Prophylactic Diclectin® reduces the incidence of postoperative vomiting

[L'administration prophylactique de Diclectin® réduit l'incidence de vomissements postopératoires]

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Background: Diclectin® (DCL) is an effective antiemetic used for relief of nausea and vomiting in pregnancy. It is unknown whether DCL is effective in the prevention of postoperative nausea and vomiting (PONV).

Methods: We conducted a randomized, stratified, double-blind placebo-controlled trial to examine the incidence of PONV in women undergoing elective laparoscopic tubal ligation in the day surgery setting. DCL (doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg) was administered orally the night before surgery, the morning of surgery, and upon hospital discharge.

Results: We enrolled 146 women in the trial, 127 of whom were included in the effectiveness analysis and 102 of whom were included in the efficacy analysis. We did not detect a difference in the incidence of nausea and vomiting in the first six hours postoperatively after adjusting for additional antiemetics administered. Patients receiving DCL as compared with placebo were significantly less likely to experience vomiting six to 24 hr postoperatively [5/59 (8.5%) vs 14/55 (25.4%), $P < 0.017$]. Treated patients tended to return to work earlier than those who received placebo (1.74 vs 3.7 days $P = \text{NS}$).

Conclusion: Perioperative oral DCL reduces the incidence of postoperative vomiting in women undergoing elective laparoscopic tubal ligation, and may accelerate return to work.

Contexte : Le Diclectin® (DCL) est un antiémétique efficace contre les nausées et les vomissements pendant la grossesse. On ne sait pas s'il peut prévenir les nausées et vomissements postopératoires (NVPO).

Méthode : Nous avons réalisé une étude randomisée, stratifiée et à double insu contre placebo pour vérifier l'incidence de NVPO chez des femmes qui subissent une ligature des trompes laparoscopique réglée en chirurgie d'un jour. Le DCL (10 mg de succinate de doxylamine et 10 mg de chlorhydrate de pyridoxine) a été administré oralement le soir avant l'opération, le matin de l'opération et lors du départ de l'hôpital.

Résultats : Nous avons recruté 146 femmes, dont 127 pour l'analyse d'efficacité et 102 pour l'analyse de l'activité. Nous n'avons pas noté de différence d'incidence de nausées et de vomissements pendant les six premières heures postopératoires après ajustement pour les antiémétiques supplémentaires administrés. Les patientes recevant le DCL, comparé au placebo, ont eu significativement moins de vomissements de six à 24 h après l'opération [5/59 (8,5 %) vs 14/55 (25,4 %), $P < 0,017$]. Les patientes traitées sont retournées plus tôt au travail que celles qui ont reçu le placebo (1,74 vs 3,7 jours $P = \text{NS}$).

Conclusion : Le DCL périopératoire oral réduit l'incidence de vomissements postopératoires chez les femmes qui subissent une ligature des trompes laparoscopique réglée et il peut hâter le retour au travail.

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NAUSEA and vomiting are common causes of postoperative morbidity. Over the past ten to 15 yr various predictors of postoperative nausea and vomiting (PONV) have been identified, including female gender, age less than 30 yr, intra-abdominal surgical procedures, and use of opioids.¹ Differences in nausea and vomiting at different times in the menstrual and reproductive cycle may be accounted for by variations in estrogen, beta human chorionic gonadotropin,² and other hormone levels.

Diclectin® (DCL; Duchesnay Pharmaceuticals, Montreal, QC, Canada) is an antiemetic medication which contains 10 mg doxylamine succinate (a common antihistamine with antiemetic properties found in over-the-counter sleeping medication) and 10 mg pyridoxine hydrochloride (vitamin B6), in a delayed release formulation. Pyridoxine prevents possible deficiencies in vitamin B6. It may have intrinsic antiemetic properties and also may be synergistic with the antinauseant property of antihistamines.³⁻⁵ DCL has been used since the 1950's and is considered to be a safe treatment for nausea and vomiting associated with pregnancy.⁶ The international Cochrane collaboration has systematically reviewed randomized trials of DCL, and concluded that it safely provides considerable relief for nausea and vomiting of pregnancy.⁷

DCL has not been formally tested for symptom relief in non-pregnant patients. Pyridoxine was traditionally used in the treatment of radiation sickness among outpatients with some success, based on uncontrolled studies.⁸ For this study, we hypothesized that DCL may be a useful antiemetic in female postoperative patients.

Methods

Study population

This study was approved by and carried out in accordance with the Ethics Committee of McMaster University. All patients scheduled for elective laparoscopic tubal ligation at McMaster University Medical Center from October 1998 to December 2000 were considered for enrollment in the study. Prospective participants were recruited through the preoperative assessment clinic, where patients were seen by a nurse and/or an anesthesiologist prior to the procedure. Inclusion criteria were non-pregnant females scheduled for elective laparoscopic tubal ligation who were American Society of Anesthesiology physical status class I to III. Patients were excluded if they were on oral contraceptives, if they did not know the date of their last menstrual period, had not resumed menses postpartum, had Parkinson's disease, or declined consent.

Study design

Patients were allocated to DCL or placebo using a computer-generated random number table kept in the preoperative assessment clinic. Because of a previous study done at our institution which showed a difference in the incidence of nausea and vomiting according to the phase in the menstrual cycle, the study design had patients stratified into two groups with respect to the phase in the menstrual cycle at the time of their surgical procedure, (group 1: day one to eight, *vs* group 2: day nine or greater).¹ Drug allocation was determined by a sealed opaque package containing four pills (four tablets of DCL, or four placebo tablets). Patients were instructed to take two pills with fluid before retiring to bed on the night prior to surgery. Upon awakening the morning of surgery, they took one more tablet with a sip of water, and any other preoperative medications as instructed by their anesthesiologist. The fourth tablet was taken postoperatively, before discharge from the short stay unit (SSU).

For the tubal ligation, patients received a standard anesthetic with no preoperative antiemetics. This was consistent with institutional practice at the time. Induction of anesthesia consisted of propofol ($1-3 \text{ mg}\cdot\text{kg}^{-1}$) plus an opioid dose equivalent to fentanyl 1 to $2 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$. Muscle relaxation was achieved with rocuronium ($0.6 \text{ mg}\cdot\text{kg}^{-1}$) or vecuronium ($0.1 \text{ mg}\cdot\text{kg}^{-1}$) at the discretion of the attending anesthesiologist. Anesthesia was maintained with nitrous oxide (70%), oxygen (30%), and isoflurane (0.5–1.5%), and the lungs were ventilated mechanically. Muscle relaxation was monitored by peripheral nerve stimulator and, at the end of surgery, was reversed with neostigmine ($50 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$) and glycopyrrolate ($10 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$). Patients were transferred to the recovery room, and to the SSU until ready for discharge home.

Data collection

Preoperatively, we collected demographic and clinical data, history of PONV, history of migraine headaches and first day of last menstrual period. We recorded the duration of the anesthetic, dose of narcotic, and dose of inhalational anesthetic agent used intraoperatively.

Postoperatively, we had three periods of observation in different venues. The first observation period was in the postanesthetic care unit (PACU) and outcomes were recorded by the PACU nurse. The second observation period was in the SSU, and outcomes were recorded by the SSU nurse. The third period spanned the time from hospital discharge until 24 hr postoperatively; data were collected for this period using interviewer-administered telephone follow-up by the principal investigator.

The outcomes measured during each of the three postoperative observation periods included incidence of nausea, incidence of vomiting, possible adverse effects including headache, epigastric discomfort, dizziness, or drowsiness, and administration of postoperative rescue antiemetic drugs.

We measured patient symptoms of nausea and vomiting separately in this trial. Nausea was recorded as absent (0), mild (1), moderate (2), or severe (3). Vomiting was recorded as absent (0), vomited once (1), vomited more than once (2). *A priori*, we determined that a difference in one point would represent a clinically important difference to patients. Data collectors were blinded to treatment allocation throughout the study.

Sample size calculation

Three previous randomized controlled trials of DCL indicate that DCL provides considerable relief for nausea and vomiting in pregnancy (pooled odds ratio 0.3 [95% confidence interval (CI) 0.16 to 0.54], as determined by the Cochrane collaboration review.⁷ We designed this trial to detect a 50% decrease in nausea and vomiting in patients receiving DCL compared to placebo. The two groups of patients (menstrual and non-menstrual) were stratified and initially analyzed separately, looking for a significant reduction in nausea and/or vomiting in each. In the menstrual group, a baseline incidence of nausea and vomiting of 60% was used. In order to detect a reduction of 50% with a power of 0.8 and alpha error of 0.05, 84 patients would be required. In the non-menstrual group, we anticipated a 50% difference with the same power and significance; 116 patients were necessary. Therefore, to show a significant reduction in nausea and vomiting, we estimated the need for 84 patients in the menstrual group and 116 patients in the non-menstrual group.

Statistical analysis

To analyze symptoms of nausea and vomiting, we examined the distribution of each scale and found it non-normally distributed. Accordingly, we assigned nausea scores of absent (0) or mild (1) as 'minimal nausea,' and scores of moderate (2) or severe (3) as 'clinically important nausea.' We assigned vomiting scores of absent (0) as 'no vomiting,' and scores of vomited once (1) and vomited more than once (2) as 'vomiting present.' Initially, a Chi-square analysis was performed to compare the proportions of patients in each group with these symptoms. Since we were unable to demonstrate a difference in the incidence of nausea and vomiting according to the phase in menstrual cycle, we analyzed all patients together. The

FIGURE 1 Patient allocation.

proportion of patients receiving DCL who vomited, had nausea or were given at least one dose of antiemetic was also compared to the corresponding proportion of patients receiving placebo. To control type I error, an adjustment was made to the standard significance level of 0.05 to account for multiple comparisons between the three time frames (PACU, SSU, 6–24 hr) for each of the responses by using a Bonferroni adjustment. Because three tests are performed for each response (one for each time period), a significance level of $0.05/3 = 0.017$ was used instead of the standard 0.05 significance level.

We then performed an adjusted two-group analysis based on exposure to DCL or placebo. A stepwise selection procedure was used to fit a multivariate logistic regression model to each of the primary and secondary outcomes in the three observation periods. The original scale we used for nausea and vomiting had more than two levels, so we used a continuation ratio logit model as outlined in Agresti (1990).⁹ We used the following covariates: patient age, weight, history of PONV, motion sickness, and migraine, recent flu-like symptoms, cumulative antiemetic dose, cumulative narcotic dose, duration of anesthetic and dose of inhalational agent for adjustment; we also tested for two-way interactions. For the effectiveness adjusted analysis, we included the above factors, and in addition we considered preoperative antiemetics mistakenly administered, treating these as a rescue antiemetic dose. We used asymptotic methods⁹ to calculate 95% CI for each odds ratio.

FIGURE 2 Effectiveness ($n = 126$) and efficacy ($n = 102$) subsets, see text for details.

The analyst was blinded to treatment allocation until the analysis was completed.

Results

A total of 146 patients were recruited in the study period (Figure 1). This was less than our calculated target of 200. Patients were stratified according to the timing of their menstrual cycle, such that 44 patients were in day zero to eight, and 102 patients were in day nine or later in their cycle. Of 146 patients enrolled in the study, 132 patients underwent tubal ligation, and surgery was cancelled in 14 patients. Of 132 patients, data were unavailable for four patients, one patient withdrew consent and one withdrew because she was breastfeeding, leaving 126 patients with full data sets for the effectiveness analysis. This population contributed to the primary effectiveness analysis. A break in protocol occurred in 11 patients in the DCL group and 13 in the placebo group; the reasons for this break in protocol were that patients did not take all four tablets (DCL = 10, placebo = 9), or the anesthesiologist administered preoperative antiemetics (DCL = 1, placebo = 4). Thus, 102 patients contributed to the efficacy analysis (Figure 2).

The clinical and demographic characteristics of patients undergoing tubal ligation and receiving DCL and placebo were similar, except for a greater proportion reporting a history of PONV in patients receiving DCL (Table I).

In Table II, we present the distribution of outcomes in each of the three observation periods (PACU, SSU and 6–24 hr postoperatively) for patients receiving DCL or placebo in the effectiveness analysis. In the PACU and SSU periods, there were no differences in nausea or vomiting, or the proportion of patients receiving a rescue dose of antiemetic between groups. In the period post discharge from six to 24 hr postoperatively, patients receiving DCL were significantly less likely to experience vomiting [5/59 (8.5%) *vs* 14/55 (25.5%), $P < 0.017$]. We also found a trend toward a more rapid return to work or usual activities among patients receiving DCL.

In Table III we present the efficacy analysis. Results show no difference in outcomes. We affirmed the findings of our primary analysis after adjusting for important determinants of postoperative symptoms. In the adjusted effectiveness analysis, we found that a patient receiving DCL was significantly less likely to

TABLE I Baseline characteristics

Characteristics	Medication		P value for the difference
	Diclectin®	Placebo	
Age	34.8 (± 5.5)	33.8 (± 5.8)	0.362
Weight (kg)	70.7 (± 17.1)	72.0 (± 14.8)	0.669
Day 0-8 in cycle	20/65 (± 30.8)	20/67 (± 29.9)	0.909
Day > 9 in cycle	45/65 (± 69.2)	47/67 (± 70.2)	0.909
History of migraine	19/65 (± 29.2)	17/67 (± 25.4)	0.619
History of postoperative nausea and vomiting	22/65 (± 33.8)	9/67 (± 13.4)	0.006
History of motion sickness	10/65 (± 15.4)	11/67 (± 16.4)	0.871

Data are presented as mean ± SD or proportion (%).

TABLE II Outcomes for effectiveness analysis

Time frame	Outcome	Allocation		P value
		DCL n = 61	Placebo n = 64	
PACU	Nausea	16/60 (26.7%)	13/62 (21.0%)	0.460
	Vomiting	4/60 (6.7%)	5/62 (8.1%)	0.768
	≥ 1 dose of antiemetic given	15/60 (25.0%)	15/63 (23.8%)	0.878
SSU	Nausea	22/60 (36.7%)	18/62 (29.1%)	0.369
	Vomiting	9/59 (15.3%)	11/63 (17.5%)	0.742
	≥ 1 dose of antiemetic given	8/60 (13.3%)	12/63 (19.1%)	0.391
6-24 hr	Nausea	16/59 (27.1%)	17/55 (30.9%)	0.656
	Vomiting	5/59 (8.5%)	14/55 (25.4%)	0.015
	≥ 1 dose of antiemetic given	1/60 (1.7%)	2/55 (3.6%)	0.606
Functional outcome	Return to usual activities (days)	1.74 (2.4)	3.7 (9.9)	0.142

The DCL group had significantly less vomiting in the 6–24 hr period postoperatively. DCL = Diclectin®; PACU = postanesthetic care unit; SSU = short stay unit.

vomit in the six to 24 hr postoperative period compared to patients receiving placebo (odds ratio 0.27, 95% CI 0.09, 0.81).

Discussion

In this randomized double-blind placebo-controlled trial of DCL among women who underwent laparoscopic tubal ligations, we demonstrated that DCL significantly reduced the incidence of late (6–24 hr) postoperative vomiting. As an effective agent for preventing postoperative vomiting, DCL is an attractive alternative to the *iv* medications currently given either prophylactically or to treat nausea and vomiting in postoperative recovery areas. DCL is an oral sustained release formulation, and because it does not require an injection, it can be taken by patients preoperatively and after discharge from hospital. Often *iv* antiemetics prevent in-hospital nausea and vomiting but have worn off by the time patients are home. In this study, we showed that DCL significantly reduces the occur-

rence of postoperative vomiting which occurs after hospital discharge during the first 24 hr at home. The trend we identified, showing an accelerated return to normal activities and work associated with DCL (Table III), is promising; however, a larger study would be required to determine whether this benefit is real.

The magnitude of the response of patients in this study is consistent with the relief provided by perioperative ondansetron continued post hospital discharge. A randomized controlled blinded trial by McKenzie *et al.* in a population of patients similar to our sample group found that a prophylactic dose of 4 mg ondansetron *iv* was 30% more effective than placebo in preventing emesis postoperatively.¹⁰ A large meta analysis of 53 randomized controlled trials by Tramer *et al.* in 1997 concluded that if the risk of PONV is very high (e.g., 60%), for every 100 patients receiving an adequate dose of ondansetron 20 patients will not vomit who would have vomited had they

TABLE III OUTCOMES FOR EFFICACY ANALYSIS

Time frame	Outcome	Allocation		P value
		DCL n = 50	Placebo n = 52	
PACU	Nausea	12/50 (24.0)	10/51 (19.6)	0.593
	Vomiting	2/50 (4.0)	4/51 (7.8)	0.678
	≥ 1 dose of antiemetic given	10/50 (20.0)	10/51 (19.6)	0.885
SSU	Nausea	20/50 (40%)	16/51 (31.4)	0.365
	Vomiting	9/49 (18.37%)	9/52 (17.3)	0.889
	≥ 1 dose of antiemetic given	7/50 (14.0)	10/52 (19.2)	0.479
6-24 hr	Nausea	14/50 (28.0)	15/48 (31.3)	0.725
	Vomiting	5/50 (10.0)	12/48 (25.0)	0.04995
	≥ 1 dose of antiemetic given	1/50 (2)	2/48 (4.2)	0.292
Functional outcome	Return to usual activities (days)	1.510 (1.67)	4.065 (10.56)	0.098

No significant difference between groups. DCL = Diclectin®; PACU = postanesthetic care unit; SSU = short stay unit.

received placebo.¹¹ This represents an average number-needed-to-treat (NNT) of five to six when comparing prophylactic ondansetron with placebo. The effectiveness analysis in our study of DCL *vs* placebo found an absolute risk reduction of 0.169 (0.0254–0.085) which represents a NNT of 5.9, in a population with an incidence of vomiting of only 25%. Therefore it appears that the effect of DCL *vs* placebo is at least similar to the effect of ondansetron *vs* placebo for the prevention of late postoperative vomiting. DCL is longer acting than ondansetron and has minimal side effects. Further studies need to be undertaken to compare DCL to ondansetron to determine if DCL has a role in the prevention of perioperative nausea and vomiting.

Several instruments exist to measure the experience of chronic nausea and vomiting; these scales are useful to describe symptoms and the health-related quality of life in patients receiving chemotherapy. Examples include the nausea profile,¹² and the Rhodes scale.¹³ These lengthy multi-faceted measurement instruments are impractical for patients recovering from anesthesia, and several items are irrelevant for sedated patients. A validated and reliable scale to measure immediate PONV was not available as we began our study in 1998. In a study of droperidol in the postoperative period, Beattie *et al.* used a scale of 0 to 4 (0 = no nausea or vomiting, 1 = nausea, 2 = retching, 3 = vomited once, 4 = vomited more than once).¹ However, this scale conflates the two separate symptoms of nausea and vomiting. Moreover, the change in score representing a clinically important difference is not known. Subsequent to commencement of this

study a validated nausea and vomiting scale intended for postoperative use has been published by Apfel.¹⁴

Previous studies had noted a differing incidence of PONV according to the phase in the menstrual cycle.¹ We did not observe these menstrual cycle differences in our patient population. Furthermore, in the time between development and approval of this protocol, subsequent completion of this study and submission for review and publication, other risk indices have been developed and validated in which menstrual cycle has not been found to be an independent predictor of PONV although age and sex are. Further studies should be conducted for different day surgical procedures, with larger numbers to see if DCL is a helpful perioperative antiemetic medication.

Limitations of this study include the fact that we cannot comment on direct comparisons with other antiemetic drugs because we used placebo for the control group. However, our goal was to isolate the effect of DCL compared to placebo. Second, we did not use a validated nausea and vomiting scale; use of this outcome would be an advance of future randomized trials.

Strengths of this study design include the randomized, stratified, concealed design, using a placebo comparison with DCL. Blinding of the patients, clinicians, data collectors, investigators and biostatistician was assured until our analysis was complete. We used multivariate logistic regression to ensure that our findings were not confounded by important unequally distributed covariates. Our outcomes were patient-centred, and we extended evaluation in this trial beyond hospital discharge to include functional measures at home. Interestingly enough, even though

patients were randomized, the DCL group had significantly more patients with a positive history of PONV, a known risk factor. Also, again by chance, the physician protocol violations (administration of prophylactic antiemetic) occurred more in the placebo group. Finally, despite having chosen a patient population anticipated to have a very high incidence of PONV, the observed incidence even in the placebo group was only 25%, lower than the 60% often reported for laparoscopic gynecologic surgery.¹¹ All three of these factors would have favoured no difference in nausea and vomiting between the two groups, but despite this we were able to show a benefit within the DCL group. In conclusion, it appears that there is reason to further investigate the utility of DCL in prophylaxis of perioperative nausea and vomiting.

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