Reports of Original Investigations

The timing of haloperidol administration does not affect its prophylactic antiemetic efficacy

[Le moment choisi pour l'administration d'halopéridol n'affecte pas son efficacité anti-émétique prophylactique]

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Purpose: Postoperative nausea and vomiting (PONV) occurs frequently after general anesthesia. We evaluated the timing of 2 mg iv doses of haloperidol on the efficacy of this drug as a prophylactic antiemetic for PONV.

Methods: Ninety-four non-smoking female patients with a history of motion sickness and/or PONV (Apfel's simplified risk score = 3; predicted incidence of PONV = 60%) were eligible to participate in this randomized, double-blind study. Patients were divided into two groups. Group 1 patients received haloperidol 2 mg iv during induction of anesthesia. Group 2 patients received haloperidol 2 mg iv approximately 30 min before the end of surgery. The occurrence of nausea and vomiting, nausea scores, pain scores, sedation levels, and adverse effects (cardiac arrhythmias, and extrapyramidal effects) were recorded by a trained, blinded investigator.

Results: The percentages of patients who experienced PONV in the first 24 hr were similar for the two groups (Group 1 = 30%; Group 2 = 26%, $P = 0.645$). The incidence of PONV was significantly smaller in both groups than that predicted (60%) according to the patients' underlying risks (Group 1, $P = 0.004$; Group 2, $P = 0.001$). Nausea scores, pain scores, sedation scores, emergence times, and time to first rescue treatment were similar in the two groups. No adverse effects attributable to the study medication were observed.

Conclusion: The timing of administration of haloperidol 2 mg iv does not influence its antiemetic efficacy. The recovery profiles were also similar whether haloperidol was administered at the start, or at the end of surgery.

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Objectif : Les nausées et vomissements postopératoires (NVPO) surviennent fréquemment après une anesthésie générale. Nous avons observé si le moment choisi pour l'administration de doses de 2 mg d'halopéridol intraveineux (iv) avait une influence sur l'efficacité de ce médicament en tant qu'anti-émétique prophylactique pour le traitement des NVPO.

Méthode : Quatre-vingt quinze patientes non fumeuses avec des antécédents de mal des transports et/ou de NVPO (cotation d'Apfel simplifiée = 3 ; incidence prédite de NVPO = 60 %) ont été choisies pour participer à cette étude randomisée à double insu. Les patientes ont été divisées en deux groupes. Les patientes du groupe 1 ont reçu 2 mg d'halopéridol iv pendant l'induction de l'anesthésie. Les patientes du groupe 2 ont reçu 2 mg d'halopéridol iv environ 30 min avant la fin de la chirurgie. L'incidence des nausées et vomissements, les scores de nausée, les scores de douleur, les niveaux de sédation et les effets indésirables (arythmies cardiaques et effets extrapyramidaux) ont été enregistrés par un observateur formé et en aveugle.

Résultats : Les pourcentages de patientes ayant souffert de NVPO durant les premières 24 h étaient semblables dans les deux groupes (groupe 1 = 30 %; groupe 2 = 26 %, $P = 0,645$). Dans les deux groupes l'incidence de NVPO était significativement moins importante que prévue (60 %) selon les risques sous-jacents des patientes (groupe 1, $P = 0,004$; groupe 2, $P = 0,001$). Les scores de nausées, scores de douleur, scores de sédation, temps d'émergence

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de l'anesthésie et le temps jusqu'au premier traitement de secours étaient similaires dans les deux groupes. Aucun effet indésirable attribuable au médicament à l'étude n'a été observé.

Conclusion : Le moment choisi pour l'administration de 2 mg d'halopéridol *iv* n'a pas d'impact sur son efficacité anti-émétique. Les profils de rétablissement étaient également similaires, que l'halopéridol ait été administré au début ou à la fin de la chirurgie.

POSTOPERATIVE nausea and vomiting (PONV) are among the most common complaints following surgery performed under general anesthesia.¹ Droperidol, a butyrophenone, has frequently been used for preventing PONV after general anesthesia.² However, recent warnings regarding the safety of droperidol have limited its routine use.³

Haloperidol is also a butyrophenone with antiemetic properties, but without the U.S. Food and Drug Administration (FDA) restrictions. Haloperidol 2 mg was used for patients undergoing orthopedic or endoscopic urologic procedures to prevent intrathecal morphine-related PONV.⁴ The incidence of PONV was reduced compared to placebo (76%), but still remained quite high (55%). Prophylactic administration of haloperidol 1 mg proved to be an effective antiemetic for the early (0–2 hr) prevention of nausea and vomiting following gynecological surgery.⁵ Yet, the overall 24 hr incidence of PONV (41%) did not improve compared to placebo (56%). In these studies, haloperidol was administered at the start of anesthesia. Haloperidol is pharmacologically similar to droperidol, but guidelines for managing PONV recommend that droperidol should be administered at the end of anesthesia to maximize its antiemetic efficacy.⁶ Recently, we have shown that haloperidol 2 mg *iv* given 30 min before the end of surgery is effective in preventing PONV, and its efficacy is comparable to that of ondansetron 4 mg, for the first 24 hr after general anesthesia.⁷ Therefore, we designed this prospective, randomized-controlled trial to test the hypothesis that administration of haloperidol at the end of surgery will enhance its efficacy, as compared to peri-induction administration of this drug, when used for PONV prophylaxis.

Methods

This study was a randomized, prospective, double-blind controlled study, which was approved by the clinical Research Ethics Committee of the Buddhist Tzu-Chi Medical Center. Patients were eligible for the

study if they were ASA status I or II, aged between 20–65 yr, and scheduled for gynecologic, thyroid, breast, or plastic surgeries. All patients were female, non-smoking, with a history of motion sickness or/and PONV (Apfel's simplified risk score = 3).^{8,9} The exclusion criteria were obvious airway problems, overweight (body mass index > 25 kg·m⁻²), pregnancy, history of cardiac arrhythmia, chronic cough, psychiatric illness, clinically significant major organ disease, and consumption of any agent with antiemetic properties within 24 hr prior to commencing the study. Preoperative factors that influenced the incidence of PONV, such as history of PONV, or motion sickness were recorded.

In the preoperative holding area, patients were randomly allocated to one of the two groups, according to a computer-generated balanced block randomization scheme, until 47 patients were assigned to each group. The study drugs were prepared in two numbered syringes (containing either haloperidol 2 mg or saline, in a total volume of 2 mL) by a nurse anesthetist not otherwise involved in patient care, to maintain the double-blind nature of the study. The study drug was administered intravenously during the induction of anesthesia (syringe 1), or 30 min before the end of anesthesia (syringe 2). The randomized process and the identity of the study drug were blinded from the patients, the anesthesiologists during surgery, and the investigators who collected the postoperative data.

The first syringe (syringe 1, containing haloperidol 2 mg in Group 1, and saline in Group 2) was administered during induction of anesthesia. Anesthesia was induced with fentanyl 2 µg·kg⁻¹ *iv*, followed by lidocaine 1 mg·kg⁻¹ *iv*, propofol 3 mg·kg⁻¹ *iv*. Tracheal intubation was facilitated with rocuronium 0.6 mg·kg⁻¹ *iv*. Anesthesia was maintained with 2%–4% sevoflurane in 1 L·min⁻¹ in air and 1 L·min⁻¹ oxygen. Additional rocuronium or fentanyl was administered as required. Approximately 30 min before the end of anesthesia, the second syringe (syringe 2, containing haloperidol 2 mL in Group 2, and saline in Group 1) was administered. At the end of surgery, the combination of atropine 0.01 mg·kg⁻¹ and neostigmine 3 mg were administered intravenously for reversal of residual muscle relaxation, and the trachea was extubated. Anesthesia emergence time, defined as the time from discontinuation of sevoflurane to tracheal extubation, was recorded. A lead II electrocardiogram (ECG) was continuously monitored in all patients intraoperatively and during the first two hours postoperatively.

In accordance with previously published guidelines on conducting PONV studies, three postoperative time periods were examined: 0–2, 2–24, and 0–24

hr after the end of anesthesia.¹⁰ For the first two hours after anesthesia, in the postanesthesia care unit (PACU), the presence or absence of nausea and vomiting, nausea score, episodes of vomiting, levels of pain and sedation experienced by the patients, and adverse effects such as cardiac arrhythmia, or extrapyramidal effects, were recorded by a trained investigator, without prior knowledge of which treatment the patients had received. Sedation was assessed using the five-point Observer's Assessment of Alertness/Sedation scale (where 1 = awake/alert and 5 = deep sleep).¹¹ Nausea was scored by using a 10 cm visual analogue scale (VAS), with 0 representing no nausea, and 10 representing the worst possible nausea. If the patient was nauseated for ≥ 15 min, or experienced retching or vomiting during the observation periods, ondansetron 1 mg *iv* was administered as an initial rescue medication.¹² These patients were considered to have failed prophylactic antiemetic therapy, and the time to failure was recorded. If ondansetron failed to control the patient's symptoms, metoclopramide 10 mg *iv* was administered. Postoperative pain intensity was assessed by the patients themselves, using the same VAS in which 0 symbolizes no pain, and 10 represented the worst pain imaginable. When a patient complained of pain and requested analgesia, ketorolac 30 mg *iv* every six hours was given. Data were collected by a blinded investigator every six hours (except during sleep), after patient discharge from the PACU. For ethical reasons, no placebo group was included. Instead, the observed incidences for both treatment groups were compared to the predicted incidence before treatment, based upon Apfel's simplified risk score for PONV.^{8,9}

Statistical analysis

In this study, all patients had three risk factors for PONV (female, non-smoking, with a history of motion sickness or/and PONV). Based upon the Apfel's simplified risk score, the predicted incidence of PONV amongst our patients before antiemetic treatment was 60%.^{8,9} Sample size estimation was performed in accordance with the results of our recently published study.⁷ In that study, the incidence of PONV was 30% when 2 mg haloperidol was used at the end of surgery. We chose a risk reduction from 60% to 30% in the incidence of PONV to be clinically relevant. With an α error at 0.05 (two-sided) and a β error = 0.2, the estimated sample size requirement was 43 patients per group.¹³ Data analysis was conducted on a modified intention-to-treat population, which included patients who underwent surgery under general anesthesia, received study drug and had at least one post-treatment assessment.¹⁴ Continuous response variables,

TABLE I Patient characteristics and variables related to PONV

	Group 1 (<i>n</i> = 47)	Group 2 (<i>n</i> = 47)	<i>P</i> value
Age (yr); mean $\pm$ SD	45 $\pm$ 9	43 $\pm$ 10	
Weight (kg); mean $\pm$ SD	55 $\pm$ 7	56 $\pm$ 5	
History of PONV <i>n</i> (%)	19 (40)	16 (34)	
History of motion sickness <i>n</i> (%)	28 (60)	31 (66)	
<i>Surgical type</i>			
Gynecologic <i>n</i> (%)	12 (26)	10 (21)	
Thyroid <i>n</i> (%)	14 (30)	15 (32)	
Breast <i>n</i> (%)	12 (26)	15 (32)	
Plastic <i>n</i> (%)	9 (19)	7 (15)	
Duration of anesthesia (min); mean $\pm$ SD	142 $\pm$ 32	147 $\pm$ 31	0.718
Fentanyl consumption (μ g); mean $\pm$ SD	117 $\pm$ 20	119 $\pm$ 19	0.818
Emergence time (min); mean $\pm$ SD	11 $\pm$ 4	12 $\pm$ 5	0.121

PONV = postoperative nausea and vomiting.

presented as means $\pm$ SD, were analyzed using a Student's *t* test. Non-parametric data, including VAS scores presented as medians and ranges, were analyzed using the Mann-Whitney U test. Categorical data are presented as numbers and percentages, and were analyzed using the Chi-square statistic and the two-sided Fisher's exact test as appropriate. A *P* < 0.05 was considered significant. Commercial SPSS 10.0 software for Windows (SPSS Inc., Chicago, IL, USA) was used for the data analysis.

Results

Of 108 patients who were screened, ten did not meet the inclusion criteria, and four patients declined to participate. Of the remaining 94 patients who met the inclusion criteria, data collection was incomplete in five patients for the 2–24 hr observation period. None of these five patients experienced nausea or vomiting in the PACU. As part of a modified intention-to-treat analysis, these five patients were included in the final analysis (*n* = 47 in each group). Patient characteristics, duration of anesthesia, types of surgery, mean intra-operative fentanyl consumption, and anesthesia emergence times were similar in the two groups (Table I).

We observed that the 24 hr observed incidences of PONV (Group 1 = 30%; Group 2 = 26%, *P* = 0.645) were significantly less than predicted (60%) according to the patients' underlying risks (Group 1: *P* = 0.004; Group 2: *P* = 0.001). During the 0–2, 2–24, and the whole 0–24 hr observation period, the incidence of

TABLE II Frequency of PONV, requirement for rescue antiemetics, highest nausea score, and the time to first rescue antiemetic

	Group 1 (<i>n</i> = 47)	Group 2 (<i>n</i> = 47)	<i>P</i>
<i>0–2 hr</i>			
Nausea only <i>n</i> (%)	4 (9)	5 (11)	0.726
Vomiting <i>n</i> (%)	3 (6)	1 (2)	0.307
Total PONV <i>n</i> (%)	7 (15)	6 (13)	0.765
Rescue antiemetics <i>n</i> (%)	4 (9)	3 (6)	0.694
Highest nausea score mean (range)	4.6 (3-7)	4.5 (3-6)	0.880
<i>2–24 hr</i>			
Nausea only <i>n</i> (%)	6 (13)	4 (9)	0.503
Vomiting <i>n</i> (%)	4 (9)	3 (6)	0.694
Total PONV <i>n</i> (%)	10 (21)	7 (15)	0.421
Rescue antiemetics <i>n</i> (%)	6 (13)	5 (11)	0.748
Highest nausea score mean (range)	3.6 (2-5)	2.9 (2-4)	0.189
<i>0–24 hr</i>			
Nausea only <i>n</i> (%)	9 (19)	8 (17)	0.789
Vomiting <i>n</i> (%)	5 (11)	4 (9)	0.726
Total PONV <i>n</i> (%)	14 (30)	12 (26)	0.645
Rescue antiemetics <i>n</i> (%)	8 (17)	7 (15)	0.778
Highest nausea score mean (range)	4.4 (3-7)	3.7 (2-6)	0.163
Time to rescue (min); mean $\pm$ SD	183 $\pm$ 180	247 $\pm$ 199	0.541

PONV = postoperative nausea and vomiting.

TABLE III Sedation scores in the postanesthesia care unit

	Group 1 (<i>n</i> = 47)	Group 2 (<i>n</i> = 47)	<i>P</i>
<i>Times</i>			
5 min	2.1 (1-4)	2.4 (1-5)	0.226
30 min	1.7 (1-3)	1.7 (1-3)	0.723
60 min	1.1 (1-2)	1.3 (1-2)	0.218
90 min	1.1 (1-2)	1.1 (1-2)	0.654
2 hr	1.0 (1-2)	1.0 (1-2)	0.968

Data presented as mean (range).

nausea, vomiting, treatment with antiemetics, and the highest nausea scores were not significantly different between the two treatment groups. The time from the end of anesthesia to the first treatment with rescue antiemetic was comparable between groups (Table II). Among the patients who received rescue antiemetic in the first two hours, two of four patients (50%) in Group 1, and one of three patients (33%) in Group 2, needed further treatment in the 2–24 hr postoperatively. During the 24 hr observation period, four of eight patients (50%) in Group 1, and three of seven patients (43%) in Group 2 who received rescue antiemetic, required two or more treatments.

These differences did not reach statistical significance ($P = 0.782$). Furthermore, analysis without the five patients with incomplete data collection also showed no significant difference in the 24 hr incidence of nausea and vomiting (Group 1 = 31%; Group 2 = 27%, $P = 0.691$).

There were no significant differences between groups with respect to mean sedation scores (Table III), and postoperative VAS pain scores at corresponding time intervals while patients remained in the PACU.

Continuous ECG monitoring (lead II) was used throughout surgery and in the PACU; no patient in either group experienced cardiac arrhythmias. No extrapyramidal reactions, such as twitching, dystonia, akathisia, or rigor, were observed during the 24 hr observation period.

Discussion

Haloperidol is a dopamine D2 receptor antagonist, which is frequently used to treat psychiatric disorders, and has potent antiemetic properties in small doses.¹⁵ A meta-analysis suggested that parenteral single doses between 1 and 2 mg are efficacious, with minimal toxicity, for the prevention of PONV.¹⁶ Despite its documented antiemetic properties, the optimal timing of haloperidol administration, to optimize efficacy as a prophylactic antiemetic, has not been studied previously. A systemic review suggested that droperidol's antiemetic efficacy, when given at the end of surgery, may have been exaggerated.² Since haloperidol is pharmacologically similar to droperidol for the control of nausea and vomiting, and since the time to peak plasma concentration from intravenous injection is only five to 15 min,¹⁷ the drug might be more effective when administered at the end of surgery, thereby producing a more sustained antiemetic effect in the postoperative period. However, our results show that haloperidol 2 mg *iv* administered during induction of anesthesia, achieves similar antiemetic efficacy as compared to the same drug dose given 30 min prior to completion of surgery. As haloperidol has a longer elimination half-life (12–35 hr, average 16 hr) compared to droperidol (two hours),^{18,19} this may explain, at least partially, why the timing of administration does not affect haloperidol's antiemetic efficacy when used in the procedures studied. Yet, droperidol's antiemetic effect was influenced by the timing of administration, as a result of its relatively short half-life.

Aouad *et al.*⁵ reported that haloperidol 1 mg decreases the incidence and severity of PONV, but only during the early (0–2 hr) postoperative period. Parlow *et al.*⁴ showed that haloperidol doses of 1 and

2 mg were effective at reducing intrathecal morphine-related PONV, particularly during the first 12 hr of follow-up. However, these investigators also observed a trend towards greater efficacy of the 2-mg dose over the entire 24 hr period *vs* the first 12 hr. Büttner *et al.*¹⁶ suggested that doses exceeding 2 mg are not justified, because of an increased incidence of adverse effects such as sedation and extrapyramidal symptoms. Accordingly, we selected a 2-mg dose of haloperidol for this study, to achieve both the benefit of extending the duration of effect, and limiting the incidence of adverse effects.

Apfel's risk score has been shown to have a strong correlation between the predicted and observed incidence of PONV.²⁰ The correlation between the predicted (x) and the observed (y) incidence of PONV was $y = 1.08x - 0.07$.¹⁰ This risk score presented with favourable discriminating and calibration properties for predicting the risk of PONV.²¹ Its simplicity also makes it a useful tool for the assessment of the risk of PONV in clinical practice, and for research purposes.^{10,21} In our study, all patients had three risk factors of PONV (female, non-smoking, history of motion sickness or previous PONV). Given that the predicted incidence for PONV based upon the Apfel's risk score was 60% before antiemetic treatment amongst our patients, in our view it would have been unethical to have added a control group which excluded patients from prophylactic management of PONV. Furthermore, haloperidol has been shown previously to have superior antiemetic effects as compared to saline.^{4,5,15} Therefore, in lieu of a placebo comparison group, the observed incidences of PONV for both treatment groups were compared to the predicted incidence of PONV before treatment based upon the risk score. The results showed that 30% of Group 1 patients and 26% of Group 2 patients reported PONV within the first 24 hr after haloperidol treatment, which was significantly less than that predicted (60%) according to patients' underlying risks.

Over the past decade, large prospective clinical trials have clearly shown that PONV is attributable to associated risk factors and less by the surgery itself.^{10,21-23} Combination of the most important risk factors can be used in an operation-independent risk score to predict the incidence of PONV.^{8,9,22,24} In our study, we used Apfel's simplified risk score instead of selecting patients undergoing just one type of surgery. All patients in this study had the same risk score and furthermore, the types of surgery were similar for both groups. We believe that the study results are directly related to the study medications.

Although one of the adverse effects of haloperidol is sedation, this problem is very rare in the doses we

studied, and many clinicians consider the drug to be non-sedating.²⁵ In our study, there were no significant differences with respect to anesthesia emergence times and sedation scores between groups. Administering a low dose of haloperidol prior to emergence from anesthesia affected neither the sedation level in the PACU, nor the emergence time, compared to those patients receiving haloperidol at induction. All patients achieved the modified Aldrete score of discharge from the PACU within 30 min.

Haloperidol is closely related to droperidol. White *et al.*²⁶ demonstrated that standard prophylactic antiemetic doses of intravenous droperidol (0.625–1.25 mg) are not associated with clinically significant prolongation of the QT interval during or immediately after surgery, and there was no evidence of any adverse effect on cardiac rhythm. They concluded that the FDA recommendations for additional 12 lead ECG monitoring after administration of low dose droperidol are unwarranted. Recently, Aouad *et al.*⁵ observed that the mean QTc interval was not significantly different after intravenous haloperidol compared to ondansetron and saline. Therefore, we did not perform 12 lead ECGs to evaluate the QT interval. Instead, a lead II ECG was continuously monitored in all patients intraoperatively and during the first two hours postoperatively. There was no evidence of cardiac arrhythmia in any patient throughout the observation period. In a meta-analysis, 1,397 patients received different regimens (0.25–5 mg) of haloperidol, without evidence of cardiac arrhythmia.¹⁶ However, multiple ventricular arrhythmias have been reported previously, in association with high dose haloperidol in the intensive care environment.²⁷ Therefore, haloperidol should be used with care in patients who are critically ill.

Büttner *et al.*¹⁶ reported on 806 patients who received haloperidol 0.25–5 mg *iv*. Only one patient (0.1%) experienced extrapyramidal symptoms with a 4-mg dose. In our study, no patient suffered from psychometric side effects. However, the design of the trial cannot lead one to the conclusion that haloperidol 2 mg is entirely benign. The number of patients in previous and current studies may have been insufficient to detect rare adverse events. A larger number of subjects, and more subtle postoperative follow-up would be necessary to exclude all possible adverse events.

Although haloperidol has been shown to have potent antiemetic properties in small doses, several questions remain. Is haloperidol any safer than droperidol? What role might haloperidol play in regards to patient-controlled analgesia? How efficacious is the drug, as a rescue antiemetic, and what is the optimal dose?

In conclusion, the administration of haloperidol 2 mg *iv* given either during induction of anesthesia, or near completion of surgery, does not influence its efficacy in preventing PONV. The recovery profiles were similar whether haloperidol was administered at the start, or at the end of surgery.

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