

Phenothiazine vs 5HT3 Antagonist Prophylactic Regimens to Prevent Post-Anesthesia Care Unit Rescue Antiemetic: An Observational Study

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Abstract

Purpose: Our practitioners are asked to consider a patient's postoperative nausea and vomiting (PONV) risk profile when developing their prophylactic antiemetic strategy. There is wide variation in employed strategies, and we have yet to determine the most effective PONV prophylactic regimen. The objective of this study is to compare prophylactic antiemetic regimens containing phenothiazines to 5HT3 antagonists for effectiveness at reducing the incidence of Post-Anesthesia Care Unit (PACU) rescue antiemetic administration. **Methods:** This is an observational study of 4392 nonsmoking, women who underwent general anesthesia for breast surgery from 1/1/2009 through 6/30/2012. Previous history of PONV or motion sickness (HxPONV/MS) and the use of PACU opioids were recorded. Prophylactic antiemetic therapy was left to the discretion of the anesthesia care team. We compared phenothiazines and 5HT3 antagonists alone and with a glucocorticoid to determine the most effective treatment regimen in our practice for the prevention of the administration of PACU rescue antiemetics. **Results:** Patients who received a phenothiazine regimen compared to a 5HT3 antagonist regimen were less likely to have an antiemetic administered in the PACU ($p = 0.0100$) and this significant difference in rates holds in a logistic regression model adjusted for HxPONV/MS and PACU Opioid use ($p = 0.0103$). **Conclusions:** Based on our findings our clinicians are encouraged to administer a combination of a phenothiazine and a glucocorticoid in female, nonsmoking surgical breast patients for the prevention of PACU rescue antiemetic administration.

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Keywords

Phenothiazines, 5HT3 Antagonists, Prophylactic Antiemetics, PACU Antiemetic Administration

1. Introduction

Without prophylactic antiemetic therapy, 48% to 70% of female patients undergoing breast surgery will suffer from early postoperative nausea and vomiting (PONV) [1]-[3] and require post-anesthesia care unit (PACU) rescue antiemetic administration. Current PONV consensus guidelines advocate multimodal prophylactic antiemetic therapy for higher risk patients [4]. Generally agreed upon risk factors include gender, smoking status (smokers versus nonsmokers), previous history of PONV or motion sickness (HxPONV/MS), PACU opioid usage, and type/anatomical location of surgery [4]-[6]. Multimodal prophylactic antiemetic therapy has shown to greatly reduce the incidence of PONV [2] [3]. There is debate surrounding the use of multimodal prophylactic therapy based on risk factors [7]-[10]. Multiple studies have been done on multimodal prophylactic antiemetic therapy; particularly regimens containing phenothiazines [11]-[13] and 5-hydroxytryptamine type 3 (receptor) antagonists (5HT3) [14]-[17]. While Apfel *et al.* [18] submit that prophylactic antiemetic interventions (specifically: droperidol, ondansetron and dexamethasone in doses used in their study) have roughly similar effects in reducing the incidence of PONV, comparisons between phenothiazines and 5HT3 antagonists are few and equivocal. In a randomized controlled trial (N = 78 patients), Chen *et al.* showed that a phenothiazine (prochlorperazine) was superior to a 5HT3 antagonist (ondansetron) in preventing PONV [13]. While Gan *et al.* showed a 5HT3 antagonist (granisetron, N = 46) was not significantly superior to a phenothiazine (promethazine, N = 47) in incidence of rescue antiemetic administration at 0 to 6 hours. However, there was a significant difference in incidence of rescue antiemetic administration at 24 hours [19]. Furthermore, their study showed a combination of the two antiemetics (N = 45) was superior to either drug alone.

Our practitioners are asked to consider a patient's PONV risk profile when developing their prophylactic antiemetic strategy; we have yet to determine the most effective PONV prophylactic regimen. Given our wide variation of prophylactic antiemetic strategies, we focused on a subset grouping phenothiazines versus 5HT3s. The primary objective of this study is to exploit these practice variations to compare prophylactic antiemetic regimens containing: phenothiazines to 5HT3s for effectiveness at reducing the incidence of PACU rescue antiemetic administration in this high risk population: female, nonsmoking patients undergoing breast surgery. Additionally, to assess multimodal prophylactic antiemetic strategies we evaluated our subgroup of phenothiazines and 5HT3s with a glucocorticoid for effectiveness in reducing the incidence of PACU rescue antiemetic administration.

2. Materials and Methods

Ethical approval for this study DR07-0525 was provided by the Institutional Review Board 4 (IRB 4) of MD Anderson Cancer Center on 20 September 2007. The original IRB 4 approval Chairperson was Linda Elting, Ph.D. The new Chairperson is Scott B. Cantor, Ph.D. The physical address is 1MC Unit 1637, 7007 Bertner St., Houston, Texas 77030. This is a retrospective observational study whereby a waiver of informed consent was granted. An anesthesia information management system (AIMS), the Picis Anesthesia Manager, was used as the source for all perioperative variables of patient demographics and care.

Inclusion criteria were all consecutive and unique (first case) female adult (age > 17 years), nonsmoking patients who underwent an anesthetic for a breast or axillary procedure that lasted no more than six hours of anesthesia time, recovered in our PACU from 1/1/2009 through 6/30/2012 and received at least one prophylactic antiemetic. Exclusion criteria were cases lasting longer than 6 hours. There were no cases with missing data. All patients received a general anesthetic: typically pre-medicated with midazolam, induced with propofol, possibly an opioid, and maintained with a volatile anesthetic most commonly desflurane. Nitrous oxide, a known emetogenic agent, was not used on these cases. Prophylactic antiemetic interventions considered were phenothiazines (promethazine, chlorpromazine and prochlorperazine), 5HT3s (ondansetron, granisetron and palonosetron) and other antiemetics: droperidol, glucocorticoids {dexamethasone and hydrocortisone}, scopolamine, metoclopra-

mide, NK1 inhibitors {aprepitant} or total intravenous anesthesia (this was considered a prophylactic antiemetic intervention equal to single drug antiemetic administration). Additionally, we distinguished between patients with and without other risk factors: HxPONV/MS and patients who received PACU opioids.

Patients were given PONV prophylactic agents based on individual practitioners' discretion. Our practitioners are encouraged to administer more than one antiemetic to patients with more than one risk factor (female gender, nonsmoking status and previous HxPONV/MS). This individual practitioner discretion has led to a wide variation in the number and type of prophylactic antiemetic drugs administered to these high risk patients. This study evaluated 4392 patients with the following breakdown of the number of prophylactic antiemetics: 527 (12%) received one, 1316 (30%) received two, 2047 (47%) received three and 502 (11%) received four or more. Given the wide variation in the number and type of prophylactic antiemetic administration strategies, we were most interested in the 1688 patients that received either a phenothiazine (N = 276) or 5HT3 (N = 1412) without the other. These 1688 patients comprise our subsample which was used for our primary analysis to compare the effectiveness of phenothiazines versus 5HT3s to reduce the incidence of PACU rescue antiemetic administration. Thus we categorized prophylactic antiemetic administration into four groups who received: 1) 5HT3, 2) phenothiazine, 3) both (phenothiazine and 5HT3), and 4) neither (phenothiazine nor 5HT3). Antiemetics in our PACU are only administered on an as needed basis for PONV. The endpoint for this study is PACU rescue antiemetic administration as recorded by the PACU RN.

Statistics

PONV rate differences among treatment groups were assessed using Fisher's exact tests. Odds ratios (OR) and the associated exact 95% confidence limits based on the method of Thomas [20] are reported. A multivariate logistic regression model was fitted to the data in order to compare PONV rates among treatment groups while adjusting for two confounding risk factors, HxPONV/MS (yes/no) and PACU narcotic administration (yes/no). Treatment group, HxPONV/MS and PACU narcotic administration were considered a class variable with reference levels of antiemetic regimens containing 5-HT3 antagonist, no HxPONV/MS and no PACU narcotic administration, respectively. Statistical significance was defined as $p < 0.05$. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Table 1 indicates the overall PACU rescue antiemetic administration rate was 10.2%. The PACU rescue antiemetic administration rate among the four antiemetic regimen groups is significantly different ($p < 0.0001$). The PACU rescue antiemetic administration rate for phenothiazines versus 5HT3 containing regimens was 9.4% and 15.4%, respectively. The lowest PACU rescue antiemetic administration rate was observed for the patients receiving a prophylactic antiemetic regimen containing both a phenothiazine and a 5HT3 (7.7%). The group that received "Neither" (*i.e.*, no phenothiazine nor 5HT3 antagonists) had a lower incidence of PACU rescue antiemetic administration (12.1%) than the 5HT3 receptor antagonist group (15.4%). The Neither group (N = 149) had received other prophylactic antiemetics, however, there was not a big enough subset of antiemetics for further analysis.

Table 2 presents the pairwise comparisons of phenothiazine regimens versus 5-HT3 regimens. As indicated in **Table 2**, generally phenothiazine regimens are more effective than 5-HT3 regimens ($p = 0.010$). This comparison was not significant ($p = 0.44$) in the single prophylactic antiemetic scenario possibly due to the small phenothiazine sample ($n = 27$). However, when a glucocorticoid is added to the antiemetic regimens there is a significant difference ($p = 0.031$) between rates for phenothiazine and 5-HT3 regimens (**Table 2**) and this significant difference holds in a logistic regression model adjusted for patients with a HxPONV/MS (36.4%) and who were administered opioids in the PACU (71.3%) $p = 0.04$.

4. Discussion

Evaluation of our clinical practice shows a wide variation in prophylactic antiemetic regimens. This observational study of 4392 female, nonsmoking patients undergoing breast surgery demonstrates that PACU rescue antiemetic administration rate is lower among patients receiving a phenothiazine regimen compared to those receiving a 5-HT3 antagonist regimen in our institution. These findings add to the scarce and equivocal literature of direct comparisons between prophylactic administrations of phenothiazines versus 5HT3s [13] [19].

Table 1. PACU rescue antiemetic administration rate by antiemetic regimen.

Antiemetic Regimen	PONV			p-Value
	No	Yes	Total	
5HT3	84.6%	15.4%	1412	<0.0001
Phenothiazine	90.6%	9.4%	276	
Both	92.3%	7.7%	2555	
Neither	87.9%	12.1%	149	
Total	89.8%	10.2%	4392	

Table 2. PACU rescue antiemetic administration—bivariate comparison of Phenothiazine vs. 5HT3.

Setting	Antiemetic Administration Rate		Odds Ratio		p-Value	
	Phenothiazine	5HT3	Ratio	95% Confidence Limits		
All Combinations	9.4% (n = 276)	15.4% (n = 1412)	0.573	0.373	0.880	0.010
Single Agent	11.1% (n = 27)	16.8% (n = 376)	0.621	0.182	2.126	0.44
w/Glucocorticoid	9.6% (n = 240)	15.0% (n = 990)	0.603	0.379	0.959	0.031

We recognize certain limitations of this study. First, the data have been retrospectively collected; the quality of data entry might suffer from inaccuracies and underreporting such as HxPONV/MS. However, we are confident about the integrity of the data concerning the drugs administered and demographic data. We acknowledge that there could be nursing practice differences with regard to treatment, however we do not believe that this was biased to one prophylactic regimen. Second, data capture was only available for an observation window limited to the PACU (less than 24 hours); there is a need to obtain information beyond the PACU period. Nevertheless, we believe this surrogate endpoint for PONV in the PACU is valid and represents “real world” effectiveness of prophylactic antiemetics and provides useful information about PONV prophylaxis regimens and PACU rescue antiemetic administration to practitioners as have others [21]. Third, PACU antiemetic administration was used as a surrogate for implied nausea and/or vomiting; we realize a PACU RN has discretion, but the orders were for “as needed for nausea and/or vomiting”, this assumption is similar to the reasoning of Habib *et al.* [22] that patients who received PACU antiemetics suffered from nausea and/or vomiting. Finally, this is a single center study; multicenter collaboration needs to be done.

Although the anesthesia literature is replete with PONV studies, there exist many controversies within prophylactic antiemetic regimen recommendations. First, the Practice Guidelines for Post-Anesthesia Care by the American Society of Anesthesiologists Task Force state “(we) are equivocal regarding whether multiple pharmacologic agents would be used for the prophylaxis of nausea and vomiting” [23]; whereas the Society for Ambulatory Anesthesia Consensus Guidelines for the Management of PONV recommend administration of combination multimodal prophylactic antiemetic therapies in patients that are high risk [4]. And both societies leave to the discretion of the attending anesthesiologist which therapies to administer. There is also controversy about the effectiveness of clinical prediction models [24]. These controversies can be settled by more studies addressing the specifics of various prophylactic antiemetic drug interventions and patient experiences in the PACU and ward/home (24 hours) to elucidate “the best practice” for the prevention of PACU rescue antiemetic administration and PONV.

5. Conclusion

In this study, we gleaned our AIMs and evaluated our PONV prophylactic antiemetic administration strategies in this high risk PONV population (female, non-smoking, breast cancer surgical patients); specifically, the effectiveness of regimens containing phenothiazines compared to 5HT3 antagonists in our clinical practice. Evaluation of our clinical practice showed a wide variation in prophylactic antiemetic regimens. In conclusion, based on our findings our clinicians are encouraged to administer a combination of a phenothiazine and a glucocorticoid in female, nonsmoking surgical breast patients for the prevention of PACU rescue antiemetic administration.

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