Reports of Investigation

Post discharge nausea and vomiting after ambulatory laparoscopy is not reduced by promethazine prophylaxis

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Purpose: To determine the incidence of post-discharge nausea and vomiting (PDNV) following outpatient laparoscopic procedures in women, and to assess the efficacy of the prophylactic administration of promethazine prior to discharge from hospital.

Methods: Ninety-five healthy women scheduled for ambulatory laparoscopic cholecystectomy or gynecological surgery completed this double blind, placebo controlled study. A standardized fentanyl-propofol-nitrous oxide-isoflurane anesthetic was used, and all patients received 0.5 mg droperidol *iv*, intraoperatively. Subjects were randomized to receive 0.6 $mg \cdot kg^{-1}$ promethazine or placebo *im* prior to transfer from the post-anesthetic recovery (PAR) unit. The incidence and severity of nausea, pain, and drowsiness were documented using patient diaries at four time intervals during the first 24 hr postoperatively using four-point self-assessment scales.

Results: After discharge home, the overall incidence of nausea was 48%, moderate to severe nausea 30%, vomiting 17% and rescue antiemetic use 28%, with no difference between those receiving saline or promethazine. The need for antiemetics in the PAR was associated with subsequent PDNV, with those requiring PAR antiemetics being four times as likely to vomit after discharge ($P = 0.008$).

Conclusion: Despite the prophylactic administration of 0.5 mg droperidol *iv*, patients undergoing ambulatory laparoscopic surgery reported a high incidence of nausea after discharge. Patients requiring antiemetics in the PAR were at higher risk for PDNV. The incidence of nausea was not altered by prophylactic administration of 0.6 $mg \cdot kg^{-1}$ promethazine *im* before discharge.

Objectif : Déterminer l'incidence de nausées et de vomissements postcongé (NVPC) après une laparoscopie ambulatoire et évaluer l'efficacité de l'administration prophylactique de prométhazine avant le départ de l'hôpital.

Méthode : Quatre-vingt-dix femmes en santé, qui ont subi une cholécystectomie laparoscopique ou une intervention gynécologique, élective et ambulatoire, ont participé à une étude en double aveugle contre placebo. L'anesthésie était standard : fentanyl, propofol, protoxyde d'azote et isoflurane. Toutes les patientes ont reçu 0,5 mg de dropéridol *iv* peropératoire. Elles ont été réparties de façon aléatoire et ont reçu, soit 0,6 $mg \cdot kg^{-1}$ de prométhazine, soit un placebo *im* avant le transfert de la salle de réveil. L'incidence et la sévérité des nausées et des vomissements, de la douleur et de la somnolence ont été documentées en utilisant ce que les patientes ont noté à quatre reprises pendant les premières 24h postopératoires selon des échelles d'évaluation personnelle en quatre points.

Résultats : Après le congé, l'incidence globale de nausées a été de 48 %; de nausées modérées ou sévères, 30 %; de vomissements, 17 % et de recours aux antiémétiques, 28 %, sans différence intergroupe (placebo *vs* prométhazine). La demande d'antiémétiques à la salle de réveil était associée aux NVPC subséquents, les patientes qui ont reçu ces antiémétiques étant quatre fois plus à risque de vomir après le départ de l'hôpital ($P = 0,008$).

Conclusion : Malgré l'administration prophylactique de 0,5 mg de dropéridol *iv*, les patientes qui subissent une opération laparoscopique ambulatoire ont rapporté une forte incidence de nausées après le congé de l'hôpital. Celles qui ont eu besoin d'antiémétiques à la salle de réveil étaient plus à risque de NVPC. L'incidence des nausées n'a pas été modifiée par l'administration prophylactique de 0,6 $mg \cdot kg^{-1}$ de prométhazine *im* avant le départ.

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POST-OPERATIVE nausea and vomiting has long been identified as a common and distressing post-surgical complication.[1,2] More recently, the problem of post-*discharge* nausea and vomiting (PDNV) occurring after out-patient surgical procedures has become apparent, with a reported incidence from 35 to over 70%.[3–5] This incidence appears highest in certain risk groups, including women, and patients undergoing laparoscopic procedures.[3–5] Such patients may experience considerable difficulty in performing activities of daily living, yet infrequently seek aid from health care personnel.[3] In addition, when potential surgical candidates were asked to prioritize the importance of a variety of post-operative symptoms, 72% listed the avoidance of nausea and vomiting as the most important.[6] Thus, although the problem of PDNV may not be readily apparent to health care workers, it can cause severe morbidity when patients return home.

Numerous pharmacological therapies have been employed in the treatment and prevention of postoperative nausea after outpatient procedures.[7–9] Previous work has shown droperidol to be a cost-effective antiemetic in ambulatory surgery,[7] and propofol to reduce the incidence of nausea as compared with other induction agents.[10] However, limited work has been done to determine if patients benefit from further prophylaxis of nausea and vomiting that may occur after discharge. The serotonin receptor antagonists, including ondansetron and granisetron, have been shown to reduce the incidence of PDNV.[4,7,8] However cost-benefit analysis has questioned whether the expense of these drugs justifies their routine use over less expensive treatment.[7] Promethazine has been shown to be an effective antiemetic with the advantages of low cost, slow intramuscular absorption, and long elimination half-life.[9,11–13] It has a mixed receptor antagonist profile, with potent antihistamine and antimuscarinic cholinergic properties as well as a modest antidopaminergic effect.[14] The long duration of action of promethazine and pharmacological antagonism of multiple receptors known to be involved in nausea and vomiting would make it a rational choice for prophylaxis of nausea and vomiting occurring post-discharge.

TABLE I Patient self-assessment scales

Score	*Nausea*	*Pain*	*Sedation*
0	none	none	wide awake
1	mild	mild	slightly drowsy
2	moderate	moderate	dozing frequently
3	severe	severe	mainly sleeping

The objectives of this study were to determine a) the incidence of PDNV following ambulatory laparoscopic surgical procedures in women, and b) whether prophylactic administration of promethazine prior to discharge can further reduce its incidence.

Methods

Approval for this randomized, double blind, placebo controlled study was granted by the Queen's University Research Ethics Board. All ASA 1 or 2 patients scheduled for day surgery elective gynecological laparoscopy or laparoscopic cholecystectomy were assessed for inclusion in the study. Exclusion criteria included underlying gastrointestinal disease or motility disorder, body mass index > 35, documented allergic reaction to any of the protocol medications, and concurrent use of antihistamines, phenothiazines, or drugs acting on the gastrointestinal system. After obtaining written informed consent, subjects were randomized to receive either intramuscular promethazine or saline placebo at the time of discharge from the post-anesthetic recovery unit. All syringes were prepared by the Kingston General Hospital pharmacy according to a computer-generated randomization schedule.

A standardized anesthetic protocol was used. Anesthesia was induced with 1-2 $\mu g \cdot kg^{-1}$ fentanyl *iv* and 1.5-2.5 $mg \cdot kg^{-1}$ propofol *iv*, and maintained with nitrous oxide 60% in oxygen and isoflurane to a maximum end tidal concentration of 1.5%. Droperidol, 0.5 mg *iv*, was administered intraoperatively for prophylaxis against early postoperative nausea as per common practice in our institution. Tracheal intubation was facilitated with 1.0 $mg \cdot kg^{-1}$ succinylcholine *iv*. Vecuronium was titrated to effect and the neuromuscular block was reversed at the end of the anesthetic with 2.5 mg neostigmine and 0.4 mg glycopyrrolate *iv*. Additional boluses of 25 µg fentanyl, were given at the discretion of the anesthesiologist. Fluid management with Ringer's Lactate was based on the fluid deficit calculated before surgery and ongoing requirements. All patients received 100 mg indomethacin *pr*, post-induction. Upon arrival in the Post-Anesthetic Recovery unit (PAR), patients were given fentanyl in increments of 25 µg *iv*, as required for pain. Dimenhydrinate, 25 mg *iv*, was available to treat nausea and vomiting in the PAR.[15] Patients were told at the preoperative interview and again in the PAR that they could request up to two doses of this antiemetic if necessary. At the time of discharge from the PAR, the patients received either 0.6 $mg \cdot kg^{-1}$ promethazine (25 $mg \cdot mL^{-1}$ solution), to a maximum of 50 mg, or an equal volume of saline placebo *im*, according to their previous randomization. The patients were dis-

TABLE II Demographic data, surgical procedure, nausea and vomiting in recovery room

		Saline (n=47)	*Promethazine (n=48)*
Patients:	Age (yr)	35 ± 9	35 ± 9
	Weight (kg)	69 ± 13	69 ± 14
	Past history severe postoperative nausea and vomiting (*n*)	4	8
	Onset last menstrual period (days)	12 ± 7	12 ± 8
Procedure:	Gynecologic (*n*)	35	35
	Cholecystectomy (*n*)	12	13
Intraoperative	Duration of surgery (min)	53 ± 41	61 ± 57
	Fentanyl (μg)	124 ± 51	130 ± 65
Recovery room	Duration of stay (min)	107 ± 51	109 ± 60
	Fentanyl (μg)	48 ± 52	43 ± 51
	Nausea: mod/severe (*n*)	4	7
	Rescue antiemetic (*n*)	7	8
	Vomiting (*n*)	4	7

Data expressed as mean ± standard deviation, or number of patients (n)
$P > 0.05$ for all parameters

TABLE III Patients experiencing post-discharge nausea and vomiting

		Arrival home	*Bedtime*	*Morning*	*Lunch*
Nausea (any)	Saline (n=47)	19 (40)	11 (23)	4 (9)	11 (23)
	Promethazine (n=48)	18 (38)	16 (33)	11 (23)	8 (17)
Nausea (moderate, severe)	Saline	9 (19)	8 (17)	0 (0)	3 (6)
	Promethazine	12 (25)	6 (13)	3 (6)	4 (8)
Vomiting	Saline	5 (11)	2 (4)	0 (0)	1 (2)
	Promethazine	4 (8)	5 (10)	2 (4)	0 (0)
Rescue antiemetics	Saline	6 (13)	5 (11)	3 (6)	1 (2)
	Promethazine	3 (6)	10 (21)	4 (8)	3 (6)
Pain (moderate, severe)	Saline	15 (32)	20 (43)	26 (55)	24 (51)
	Promethazine	17 (35)	26 (54)	21 (44)	17 (35)
Drowsiness ("mainly sleeping")	Saline	10 (21)	3 (6)	11 (23)	1 (2)
	Promethazine	17 (35)	21 (44)	6 (13)	4 (8)

Data expressed as number of patients (percentage).

charged home from the outpatient procedure unit with dimenhydrinate tablets and suppositories for use as rescue antiemetics if required. For analgesia, patients were provided with non-steroidal anti-inflammatory drugs and a prescription for an acetaminophen/codeine preparation.

Data obtained for each subject included age, weight, concurrent medication, timing of menstrual cycle, smoking, alcohol use, and duration of trip home. The duration of surgery and anesthesia, and total fentanyl and dimenhydrinate received in the recovery room were documented. Patients were provided with a diary containing four-point categorical scales for pain, drowsiness, and nausea (Table I), to be used for self-assessment at four times: a) upon arrival home, b) at bedtime the day of surgery, c) upon awakening the morning after surgery and d) at lunch time the day after surgery. These scales have been advocated as simple and reliable measuring tools for self-assessment of nausea.[16] In addition, patients were asked to record analgesic and dimenhydrinate usage at home, and all episodes of emesis. All data recorded on diaries were retrieved by telephone interview.

The number of subjects required for this study was calculated to detect a 50% change in post-discharge nausea, assuming a 65% incidence,[3-5] with a power of 80% at the 0.05 level of significance. Based on these criteria, 42 subjects were required in each group. Data were analyzed using unpaired t tests for parametric data and chi-square and Fisher Exact tests for proportionate data. Data are reported as mean ± standard deviation, or percentage for incidence.

Results

One hundred and one patients were enrolled into the study. Three patients were withdrawn prior to study drug administration due to anesthetic protocol violations, and three patients having laparoscopic cholecys-

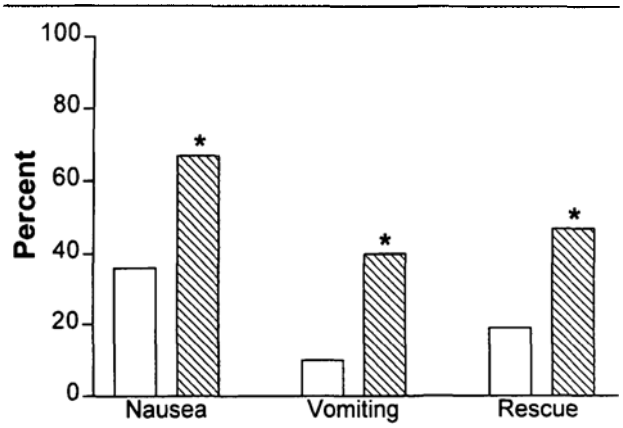

FIGURE 1 Incidence (percent) of moderate or severe nausea, episodes of vomiting, and need for rescue antiemetics during the day of surgery following discharge home (data combined for time periods "arrival home" and "bedtime"). Columns indicate those patients not having received (white bars, n=80) and those having received (shaded bars, n=15) antiemetics in the post-anesthetic recovery unit. * indicates $P < 0.05$ *vs* no antiemetic in recovery room.

tectomy were admitted to hospital and never received the study drug (one required laparotomy for bleeding, one was admitted for pain and one for intractable nausea and vomiting). Thus, data from 95 patients (n = 48 promethazine and 47 placebo) were analyzed. The two groups had similar demographic characteristics (Table II). In addition, there was no difference in type of procedure, duration of anesthesia, or intraoperative fentanyl administration. The incidence of nausea, vomiting, and dimenhydrinate use in the recovery room was also similar between the two groups (Table II). Patients were discharged from hospital 103 ± 77 min after receiving promethazine.

Post-discharge nausea, vomiting, sedation, and antiemetic requirements

Forty-eight percent of all patients experienced nausea at some time after discharge (51% and 46% for saline and promethazine groups respectively, *P*:NS). Overall, 30% of patients experienced moderate to severe nausea, 28% required rescue antiemetics at home, and 17% vomited. There was no difference between the saline and promethazine groups in the worst level of nausea reported, the incidence of nausea of any severity (51 *vs* 46% respectively), moderate to severe nausea (32 *vs* 42%), vomiting (15 *vs* 19%), or the need for rescue antiemetics following discharge (28 *vs* 29%). Table III details the incidence of symptoms at all time intervals after discharge. The groups were also similar in all of these parameters when gynecological and cholecystectomy patients were anaylzed separately, and when the data were stratified to take into account patients reporting a past history of severe PONV. However, the incidence of excessive drowsiness ("mainly sleeping") was substantially higher in those patients receiving promethazine on arrival home (33 *vs* 20% for placebo, P = 0.001), and particularly at bedtime (41 *vs* 6% for placebo, $P < 0.001$). Despite the increased drowsiness with promethazine after discharge, there was no delay in discharge of these patients (time from PAR discharge to arrival home 98 ± 87 *vs* 107 ± 67 min for placebo and promethazine group respectively).

Sixteen percent of patients requested an antiemetic drug in the PAR. The need for antiemetics in the PAR was associated with increased nausea and vomiting after discharge (Figure 1). Overall, patients who required dimenhydrinate in the recovery room were twice as likely to require rescue antiemetics (P = 0.04), three times as likely to report moderate to severe nausea (P = 0.05), and four times as likely to vomit (P = 0.008) on the day of surgery after discharge (arrival home and bedtime: Figure 1). This relationship between requirement for antiemetics in the recovery room and PDNV was not altered by promethazine administration. In addition, there was no difference in PDNV between groups when those not receiving PAR dimenhydrinate were analyzed alone.

Comparison by procedure

The laparoscopic cholecystectomy patients were more likely than the gynecological patients to vomit (28 *vs* 6%, $P < 0.01$), and receive antiemetics (36 *vs* 9%, $P <$ 0.01) in the recovery room. Cholecystectomy patients also reported a higher incidence of moderate to severe nausea after discharge home during the day of surgery (32% *vs* 9% for gynecologic, $P < 0.01$) and greater requirement for rescue antiemetics (32% *vs* 10%, P = 0.02), although the incidence of vomiting was equal. The incidence of patients reporting moderate to severe pain at any time after discharge was 80% after cholecystectomy and 71% following gynecological surgery (*P*:NS). Pain was still an important complaint at lunch time on the day following surgery (moderate or severe pain in 48% of cholecystectomy and 41% of gynecological patients, *P*:NS). The administration of promethazine had no influence on the incidence or severity of pain at any time after discharge.

Discussion

This study has documented that nausea and vomiting is an important problem following discharge from hospital after ambulatory laparoscopic surgical procedures in women. Despite the use of prophylactic droperidol and

induction with propofol, both of which have been demonstrated to play a role in reducing postoperative nausea and vomiting,[5,10,17] almost half of all patients experienced post-discharge nausea, with 28% of patients requiring rescue antiemetics. These findings underscore the frequency of this problem, the difficulty in its prevention, and its multifactorial nature.

We studied a group of healthy women since this population has been identified as being at high risk for postoperative nausea.[2] In particular, women undergoing gynecological procedures have demonstrated an incidence of nausea or emesis of up to 70%.[4] Laparoscopic cholecystectomy is associated with a similar risk, with over 70% of those not receiving antiemetic prophylaxis experiencing emetic episodes.[3] In the current study, comprised of both laparoscopic gynecological and cholecystectomy patients, the incidence of early postoperative nausea and vomiting as well as early PDNV was higher in the cholecystectomy group, although sample size limitations precluded further subgroup analysis.

A number of drugs have been studied for their potential to reduce PDNV, including serotonin receptor antagonists, droperidol and promethazine, although the population, efficacy and cost effectiveness has varied among studies.[4,5,7,9] Promethazine was studied as a potentially useful prophylactic agent because it is an effective antagonist of histaminergic, muscarinic cholinergic, and, to a modest degree, dopaminergic receptors,[14] offering a multifaceted approach to the prevention of nausea and vomiting. The clinical efficacy of promethazine is supported by several trials.[9,10–12] In addition, promethazine offers the advantage of low cost, slow intramuscular absorption, and long elimination half-life,[14] making it potentially attractive for use in day-surgery patients.[9] In the current study, promethazine had no effect on post-discharge nausea scores, vomiting, or rescue antiemetic requirements, and its use was associated with a seven-fold increase in the incidence of excessive drowsiness on the evening following surgery. We chose to use a dose of 0.6 $mg \cdot kg^{-1}$ promethazine in this study in order to prolong the antiemetic effect after discharge. This dose is higher than that used in other studies during labour (25 mg),[18] in conjunction with patient controlled analgesia with morphine (mean 17.6 mg over 24 hr),[13] and after intrathecal morphine (10 mg *po*).[11] Thus, it is unlikely that a higher dose of promethazine would have proved more effective, and would likely have led to an inappropriately high incidence of sedation.

Prophylactic droperidol was given intraoperatively due to its demonstrated benefit in reducing postoperative nausea and vomiting, even in small doses.[5,17,19] The antiemetic properties of droperidol are recognized to last up to 6 to 12 hr[19] and, therefore, would likely have decreased the incidence of post-discharge nausea and vomiting in both groups until after arrival home. It was postulated that the effect of promethazine may be additive to that of droperidol, as promethazine is primarily effective through histamine and muscarinic cholinergic receptors while droperidol acts primarily on dopaminergic receptors. Droperidol was thus included in this study to document the incidence of PDNV after an anesthetic technique employing an effective prophylactic antiemetic, and also to reduce the requirements for additional antiemetics in the PAR. It is possible that the use of droperidol, by reducing the overall incidence of PDNV, may have masked any beneficial effects of promethazine which might otherwise have been seen. However the placebo group had an incidence of post-discharge nausea similar to that reported previously in the literature,[3] making this explanation unlikely.

Poorly-controlled pain is another factor which can itself lead to nausea and vomiting.[20] Since 72% of patients reported moderate to severe pain at some time after discharge, it is possible that better pain control may have reduced the incidence of PDNV. Post-discharge pain appeared to be a considerable problem for patients undergoing gynecological procedures as well as cholecystectomy. However, the relatively small number of cholecystectomy patients in each group limit the ability to sub-stratify the groups for further analysis. Finally, it is possible that promethazine is not effective for postoperative nausea associated with laparoscopic procedures compared with other situations.

A further important finding of this study was the relationship between rescue antiemetic requirement in the recovery room and subsequent nausea and vomiting after discharge home. Specifically, patients who requested rescue antiemetics while in hospital went on to use rescue antiemetics twice as often, experienced nausea three times more frequently, and vomited four times as often at home. Thus, it may be warranted to target this subgroup of patients for prophylaxis of PDNV.

In summary, PDNV remains an important problem in women undergoing ambulatory laparoscopic procedures, despite the use of prophylactic antiemetics. The need for antiemetics in the PAR was associated with PDNV. Finally, prophylactic promethazine, 0.6 $mg \cdot kg^{-1}$, given prior to discharge did not change the incidence of PDNV, but did increase sedation scores following discharge. Further work is needed to determine an effective regimen to reduce the unacceptably high incidence of this distressing problem.

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