Cost-effectiveness of prophylactic dolasetron or droperidol *vs* rescue therapy in the prevention of PONV in ambulatory gynecologic surgery

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Purpose: To assess the cost-effectiveness of prophylactic therapy (1.25 mg droperidol or 50 mg dolasetron *iv*) *vs* no prophylaxis (rescue therapy) for the prevention of post-operative nausea and vomiting (PONV) from a Canadian hospital perspective.

Methods: *Design:* A predictive decision analytic model using previously published clinical and economic evaluations, and costs of medical care in Canada. *Subjects*: Ambulatory gynecology surgery patients. *Interventions*: Three strategies administered prior to emergence from anesthesia were compared: 1.25 mg droperidol *iv*, 50 mg dolasetron *iv*; and no prophylaxis (rescue therapy).

Results: The base case mean cost per patient receiving dolasetron prophylaxis was $28.08 CAN compared with $26.88 CAN per patient receiving droperidol prophylaxis, resulting in a marginal cost of $1.20 CAN. This difference translated in an additional cost of $12.00 CAN for the dolasetron strategy per adverse event avoided over the droperidol strategy. The base case mean cost per patient not receiving prophylaxis was $26.92 resulting in marginal costs of $1.16 CAN and $0.04 CAN when compared to dolasetron and droperidol, respectively. Compared with the no prophylaxis strategy, dolasetron prophylaxis resulted in an incremental cost-effectiveness ratio of $5.82 CAN per additional PONV-free patient. The mean costs incurred per PONV-free patient were calculated to be $48.41 for the dolasetron strategy, $46.34 for the droperidol strategy and $70.83 for the no prophylaxis strategy.

Conclusions: Dolasetron and droperidol given intraoperatively were more cost-effective than no prophylaxis for PONV in patients undergoing ambulatory gynecologic surgery. The difference between the two agents was small and favoured droperidol. The model was robust to plausible changes through sensitivity analyses.

Objectif : Évaluer la rentabilité d'une thérapie prophylactique (1,25 mg de dropéridol ou 50 mg de dolasétron *iv*) *vs* aucune prophylaxie dans le but de prévenir les nausées et vomissements postopératoires (NVPO) dans le contexte d'un hôpital canadien.

Méthode : *Devis de recherche* : Un modèle analytique de décision prédictive basé sur les évaluations cliniques et économiques déjà publiées et sur le coût des soins médicaux au Canada. *Sujets* : Patientes de chirurgie gynécologique ambulatoire. *Interventions* : Trois prescriptions administrées avant le réveil ont été comparées; 1,25 mg de dropéridol *iv*, 50 mg dolasétron *iv*; et aucune prophylaxie.

Résultats : Le coût moyen de base par patient qui a reçu du dolasétron a été de 28,08 $ CAN comparé à 26,88 $ par patient qui a reçu du dropéridol, une différence de 1,20 $. Cette différence s'est traduite en un coût additionnel de 12,00 $ CAN, avec la thérapie au dolasétron comparée à la thérapie au dropéridol, pour chaque événement défavorable évité. Le coût de base moyen par patient sans prophylaxie était de 26,92 $ établissant une différence de 1,16 $ et 0,04 $ comparé au dolasétron et au dropéridol, respectivement. Comparée à la stratégie de non-prophylaxie, la prophylaxie au dolasétron a entraîné une rentabilité accrue au coût de 5,82 $ par patient supplémentaire sans NVPO. Le coût moyen encouru par patient sans NVPO a été de 48,41 $ avec le dolasétron, de 46,34 $ avec le dropéridol et de 70,83 $ sans mesure de prévention.

Conclusion : Le dolasétron et le dropéridol administrés pendant l'opération ont été plus rentables que l'absence de prophylaxie des NVPO chez des patientes subissant une intervention gynécologique ambulatoire. La différence de rentabilité était mince entre les deux médicaments, mais favorisait le dropéridol. C'est un modèle valable pour amener des changements plausibles dans les analyses de sensibilité.

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POSTOPERATIVE nausea and vomiting (PONV) are commonly reported adverse reactions in ambulatory surgery.[1] The incidence of post-operative nausea and vomiting after gynecologic surgery ranges from 61% to 75%.[2] Besides the discomfort caused by nausea and vomiting following surgery, PONV can contribute to the development of aspiration, wound dehiscence and increased bleeding.[3] Patients who experience PONV consume more resources and require additional health care professional time compared with those in whom these complications are avoided. This increased resource consumption leads to a higher cost of care from the hospital's perspective and a higher cost to the patient.[4]

Prophylaxis with antiemetics has been shown to reduce the incidence of PONV in ambulatory gynecological procedures by 15% to 30% (absolute risk reduction-ARR).[5–7] Use of antiemetics for the prevention and optimal management of PONV has been shown to: (1) improve patient satisfaction; (2) decrease recovery and discharge times; and (3) reduce unanticipated hospital admissions.[8–12]

Several different antiemetics have been studied for the prevention of PONV in gynecological surgery including metoclopramide, perphenazine, droperidol, ondansetron, and dolasetron, all of which have been associated with varying degrees of success.[3,5–7,9,13–15] In these clinical trials, the most effective of these agents were shown to be droperidol and the serotonin ($5\text{-}HT_3$) receptor antagonists (ondansetron and dolasetron). Although the acquisition cost of droperidol is less than the $5\text{-}HT_3$ receptor antagonists, its prophylactic use has been associated both with sedation and extrapyramidal side effects with dysphoria.[16,17] The prophylactic use of ondansetron and dolasetron is potentially associated with less serious adverse effects but at a higher acquisition cost.[18]

Dolasetron is a new $5\text{-}HT_3$ receptor antagonist that has been evaluated for the prevention of PONV in ambulatory gynecologic surgery.[6,15,19,20] The effectiveness of this agent appears to be similar to that of ondansetron.[21,22] From the Canadian institutional perspective, it is not known whether prophylaxis with dolasetron or droperidol is more cost-effective for the

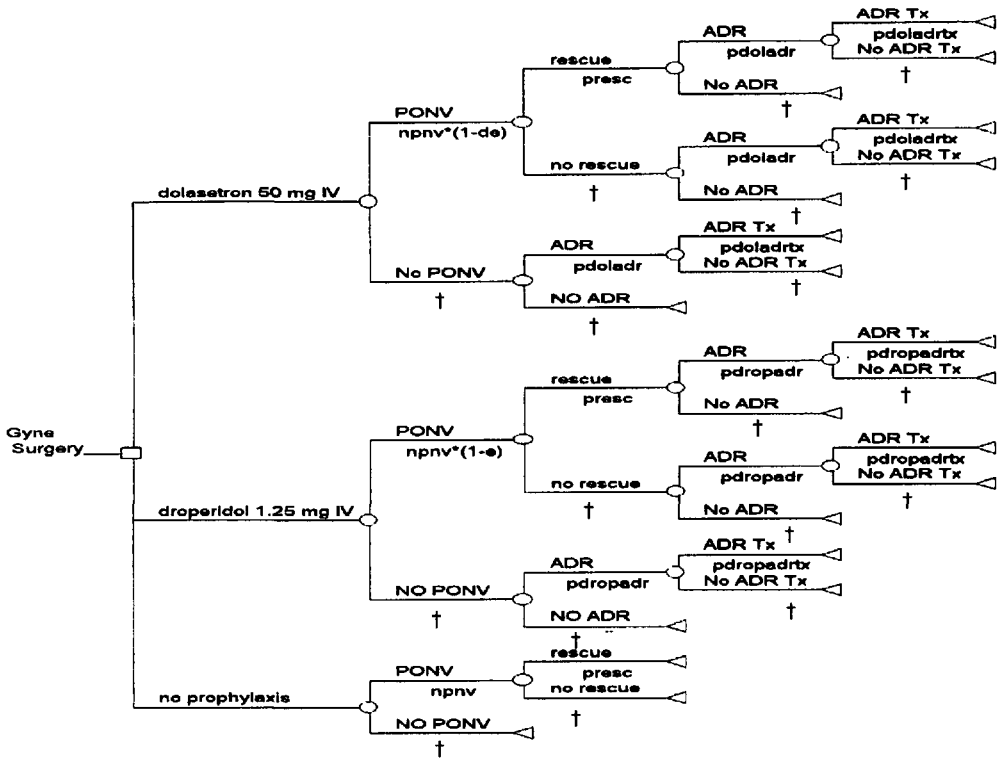

FIGURE 1 Decision analytic model used for the cost-effectiveness analysis
Legend: npnv*(1-de) = probability of PONV after prophlyaxis with dolasetron; npnv*(1-e) = probability of PONV after prophylaxis with droperidol ; npnv= probability of PONV after no prophylaxis; presc = probability of administering rescue antiemetic therapy; pdoladr = probability of adverse reaction to dolasetron; pdropadr = probability of adverse reaction to droperidol; pdoladrtx = probability of treatment of adverse reaction to dolasetron; pdropadrtx = probability of treatment of adverse reaction to droperidol.
† refers to 1 minus the probability of the alternative arm at each branch.

prevention of PONV. In addition, it is unknown whether the pharmacological prophylaxis of PONV is more cost-effective than rescue therapy. To our knowledge, there have been no published economic evaluations comparing dolasetron to other antiemetics for the prevention of PONV in ambulatory gynecologic surgery. The objectives of our study were to: 1) determine the cost-effectiveness ratios of prophylactic therapies and rescue therapy; and 2) utilizing a cost-minimization design, determine the least costly strategy between 50 mg dolasetron *iv* and 1.25 mg droperidol *iv* administered prior to anesthetic emergence for the prevention of PONV in ambulatory gynecologic surgery from the Canadian hospital perspective.

Methods

The decision model

A decision analysis model was used to assess the costs and outcomes associated with prophylactic therapy (1.25 mg droperidol *iv* or 50 mg dolasetron *iv*) *vs* no prophylaxis for the prevention of postoperative nausea and vomiting from a Canadian hospital perspective. Figure 1 shows the decision model used in our analysis created with DATA 3.0 (Treeage Software Inc. 1996). The prophylactic strategies consisted of intravenous administration of either drug prior to emergence from anesthesia. The primary endpoint was defined as the occurrence of either nausea or vomiting that necessitated intervention by a health care professional.

Probability estimates

The probability estimates for clinical outcomes used in the model were obtained from published clinical trials evaluating the prevention and treatment of PONV in ambulatory gynecologic procedures (Table I).[6,9,13,14,19] Numerous trials comparing droperidol with ondansetron have produced inconsistent results.[9,13,14,22-26] Although the results of some trials favour droperidol prophylaxis while others reveal ondansetron to be superior, most trials report no difference in efficacy between the two agents. The results from these similarly designed trials are not surprising for drugs with similar efficacy. Since ondansetron and dolasetron appear to have similar efficacy, we assumed that droperidol and dolasetron would also result in similar success rates for the prophylaxis of PONV.[21] When PONV occurred despite antiemetic prophylaxis, it was estimated that half of these patients would be treated with rescue therapy.[27] The pharmacological treatment for PONV was based on an algorithm in use at our institution's surgical daycare center. A step-wise approach is utilized in which 10 mg metoclopramide *iv* is the first-line agent for the treatment of PONV followed by 0.625 mg droperidol *iv* for patients who fail on metoclopramide. Prochlorperazine 10 mg *iv* is used after failure with the previous two antiemetic agents. The probabilities of failure with rescue medications were estimated to be 38% with metoclopramide and 15% with droperidol.[28,29] Prochlorperazine was assumed to be terminal therapy when used in this man-

TABLE I Probability and Cost Estimates

Parameter	*Base case value*	*Reference*
Probability of PONV (%)		6,9,13,14,19,21-27,28
Droperidol	42	
Dolasetron	42	
No prophylaxis	62	
Probability of rescue therapy (%)	50	27
Probability of readmission due to PONV (%)	0.0018	12
Probability of adverse effects (%)		16,17
Droperidol	20	
Dolasetron	10	
Probability of treatment of adverse effects (%)	50	27
Prophylactic anti-emetic cost ($)		CSU Pharmaceutical Sciences
Droperidol	8.59	
Dolasetron	9.84	
Cost of PONV ($)	27.29	Patient Costing Department, 39
Cost of rescue therapy ($)	9.96	CSU Pharmaceutical Sciences
Cost of treatment of adverse effects ($)		CSU Pharmaceutical Sciences
Droperidol	5.49	
Dolasetron	1.39	
Cost of readmission to a gynecological surgical ward ($/day)	746	Patient Costing Department

ner. The probability of readmission to the hospital due to PONV was obtained from a recently published Canadian trial by Fortier *et al.* in which the incidence, reasons, and predictive factors for unanticipated admissions after ambulatory surgery were determined.[12] Data pertaining specifically to patients undergoing gynecologic procedures were extracted from this trial.

Estimates for adverse reactions to droperidol were obtained from two published evaluations[16,17] whereas estimates for dolasetron were obtained from clinical trials in ambulatory gynecologic procedures.[19,20] Adverse effects due to droperidol included agitation and restlessness whereas only headaches were considered for dolasetron. The probability of treatment of adverse effects of droperidol and dolasetron was derived from the cost-effectiveness analysis of antiemetic therapy conducted by Watcha and Smith.[27] Due to the lack of significant medical intervention for minor adverse reactions and the infrequent occurrence of more significant adverse events (extrapyramidal reactions), these complications were not included as they would not affect the results of our analysis. Other investigators have dealt with minor and infrequent adverse reactions in a similar fashion.[30]

Cost estimates

This analysis was performed from the institutional perspective and assessed only direct medical costs incurred due to prophylactic therapy with droperidol or dolasetron, treatment of PONV, and treatment of adverse reactions. All costs were expressed in 1998 Canadian (CAN) dollars and discounting was not required due to the short time frame involved with the development and treatment of PONV.

The acquisition costs for prophylactic and rescue antiemetic therapy and agents used to treat adverse drug reactions were obtained from the Clinical Service Unit (CSU) Pharmaceutical Sciences' drug distribution computer database. The cost for the treatment of adverse effects included the use of 1 mg lorazepam *iv* for droperidol-induced agitation and restlessness and the use of 325 mg acetaminophen *po* for the treatment of dolasetron-induced headache. Preparation and delivery costs were based upon an analysis previously conducted by the investigators and were updated to reflect current costs.[31] Additional costs for nursing labour associated with direct patient care due to nausea and vomiting (comfort measures, monitoring, and clean up) were obtained from the hospital's Patient Costing Department. Labour costs of janitorial staff were not included since these costs were assumed to be fixed and not directly affected by PONV prophylaxis. The additional cost associated with re-admission to a gynecological surgical unit for one day was estimated by taking the total yearly clinical care expenditures for this unit and dividing this value by the number of patient days for this same period.

Pharmacoeconomic comparisons

The comparison of dolasetron with droperidol prophylaxis was analysed via cost-minimization technique due to the estimation of equivalent PONV outcomes. Cost-minimization analysis is appropriate when equivalence in effects is assumed between interventions.[32] Incremental cost-effectiveness ratios are appropriate when comparing the cost of a more expensive but more effective intervention with that of a less expensive but less effective intervention. The difference in cost is divided by the difference in effectiveness.[33] This ratio allows the assessment of cost per unit benefit of switching from one treatment strategy to the second treatment strategy. When a treatment is both more effective and less costly, this strategy is referred to as dominant and the calculation of cost-effectiveness ratios are unnecessary. Thus, in this analysis involving multiple comparisons, incremental cost-effectiveness ratios were used when appropriate.

Sensitivity analyses

Estimates of the probabilities of PONV, rescue therapy, readmission, adverse drug reactions, treatment of adverse reactions as well as costs of antiemetics, vomiting, and hospitalization were varied over a plausible range of values. We used univariate sensitivity analyses to calculate the effects of these changes on clinical outcomes, costs, and cost-effectiveness for all model variables. Multivariate sensitivity analyses were also conducted by combining the most extreme estimates of costs and probabilities. Threshold values were determined for probabilities and costs when applicable.[34]

Results

Base case analysis

After surgery, the proportion of patients who developed nausea and vomiting after receiving prophylaxis with dolasetron and droperidol was 42% compared with 62% of patients not receiving prophylaxis. This difference translates to an absolute risk reduction (ARR) of 20%. Thus, five patients undergoing gynecological ambulatory surgery would need to receive prophylaxis (number needed to treat, NNT) with either of these agents to result in one additional PONV-free patient.

Overall, the risk of a significant adverse drug reaction in patients receiving prophylactic therapy with droperidol was two times greater than for patients

receiving prophylaxis with dolasetron (20% and 10%, respectively). Thus, 10 patients would need to be treated with droperidol to harm one additional patient (number needed to harm, NNTH).

The base case mean cost per patient receiving dolasetron prophylaxis was $28.08 CAN compared with $26.88 CAN per patient receiving droperidol prophylaxis resulting in a marginal cost of $1.20 CAN. The base case mean cost per patient not receiving prophylaxis was $26.92 CAN resulting in marginal costs of $1.16 CAN and $0.04 CAN when compared with dolasetron and droperidol, respectively. When compared with the no prophylaxis strategy, droperidol prophylaxis was both less costly and more effective and, thus, was the dominant strategy. Finally, when compared with the no prophylaxis strategy, dolasetron prophylaxis resulted in an incremental cost-effectiveness ratio of $5.82 CAN per additional PONV-free patient. The mean costs incurred per PONV-free patient were calculated to be $48.41 CAN for the dolasetron strategy, $46.34 CAN for the droperidol strategy and $70.83 CAN for the no prophylaxis strategy. Overall, prophylaxis with dolasetron or droperidol is more cost-effective than no prophylaxis. Between the two antiemetic agents, droperidol prophylaxis is the least costly strategy. When compared with the droperidol strategy, dolasetron prophylaxis prevents one additional significant adverse event at an additional cost of $12.00 CAN.

Sensitivity analyses

Extensive univariate sensitivity analyses were conducted (Table II). These analyses revealed that the model was robust to changes in both probabilities and costs. Threshold values were determined for probabilities of PONV and costs of antiemetic agents. Multivariant analysis was performed for the probabilities of PONV for droperidol and dolasetron (Figure 2). This analysis showed that as differences in the incidence of PONV between the prophylactic and the rescue strategies decreased, so did the economic advantage of the prophylactic strategies.

Discussion

As in all areas of pharmacotherapeutics, clinicians must consider both the clinical attributes and costs of using particular drug therapies. We have attempted to accurately represent, using a decision analytic model, the costs and outcomes associated with prevention of PONV using two different antiemetics compared with the costs and outcomes associated with no prevention. Previous authors have used similar methodologies to compare other strategies of PONV prophylaxis in adult patients.[9,27]

Three cost-effectiveness analyses in adults undergoing ambulatory surgery have been conducted from the United States' (US) institutional perspective. Watcha *et al.* utilized a predictive decision analytic model to compare the relative cost-effectiveness of ondansetron, droperidol, and metoclopramide for the prevention of PONV in patients at high risk for PONV.[27] Droperidol was shown to be more cost-effective than the other two agents with a cost per nausea-free patient $40.93 US less than metoclopramide and $25.76 US less than ondansetron. In addition, the cost per emesis-free patient was $49.22 US less than metoclopramide and $35.41 US less than ondansetron. A major limitation of this study was the omission of the reporting of the doses of the drugs studied. Tang *et al.* prospectively evaluated the effectiveness, cost-effectiveness, and cost-benefit of ondansetron 4 mg *iv* administered before or after outpatient gynecologic laparoscopic surgery compared with placebo in a randomised double-blind fashion.[35] The authors concluded that ondansetron administered immediately before the end of surgery was associated with the highest patient satisfaction, the lowest nausea and vomiting scores, and the lowest cost-effectiveness ratios. In patients undergoing elective gynecologic laparoscopic procedures, Tang *et al.* compared the cost-effectiveness of prophylaxis with 4 mg ondansetron *iv* with 0.625 or 1.25 mg droperidol *iv* or placebo using a decision analytic model which was based on a concurrent prospective trial.[9] These authors determined that the costs per PONV-free patient were $11.93 US for 1.25 mg droperidol *iv*, $8.39 US for 0.625 mg droperidol *iv*, $28.49 US for ondansetron, and $39.19 US for placebo. Thus, both of the analyses which compared ondansetron with droperidol found droperidol to be the most cost-effective strategy. All of the analyses published to date, including ours, show that administering a prophylactic agent to be more cost-effective than the no prophylaxis strategy. Of note, an analysis in children comparing granisetron, another 5-HT_3 antagonist, with placebo found that the placebo strategy was more cost-effective.[36]

The present study is the first cost-effectiveness analysis comparing dolasetron with droperidol for PONV prophylaxis in a high-risk population such as those patients who undergo ambulatory gynecologic procedures. Both droperidol and dolasetron were more cost-effective than no prophylaxis and the cost per PONV-free patient was very similar between dolasetron and droperidol. An important assumption made in the analysis was that the efficacy of droperidol and dolasetron were similar. This assumption is supported by results of dolasetron PONV prophylaxis trials in which the efficacy rate was 60% which is similar

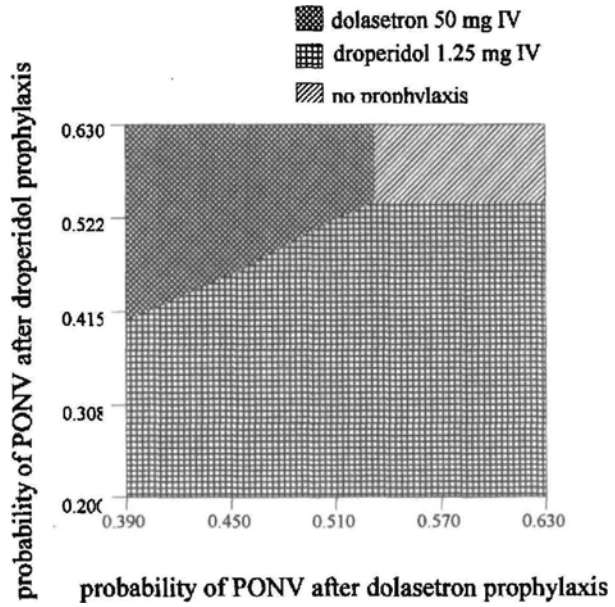

FIGURE 2 Two-way sensitivity analysis of the probabilities of PONV with droperidol and dolasetron

to the results obtained from those studies using ondansetron.[6,19,20,21,37,38]

Estimation of the efficacy rates for the drugs and placebo in our analysis was complicated by the varying definitions and detection techniques for nausea, vomiting, and overall response to therapy used in the published literature. Sensitivity analysis in our model indicates that the pharmacologic prophylaxis strategies are the least costly when the incidence of PONV in the no prophylaxis group is greater than 52%. Thus, our results cannot be extrapolated to surgical procedures that have a low incidence of PONV.

Cost-effectiveness ratios for dolasetron and droperidol were similar in our analysis, with droperidol having a slightly lower cost per PONV-free patient. If the cost of dolasetron decreased from $9.84 CAN as utilised in our model to less than $8.60 CAN, or its effectiveness increased to greater than 60% , dolasetron would have had the lowest cost per PONV-free patient.

Some clinicians are concerned about the higher rate of adverse reactions to droperidol such as sedation and extrapyramidal symptoms (EPS), although EPS is rare when lower doses (e.g. 0.625 - 1.25 mg) are used.[16,17] Our model did not take into account the costs associated with treating EPS because the very low incidence of

TABLE II Univariate Sensitivity Analyses

Parameter	*Base value (range varied)*	*Mean cost per PONV-free patient ($/PONV-free patient)*		
		Dolasetron strategy	*Droperidol strategy*	*No prophylaxis strategy*
Probability of PONV				
Dolasetron prophylaxis	0.42 (0.39 - 0.63)	43.90 - 100.53*	-	-
Droperidol prophylaxis	0.42 (0.20 -0.63)	-	21.66 - 97.28†	-
No prophylaxis	0.62 (0.51 - 0.89)	-	-	45.18 - 351.25‡
Probability of rescue therapy	0.50 (0.25 - 0.99)	46.63 - 51.92	44.55 - 49.84	66.80 - 78.72
Probability of readmission due to PONV	0.00018 (0.0001 - 0.06)	40.36 - 72.72	38.29 - 70.65	52.70 - 125.60
Probability of adverse effects				
Dolasetron - headache	0.10 (0.04 - 0.12)	48.41 - 48.42	-	-
Droperidol - agitation and restlessness	0.20 (0.05 - 0.50)	-	46.27 - 46.48	-
Probability of treatment of adverse effects				
Dolasetron	0.05 (0 - 99)	48.40 - 48.64	-	-
Droperidol	0.05 (0 - 99)	-	46.25 - 48.12	-
Antiemetic Cost ($)				
Dolasetron	9.84 (5.00 - 20.00)	40.07 - 65.934§	-	-
Droperidol	8.59 (5.00 - 15.00)	47.92 - 49.30	39.66 - 58.28¶	69.72 - 72.82
Cost of PONV ($)	27.29 (10.00 - 100.00)	35.90 - 101.07	33.82 - 99.00	42.63 - 189.47
Cost of readmission to a gynecological surgical ward ($)	746.00 (350.00 - 1400.00)	44.11 - 55.52	42.04 - 53.05	61.14 - 86.84

* Threshold value of 0.406; droperidol is the least costly strategy at values greater than the threshold
† Threshold value of 0.432; droperidol is the least costly strategy at values beneath the threshold
‡ Threshold value of 0.516; no prophylaxis is the least costly strategy at values beneath the threshold
§ Threshold value of $8.60; droperidol is the least costly strategy at values greater than the threshold
¶ Threshold value of $9.80; droperidol is the least costly strategy at values less than the threshold

this adverse effect would have little effect on the cost per PONV-free patient and would not alter the rank order of the strategies. Since the cost-effectiveness ratios were similar and the incidence of significant adverse effects was lower with dolasetron, it could be argued that the most appropriate strategy for PONV prophylaxis in high-risk patients was 50 mg dolasetron *iv* intraoperatively despite the lower cost per PONV-free patient with droperidol. If the dolasetron strategy was used, it would cost an additional $12.00 CAN above the droperidol strategy to avoid one adverse event with droperidol. We believe that the avoidance of these adverse events is worth the slight additional expense.

An assumption made in our model, as in all previously published analyses, was that patients placed the same importance on the avoidance of PONV as they did on the avoidance of side-effects to anti-emetic therapy. This assumption may not be accurate as data show that patients are willing to accept some side effects of an anti-emetic agent if it decreases PONV.[8] A prospective cost-utility analysis would be required to account for this factor.

Since our analysis is based on a model that utilised probabilities of success, failure, and adverse reactions reported in the literature, it is important to validate these estimations in a controlled fashion. As there have been no published randomised, controlled trials (RCT) comparing dolasetron with droperidol for prophylaxis of PONV, such a RCT should be the focus of future research. An economic analysis that prospectively assesses resource utilisation of study patients should be "piggybacked" onto such a trial.

In conclusion, our analysis demonstrates that dolasetron and droperidol given intraoperatively are potentially more cost-effective than no prophylaxis for PONV in patients undergoing gynecologic day-case surgery. The predicted difference between the costs associated with the dolasetron and droperidol strategies is small and is dependent on costs and probabilities utilised in the model. Although dolasetron prophylaxis has a slightly higher cost, our model predicts that it would result in fewer significant adverse events.

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