative nausea and vomiting

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Background: To give prophylactics or timely treatment for post-operative nausea and vomiting (PONV) is the question. We compared the intensity and number of disturbing post-operative symptoms (i.e. pain, PONV, headache, fatigue, etc.) after prophylactic antiemetic treatment in a group of patients with >30% risk for post-operative vomiting.

Methods: Four hundred and ninety-five patients, from three hospitals, planned for gynaecological surgery were randomized double blind. They were given granisetron 3 mg, droperidol 1.25 mg or no prophylactic antiemetic. Post-operative symptoms were followed for 24 h using a questionnaire. Symptoms were analyzed both according to their intensity and in a dichotomous fashion.

Results: The intensity of different symptoms differed depending on whether droperidol, granisetron or no antiemetic had been given ($P = 0.005$) but the overall incidence of moderate to very severe symptoms was similar in all groups. No group fared better in general. The total number of symptoms was higher in the groups given prophylactic treatment ($P < 0.05$). The relative risk reduction for PONV with granisetron or droperidol prophylaxis was 27% [95% confidence interval (CI) 8–43] and 22% (2–38), respectively. The NNT (number needed to treat) for granisetron (0–24 h) was 7 and for droperidol 8. The NNH (number needed to harm) (0–24 h) for headache and visual disturbances was 6 and 13 (NS) for granisteron and, 50 (NS) and 6 for droperidol.

Conclusion: The intensity of symptoms or the total number of disturbing symptoms did not decrease after prophylactic antiemetic treatment in a group of patients, but the profile of disturbing symptoms changed. The relevance of post-operative symptoms in terms of patients' well-being needs to be addressed.

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Key words: antiemetic prophylaxis; droperidol; granisetron; headache; post-operative fatigue; post-operative nausea and vomiting.

The incidence of post-operative nausea and vomiting (PONV) varies from 24% to 75% in women undergoing gynaecological surgery (1). The optimal strategy for the prevention and management of PONV remains disputed (2, 3). The use of prophylactic antiemetic treatment has been suggested to improve patients' satisfaction (4). Nevertheless, it has remained unclear whether this is reflected in improvement in more objective measures of outcome such as overall patient satisfaction with their surgery experience, unanticipated admission, and the time required in returning to normal daily activity (4). Meta-analysis has shown that the efficacy of prophylactic antiemetic strategies is limited (5). Some studies have even suggested that antiemetic prophylaxis offers no advantage over timely symptomatic treatment (2–4). Thus, prophylactic antimetics appear justified only in patients at increased risk of PONV (6–8). Risk scores have provided an objective risk assessment for PONV (9–12). Several studies have shown that the risk assessment derived from such scores is robust enough to be valid in other hospitals and under different conditions (13, 14).

In a study of all post-operative symptoms, incisional pain, headache, drowsiness, dizziness and nausea/vomiting were most frequently reported (15). To improve post-operative outcome and provide patients with the best possible care, the patient's own assessment of their recovery (16) is required. Patients are best served by making choices based on evidence of drug effectiveness, side-effect profile, patient preference, and an associated reduction in total cost (6).

Our aim was to investigate how prophylactic antiemetic treatment, with two different well-studied

and effective antiemetics, affects disturbing *post-operative symptoms* in a group of women at high risk of PONV.

Materials and methods

The study was approved by the Ethics Committee at the Faculty of Health Sciences, University of Linköping.

Participants

Women at high risk of PONV, scheduled for elective gynaecological surgery under general anaesthesia from May 2000 to January 2001, were recruited to the study. Inclusion criteria were: (i) women undergoing gynaecological surgery, such as abortion, dilatation & curettage, conization, hysterectomy, prolapse or laparoscopic surgery; and (ii) with a risk of >30% for post-operative vomiting (PV) according to a score based on gender, age, smoking, history of motion sickness or PONV and length of anaesthesia (10). Exclusion criteria were women who: (i) had experienced nausea and vomiting during the last 24 h before surgery; (ii) had taken antiemetics within 24 h before surgery; or (iii) were breast-feeding. For demographic details see Table 1.

Objective

To assess patients' overall rating of intensity, incidence, and number of disturbing post-operative symptoms after prophylactic antiemetic treatment [Granisetron (Kytril®, Smithkline Beecham Pharma, Solna, Sweden) and Droperidol (Dridol®, Janssen-Cilag AB, Sollentuna, Sweden)] compared with a control group (control event) which did not have a prophylactic treatment but received timely treatment for PONV. No placebo group was used.

Planned interventions, their timing, and measurements

Design

This was a multicentre, prospective, consecutive, double blind and controlled clinical trial.

Randomization

After agreeing to participate in the study, the patients were randomised according to a randomisation list, generated by the pharmacy. Block randomization was used for nine patients in each group. Twelve patients were lost to follow-up. These were replaced by randomization with sealed envelopes.

Prophylactic antiemetic treatment

Group 1 received droperidol 1.25 mg, group 2 received granisetron 3 mg, and group 3 was a control event group. The drugs were administered intravenously over 2–5 min immediately before induction of anaesthesia.

Blinding

All study drugs were diluted by a pharmacist to a fixed volume of 3 ml and marked with a coded label. The two groups treated with antiemetic were blinded to all involved in administration and anaesthesia. The control group was not blinded to the anaesthetist but to all other personnel. During analysis the treatment groups were concealed and only the labels provided by the pharmacy identified which group the patient belonged to. When all material had been registered in the database, the statistical analysis was performed and the result section written before the pharmacy was contacted to break the code. Thereafter the names of the drugs were inserted in the text.

Anesthesia

Paracetamol 1 g and diazepam 5 mg were given preoperatively. All patients were hydrated with 10 ml/kg of a balanced solution of glucose 2.5%. Anaesthesia was induced with propofol 2 mg/kg bodyweight, $n = 413/495$, or thiopentone 3–5 mg/kg bodyweight, $n = 82/495$. Alfentanil 0.5 mg, $n = 218/495$, or fentanyl 0.2 mg, $n = 271/495$, was used for intra-operative analgesia. Rocuronium ($n = 245/495$) or suxamethonium (32/495) was used to facilitate tracheal intubation. For maintenance of anaesthesia, 66% nitrous oxide in oxygen and isoflurane ($n = 2/495$), desflurane ($n = 13/495$) or sevoflurane ($n = 269/495$) were used. Intravenous glycopyrrolate 0.5 mg and neostigmine 2.5 mg ($n = 243/495$) were used for reversal of muscle relaxation. For more details on medication in the different groups see Table 1.

Risk score for post-operative vomiting (PV)

We used a table of risk scores derived from Apfel (10) with the individual risk factors. The risk score is based on gender, age, non-smoking, history of motion sickness or PONV and length of anaesthesia.

Assessment of questionnaire

None of the available assessment forms were sufficient for the purposes of our study, so we developed a specific assessment form for the study (Appendix 1). The questionnaire was given to 10 people, 2 doctors, 3 anesthetic nurses, 4 PACU nurses, and 1 statistician,

Table 1

Demographic data.

	Droperidol $n=165$	Granisetron $n=165$	Control $n=165$
Age (years)	42 (14)	41 (14)	46 (15)
Body mass index = weight/(height^2)	24 (4)	23 (4)	25 (5)
Risk factors			
History of motion sickness (%)	43	43	42
History of previous PONV (%)	41	42	43
Smoker (%)	27	22	19
Apfel risk score %	45 (11)	43 (11)	43 (10)
Anaesthesia			
Thiopentone (%)	15	16	18
Propofol (%)	84	85	82
Fentanyl (%)	58	52	54
Alfentanil (%)	41	46	46
Intubation (%)	59	52	57
Use of reversal (%)	48	46	45
Operation in min. Median (range)	30 (5–270)	20 (5–240)	25 (6–270)
Anaesthesia in min. Median (range)	45 (10–285)	35 (12–270)	40 (15–330)
Surgical procedure			
Abdominal	32	24	30
Laparoscopy	53	43	37
Vaginal	80	98	98
Post-operatively (0–24)			
Antiemetic treatment (%)	18	19	31
Morphine in mg.	3 (5)	4 (5)	4 (6)
Morphine (%)	41	45	44
Time to discharge in min. Median (range)	120 (45–1320)	120 (20–1500)	120 (30–420)

Details on anaesthesia, and post-operative care. Numbers are given as mean (SD) unless otherwise stated.

who were asked to judge whether or not the questions were appropriate and reasonable. After some changes the questionnaire was considered valid. This questionnaire was then tested in a pilot study including 43 gynaecological surgery patients. Reliability was investigated with a test–retest in a further 18 patients. The test–retest correlation coefficient was between 0.77 and 0.95. The questionnaire was described as appropriate and gave a correct picture of their experience by 98% of the patients.

Description of questionnaire

The questionnaire (Appendix 1) 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. 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). We did not ask directly about patients' satisfaction, as this is a very complex psychological construct in health care. The simple ratings of patients' satisfaction used in most anaesthesia surveys are inadequate.

Nausea and vomiting

Nausea was defined as a subjective unpleasant sensation with awareness of urge to vomit. Vomiting was defined as a forceful expulsion of gastric content. Retching was defined as a spasmodic contraction of the abdominal wall without forceful expulsion of gastric content. Retching was classified together with vomiting in our study (18). Nausea was estimated using a 7-point scale of Lickert-type in which 0 = no nausea, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe and, 6 = worst possible nausea. If patients scored 1 or more at any time they were classified as having nausea. If at any time they scored

3 or more they were classified as having moderate to very severe nausea. The nurses recorded the frequency of vomiting while the patient was still in hospital. At home the patient noted this. The patients were asked to assess their degree of nausea after arrival at the post-operative care unit (PACU) and every hour until discharge from the PACU. When leaving the PACU all patients received a questionnaire where common symptoms reported after surgery were asked for, ending with some open questions. Nausea/vomiting were recorded at 20.00 hours on the day of surgery and at 20.00 hours on the first day after surgery.

Pain and analgesia
The patient assessed pain on a 7-point Lickert-type scale. Paracetamol 1 g four times daily was given to all patients. If further analgesia was required morphine hydrochloride was titrated in doses of 2 mg intravenously. Day cases were asked to continue with paracetamol at home.

Assessment of other symptoms
Please see description of questionnaire above.

Procedure
A letter about the study was sent to the patient before admission. Patients were also informed verbally on the day of surgery and consent was obtained. A risk score for PV was established after the patient's history and examination was complete. If the risk for vomiting according to Apfel (10) was >30% 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) for prophylactic antiemetic treatment or no treatment. An anaesthetic nurse who was not involved in the assessment of treatment effect administered the drug intravenously immediately before induction of anaesthesia. The 12 patients that were lost to follow-up were replaced by others (see randomization). The questionnaire was later returned by mail to the hospital.

Indications for antiemetic treatment and rescue medication
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 intolerable (between 3 and 6 on the same scale) or the patient vomited twice, she was given dixyrazine 5 mg intravenously. If PONV continued for more than 30 min droperidol 1.25 mg was used, and the next option was granisetron 1 mg. Eight patients in the control group wanted to have prophylactic treatment on the post-operative ward. These patients got antiemetics though they did not qualify according to our treatment criteria.

Cost of prophylaxis
The cost per patient of granisetron for a 3 mg ampoule (one ampoule is used for each patient) together with the cost of a syringe and needle is 161 SKr (US$ 16). The cost per patient of droperidol is 11 SKr (US$ 1.1). The difference per patient between the two treatments is 150 SKr (US$ 15).

Cost of rescue medication
The cost per patient for one treatment of dixyrazine is 8 SKr (US$ 0.80). The cost per patient of granisetron for a 1 mg ampoule is 98 SKr (US$ 09.8).

Statistics
Values are given as mean ± SD, median and range, or number. Symptoms were analyzed 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, that is there a symptom, yes or no? A logistic ordinal regression analysis was used to describe differences in intensity profiles for post-operative symptoms based on question 7 for the three groups. Number of symptoms was counted. The incidence of PONV and other specified symptoms was analyzed with Fisher's exact test. A *P*-value below 0.05 was regarded as significant.

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 of PV to draw meaningful conclusions.

The number needed to treat (NNT) and number needed to harm (NNH) was used to compare the relative efficacy of a treatment (14, 19). The NNT identifies the number of patients that have to be treated to prevent one adverse event (4). The number needed to harm (NNH) identifies the number of patients that have to be treated to lead to one additional patient being harmed (19).

Results

Inclusion and exclusion numbers
Four hundred and ninety-five women (ASA I–III) were included in the primary data analysis. Twelve

out of the 495 patients were lost to follow-up. Another 12 patients were added at the end of the study. Response rate was 98%.

Demographics

Demographics are presented in Table 1. The groups were similar regarding age, risk for PONV, anaesthetic technique, and type of surgery.

Postoperative nausea and vomiting

The incidence of PONV was significantly lower in the granisetron and droperidol groups compared with the control ($P < 0.05$) (Table 2). The number needed to treat (NNT) (0–24 h) to prevent one patient from having PONV was 7 with granisetron and 8 with droperidol (Table 3). After prophylaxis with granisetron the number needed to harm (NNH) (0–24 h) for one extra patient to have a headache was 6 and for visual disturbances 12 (NS). After prophylaxis with droperidol the corresponding numbers were 50 (NS) and 6 (Table 3).

Intensity of all post-operative symptoms

The intensity of different symptoms differed depending on whether droperidol, granisetron or no prophylaxis was given, $P = 0.005$. But the difference between the groups differed at different intensity levels and it is not possible to describe any of the groups as faring better (Table 4). Accumulative incidences of moderate to very severe (three or more on scale 0–6) disturbing symptoms experienced by patients are seen in Fig. 1. 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.

Symptoms reported

There was a high accumulative incidence of symptoms reported (Fig. 2). In the figure only symptoms with an incidence more than 10% is given. Total number of symptoms reported was lower in the control group ($P < 0.05$) than in the two treatments groups (Table 5). The number of moderate to very severe symptoms was similar (Table 5). Symptoms reported but not shown in Fig. 2 were in percent (%) in the three groups (droperidol, granisetron respective control group): dizziness and hypotension (4, 2, 2), difficulty in urinating (2, 2, 5), mental problems (2, 1, 2), expectorate, cough, dry mouth (5, 7, 2), feeling cold (2, 1, 1), abdominal distension (2, 6, 4), and bleeding (2, 1, 1).

Table 2

Post-operative nausea and vomiting (0–24 h).

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

Number of patients (percent).
*$P < 0.05$ when droperidol is compared with the control group.
†$P < 0.05$ when granisetron is compared with the control group.

Costs

The cost of prophylactic granisteron per effectively treated patient was SKr 1124 (US$ 112) and for droperidol SKr 84 (US $8). The average cost of rescue medication per patient was SKr 27 (US$ 2.7) for the granisetron group, SKr 20 (US$ 2) for the droperidol group and SKr 19 (US$ 1.9) for the control group.

Discussion

Prophylactic treatment with droperidol or granisetron reduced the incidence of PONV after gynaecological surgery compared with the control group but did not decrease the total incidence of disturbing post-operative symptoms. Thus, the objectively measured reduction in PONV was not translated into greater benefits for the patient even though we studied a group at high risk of PV. Similar results for other prophylactic PONV regimens have been described (4). Some disturbing symptoms such as nausea and vomiting decrease, but others such as headache and difficulty with accommodation increase significantly. As the intensity of disturbing symptoms varied in an inconsistent way it is not possible to describe any of the groups as faring better. Thus, instead of patients benefiting from prophylaxis, actual benefit is limited. The relative risk reduction (RRR) for PONV with granisetron or droperidol prophylaxis is 27% and 22%, respectively. The relative risk increase for headache is 63% after granisetron and 44% for difficulty with accommodation after droperidol. This has been described before (4, 5).

To measure PONV alone could be regarded as a surrogate end-point of patient satisfaction (2). The question is 'Which symptom is the worst' or 'What is most important to you, immediate recovery or to avoid pain and/or PONV' would be more adequate (20). It is important to incorporate patients' preferences into decisions about care (19, 20). The key information required for this is 'likelihood of being helped' vs. 'likelihood of being harmed (LHH). To obtain this

Table 3

Number needed to treat (NNT) and number needed to harm (NNH) (0–24 h) after prophylactic antiemetic treatment with granisetron and droperidol in patients at high risk of PONV and after gynaecological surgery.

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

Formula for computing NNT = 1/ARR, NNH = 1/ARI, RRR = (CER–EER)/CER, ARR = CER–EER.

information you need information about the number needed to treat (NNT) and number needed to harm (NNH) (19). Then LHH is (1/NNT) vs. (1/NNH). LHH may be presented to the patient who then can decide whether it is favourable enough to offset the side-effects and inconvenience of taking an antiemetic drug.

The rationale for giving prophylaxis could be as follows: if an antiemetic is given to a patient that will actually suffer from PONV, you have saved the patient an unpleasant experience. But then, can you be sure that this patient would have suffered from PONV? If not, then it is possible that you have given medication without effect and with extra cost. Furthermore it is possible that the patient will experience side-effects from the medication.

To increase the likelihood of choosing the right patient, a risk score of PONV could be used to identify patients who may benefit from prophylactic antiemetic treatment. Various risk scores for PV and PONV have been devised (9–11, 21) and prophylactic antimetic treatment appears justified in patients at increased risk of PONV (6, 7). We have used Apfel's risk score for PV (10). This score depends on the fact that the incidences of post-operative vomiting (PV) after inhalational anaesthesia are mainly related to patient-specific characteristics such as female gender, being a non-smoker, having a history of

Table 4

Intensity of disturbing symptoms after gynaecological surgery.

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

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

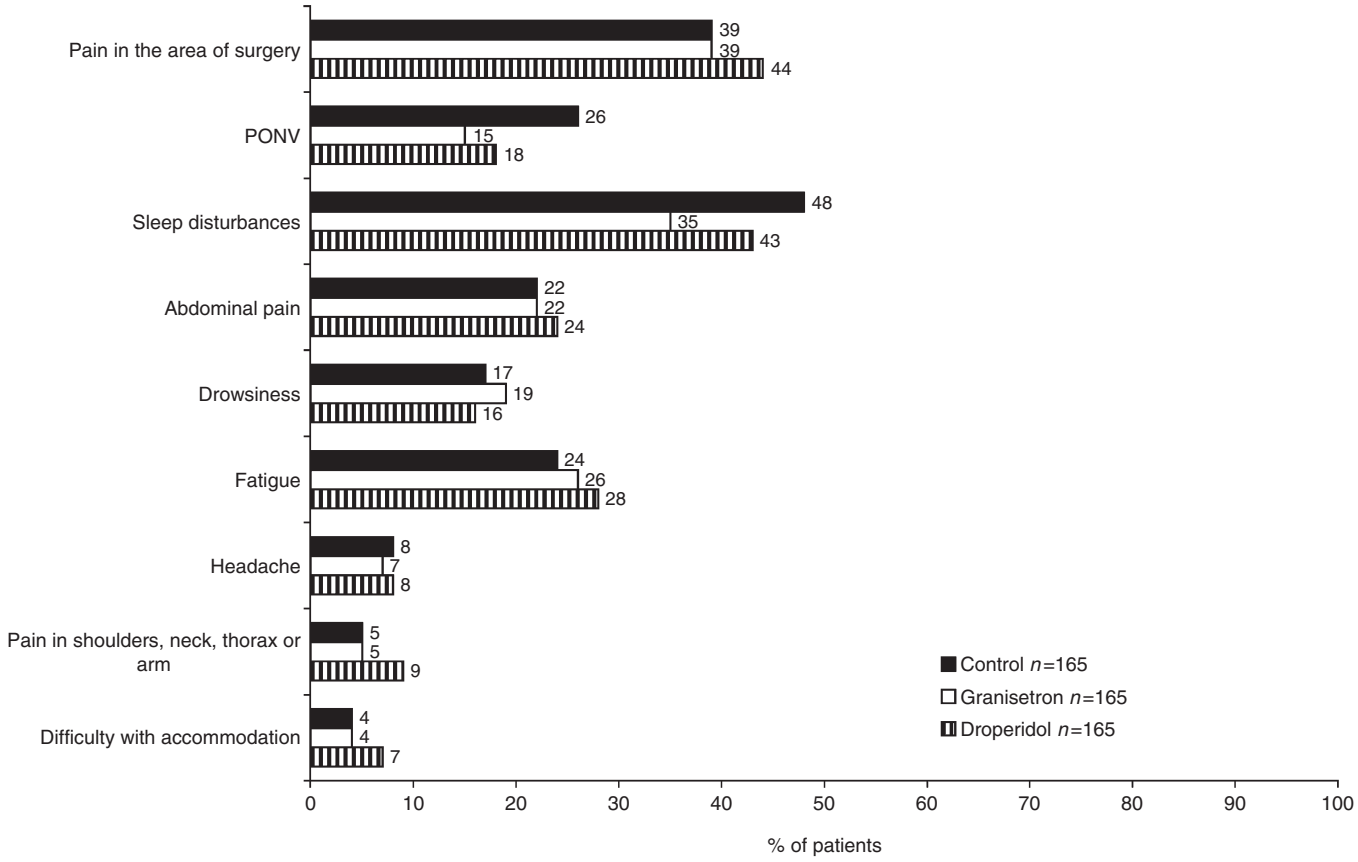

Fig. 1. Accumulative incidence of moderate to very severe disturbing symptoms (0–24 h) after gynaecological surgery.

motion sickness or PONV, being young, and the length of anaesthesia (10). The relevance of these factors is supported by previous reports from several authors (9, 12, 21) and is superior to single predictor models using a history of PONV or female gender alone (11). The risk score is useful both as a method to estimate an individual's risk of PONV and as a method for comparing groups of patients in antiemetic trials (11). Though patients with a risk >30% of post-operative vomiting were entered into the study we could not demonstrate an improved outcome. This is in agreement with the findings of Scuderi (4) who advocates a timely treatment of symptoms instead of prophylaxis.

We used a score for vomiting when we designed our study (10). All patients are in a high-risk group for PV. When we are analysing our data again, taking into consideration the simplified risk score of Apfel for PONV (11), the women in this study had on average three risk factors for PONV which is equal to an approximately 40–60% risk of PONV.

It seems reasonable to use the most effective, longest acting, side-effect free and least expensive drug when choosing an antiemetic (6). Granisetron, a selective 5-hydroxytryptamine type-3-receptor antagonist, possesses few side-effects (22) and has a good antiemetic effect (23, 24). It is believed to act specifically at 5-HT_3 receptors on the vagal afferent nerves of the gut (25). The most commonly reported side-effects are headache, dizziness, flushing, increased hepatic enzymes and epigastric sensation (8). Headache was significantly the most common side-effect of granisetron in our study, 44% (72/165) (Table 3).

A dose–response curve for granisetron has been suggested for granisetron and PONV but has not been confirmed (26). When designing this study we wanted to be sure to give enough and hoped for an effect for 24 h. The effective dose of granisetron for the treatment of PONV was at that time suggested to be between 5 and 40 mikrog/kg (23, 24, 27). A low dose of granisetron was ineffective with a RR of 0.84 (0.68–1.04) while a high dose of granisetron led to a strong decrease with a RR of 0.30 (0.26–0.36) (26). The effective doses of granisetron were known to be 40 mikrog/kg for the treatment of cancer therapy induced nausea and vomiting (28). We know now better and as the work of Kranke et al. has shown we have been mislead by one dominating centre (26).

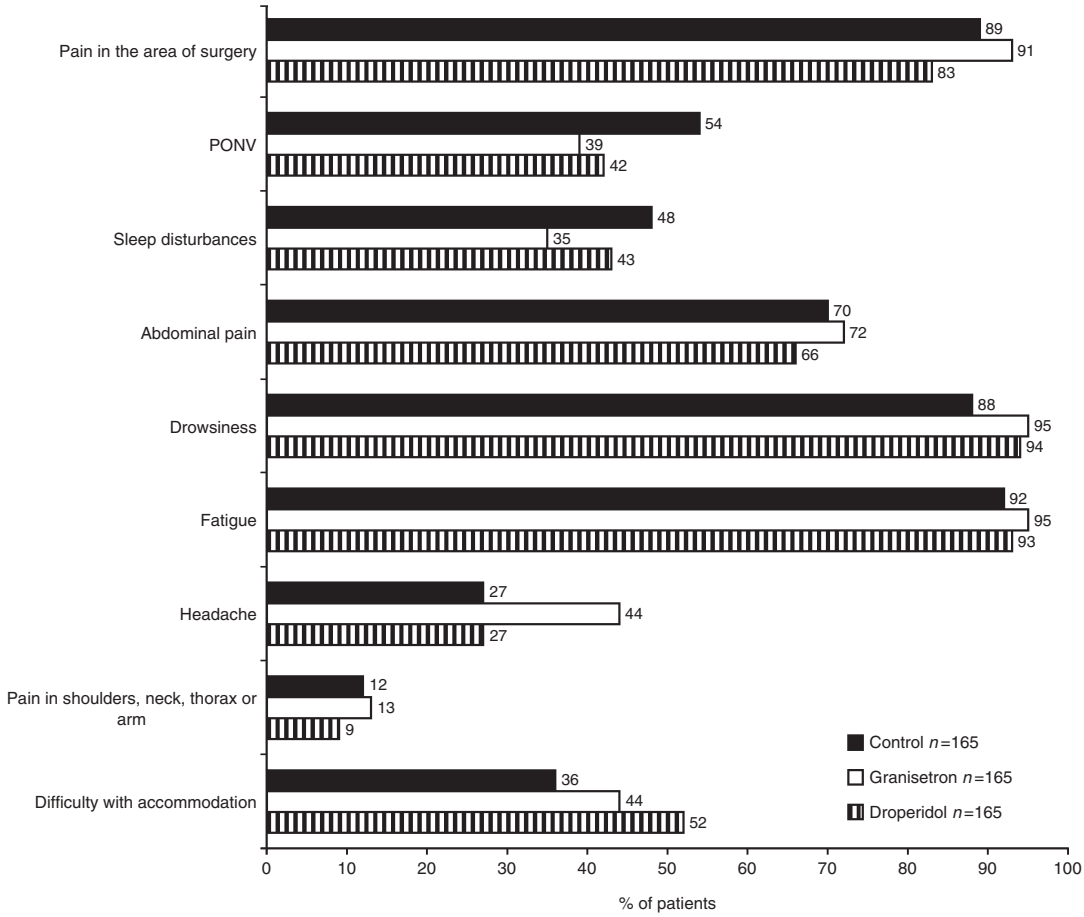

Fig. 2. Accumulative incidence of symptoms (incidence > 10%) after gynaecological surgery given in a dichotomous fashion (yes or no) (0–24 h).

We used 3 mg of granisetron (40 mikrog/kg). This has now clearly been demonstrated to be a high dose and in most countries a dose of 1 mg of granisetron is recommended. The higher dose used by us may of course have increased the amount of undesirable side-effects (29). When we compare our study to others

Table 5

Number of symptoms after gynaecological surgery (see Figs 1,2) 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).

	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*	76	123†	69	107*†	76

*$P < 0.05$ when droperidol is compared with the control group.
†$P < 0.05$ when granisetron is compared with the control group.

that have investigated granisetron a similar profile can be observed but our incidence of headache is higher, 44% compared with 17% (30, 31). On the other hand, the incidence of moderate to severe headache is only 7% and actually not higher than the incidence of headache in the groups treated with droperidol and the control group (Figs 1 and 2). Assuming that the 'true' incidence of headache is 17% then the high dose used by us could have resulted in 27% more patients having headache than could be expected by a dose of 1 mg. That would decrease the number of symptoms reported from the granisetron-treated group. But this does not change the conclusion of this study namely that a prophylactic treatment *does not improve outcome* counted in intensity of disturbing symptoms or in number of symptoms experienced.

Droperidol, a dopamine receptor antagonist, has a potent antiemetic effect (18). The most commonly reported side-effects are sedation, anxiety, drowsiness, dizziness, extrapyramidal symptoms (32) and lately reports on malignant ventricular dysrhythmias (33). Dose–response studies have concluded that 20 mikrog/kg is the optimal dose of droperidol when used as an antiemetic (34, 35). Side-effects may limit its suitability in anaesthetic practice particularly in high doses (36). When lower doses of droperidol (e.g. 0.625–1.25 mg) are used (34, 37) adverse reactions are rare. We found that difficulty with accommodation was the most common side-effect of droperidol, 52% (85/165) (Table 3). This has been shown before (9, 38). There is convincing evidence from a systematic review that ondansetron is not more effective than 1.25 mg of droperidol for PONV prophylaxis in adults (39). When the results of a systematic review were pooled by type of surgery, the $5HT_3$ receptor antagonist was superior to traditional agents in gynaecological surgery only for the end-point of both nausea and vomiting (30).

This is a large randomized controlled clinical trial. We have aimed at a study on clinical efficiency and thus allowed the anaesthetist to use the drugs he/she finds most appropriate for the patient. This means that the anaesthetic technique is not totally standardized apart from the use of antiemetics. All drugs used were reported, as is the incidence of their use in each group. We have used a uniform method of data collection and an adequate number of subjects to have the necessary power to draw conclusions regarding clinical outcome (39) rather than surrogate endpoints (e.g. the occurrence of PONV) (2).

The cost-effectiveness of an antiemetic depends on its effectiveness, cost, frequency and severity of PONV, and whether the antiemetic is used as prophylactic or rescue medication (40). In our study, seven patients needed to be treated with granisetron (3 mg) to prevent one patient from experiencing PONV. The equivalent number for droperidol (1.25 mg) was eight patients. The cost of the treatment was SKr 1124 (US$ 112) for granisetron and SKr 84 (US$8) for droperidol. That is a difference in cost per effectively treated patient of more than 100 US$. To identify a high-risk group, where PONV compromise surgery, delay recovery, cause hospital admission could be a way to increase the cost-effectiveness ratio (14, 21). Tools to predict risk of PONV could be useful in clinical practice (41) but the power to discriminate which individual will suffer from PONV is still limited and imperfect even when more predictors are considered (42).

In our study the efficiency of prophylactic antiemetics could be questioned as the patients reported disturbing symptoms to a similar degree in all groups. Only the profile of symptoms changed depending on if and which antiemetic treatment had been given. 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. Others have reported similar results (7, 40).

Summary and conclusion

The overall intensity and number of disturbing post-operative symptoms did not decrease after prophylactic antiemetic treatment in a group of patients at high risk of PONV, but the profile of disturbing symptoms changed. The relevance of disturbing post-operative symptoms in terms of patients' well-being needs to be addressed.

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Appendix 1

Post-operative symptom questionnaire

Pain/Discomforts

To be answered on the evening of the day of your operation

We would like you to describe how much pain you have had today after your operation.

We would also like you to describe how much discomfort you have experienced, such as nausea, headache, abdominal pain, etc. Could you please answer the first two pages (sides 1 and 2) on the day of operation and pages 3 and 4 on the first day after operation. If possible answer between 8:00 and 9:00 p.m. Most questions can be answered by marking your alternative with a cross.

First some questions concerning how you feel just now, when you complete this form Please put a cross where most appropriate.

No Yes, a little Yes

(1) Pain in the area of surgery.
Do you still have pain in the area of surgery?

(2) Discomforting symptoms
Do you feel nausea?
Are you retching?
Do you have headache?
Do you have abdominal pain?
Are you tired?
Are you drowsy?
Are you having difficulty with accommodation?
Do you have any other discomfort?
If any other discomforting symptoms, please describe here . . . . . .

(3) How was the pain at its worst after your operation?
No pain Very mild Mild Moderate
Bad Severe Very severe

(4) How much discomfort did you suffer at its worst? (apart from pain after the operation).
No discomfort Very mild Mild Moderate
Bad Severe Very severe

(5) What was particularly discomforting? (can be more than one answer)
Nausea/vomiting Headache Abdominal pain
Difficulty with accommodation Drowsiness
Other discomforts If yes, please specify . . . . . .

(6) Describe your average level of pain after the operation? Try to give an overall rating for the whole period.
No pain Very mild Mild
Moderate Bad Severe Very severe

(7) How much discomfort did you suffer after the operation apart from pain? Try to give an overall rating for the whole period.
No discomfort Very mild Mild Moderate
Bad Severe Very severe

(8) What symptom on average was most disturbing? (can be more than one answer)
Nausea/vomiting Headache Abdominal pain Difficulty with accommodation Drowsiness
Other discomforts If yes, please specify. . . . . .

(9) Have you vomited today? No Yes, once Yes, many times
What time is it now, when answering this questionnaire?. . . . . .

On the next day, same questions as above but starting with:

How did you sleep the first night after operation?
Well Neither well nor badly Badly

The questionnaire ends with the following question:

Do you think we know how you feel after we have read your answers?
Yes No If not, please tell us what we have missed. . . . . .