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Effect of Addition of Ondansetron for PONV Prophylaxis in Ambulatory Hysteroscopy with Propofol Total Intravenous Anesthesia

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Background: In female patients undergoing hysteroscopy in outpatient unit, total intravenous anesthesia (TIVA) technique with propofol is frequently used as induction and maintenance drug. Ondansetron is often given as an antiemetic drug even if propofol infusion has proven to have antiemetic effect. We hypothesized that the addition of ondansetron prophylaxis does not alter incident of postoperative nausea and vomiting (PONV) and post discharge nausea and vomiting (PDNV) in patients undergoing hysteroscopy with propofol TIVA technique in the ambulatory setting.

Method: One hundred and ten female adult patients scheduled for hysteroscopy in an ambulatory setting were randomized into a control group (C group) who did not received any antiemetic drug other than propofol infusion and an ondansetron group (O group) who received 4 milligrams of ondansetron after induction. Patients' baseline characteristics, including Apfel's score, duration of anesthetic and surgical procedure, and dose of any drug given were recorded. The incidence of PONV was recorded in PACU and 2-day incidence of PDNV was gathered by telephone interview within 2 weeks.

Results: There were no incidences of PONV reported in PACU in both groups (P>0.99). The overall incidences of PDNV were lower in the control group, but not statistically significant (14% vs 5.9%; P=0.2). Daily incidences of PDNV had no statistic differences. Pain scores, inpatient admissions, and other complication incidences had no significant differences.

Conclusion: Addition of ondansetron prophylaxis does not alter incident of PONV and PDNV in patients undergoing hysteroscopy with propofol TIVA technique in the ambulatory setting.

Keywords: ambulatory anesthesia, hysteroscopy, ondansetron, PDNV, PONV, propofol TIVA

วิสัญญีสาร 2563; 46(3): 154-9. • Thai J Anesthesiol 2020; 46(3): 154-9.

Introduction

In female patients who are undergoing hysteroscopy in outpatient units, propofol total intravenous anesthesia (TIVA) technique is commonly used as induction and maintenance method. Anesthesia maintained by propofol infusion has been proven to have antiemetic effect.[1] However, ondansetron is still concomitantly given to prevent postoperative nausea and vomiting, which can lead to routine practicing and cause patient unnecessary drug administration.

Postoperative nausea and vomiting (PONV) is the most common anesthetic complication in PACU, in which severe case can lead to prolong hospital stay or unexpected admission in outpatient case. Furthermore, ambulatory patients also have incidence of post-discharge nausea and vomiting (PDNV) which

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Received 22 Feb 2020, Revised 10 Mar 2020, Accepted 10 Mar 2020

can be defined by experiencing any nausea or vomiting symptom after discharged from hospital. The overall incidence of PDNV in 7 days can be as high as 56.9%, with the highest single-day incidence at post-operative day 0.[2] The incidence of PDNV then significantly decreases after post-operative day 2.[2] Female population has higher 7-day PDNV incidence at 63.6%.[2]

Unlike major operation, the incidence of PONV in minor gynecological procedure was founded to be 0-2.5% depending on anesthetic technique used.[3] Thus; in patients undergoing hysteroscopy under TIVA technique, while the patients themselves usually have at least two or more risks according to Apfel's simplified risk score for predicting PONV[4]; there are also protective factors such as: TIVA technique, and propofol infusion. We questioned the necessity of routinely adding ondansetron as antiemetic drugs for benefit of cost-effectiveness and general anesthetic practice.

Objectives

Objective of the study was to find out the effectiveness of addition of ondansetron for prophylaxis of PONV/PDNV in patients undergoing ambulatory hysteroscopy with propofol TIVA technique.

Methods

The study is a prospective randomized controlled trial conducted in ambulatory patients undergoing hysteroscopy at Ramathibodi Hospital. After the trial has been approved by Ramathibodi ethic committee, the trial was conducted from March 2014 to June 2015. Inclusion criteria were female patients ranged from 18 to 65 years old with ASA physical status I or II whom were undergoing hysteroscopy with propofol TIVA. Pregnancy, antiemetic premedication, plan of artificial airway, history of arrhythmia, or any experimental drug allergy was excluded.

All participants were asked for informed consent orally via telephone. Written informed consent was obtained at the morning before induction of anesthesia. The patients then would be randomized into two groups according to computer-generated codes: Ondansetron group (O) and controlled group(C).

In anesthetic period, the patients had routine monitoring, oxygen supply via nasal cannula 3-5 LPM, and would be given fentanyl 0.5 mcg/kg and parecoxib 40 mg, or ketorolac 30 mg in case of sulfa allergy. Then, they would be inducted and maintained by propofol TIVA, whether by infusion pump or bolus based on anesthetist's preference. Patients in group O would receive 4 milligrams of ondansetron after induction, while patients in group C would receive 2 ml of normal saline as sham injection. Intravenous ephedrine and nicardipine were used to correct hypotension and hypertension respectively to control blood pressure variation within 20% from baseline. Details of anesthetic technique are adjusted according to anesthetist's discretion.

In post-anesthetic care units (PACU), the patients had routine monitoring. Nausea and vomiting symptom would be first treated by intravenous metoclopramide 10 mg. Fentanyl 0.25 mcg/Kg would be given for pain control when necessary every 15 minutes. The patients were discharged from hospital if they passed standard discharged criteria for outpatient case.

At post-operative day three, telephone interview would be conducted for data gathering by an anesthesia resident, who was blinded to the group of the patient. The interview included the general abnormal event after discharge from hospital, any nausea/vomiting symptoms and the returning of normal daily activity. Advice and answering to the question would be provided if needed. If the patients could not be contacted in 2 weeks after daily attempts, they would be declared as lost follow-up.

Measurement

We collected patients' baseline characteristics as followed: age, ASA physical status, height, weight, underlying diseases, risk factors from Apfel's simplified risk score [4], and the sum of Apfel's simplified risk score. Risk factors according to Apfel's/s simplified risk score includes: female sex, history of PONV or motion sickness, non-smoking status and post op opioids used.[4] Intraoperative data about duration of anesthesia and procedure, drug dosage (including propofol, NSAIDs,

opioid, nicardipine, and ephedrine), intravenous fluid received, and amount of blood loss were recorded. Time to awaken was also recorded, which is defined by the time between termination of propofol infusion and patient first response to calling patients' name.

In post-anesthetic period, nurses would record PONV symptoms into 3 categories (no nausea and vomiting, nausea but no vomit and vomiting) at PACU, post-operative day 0, 1, and 2. At PACU, numbers of episode of nausea and vomiting, incidence and cause of inpatient admission, incidence of headache or hypotension, duration of stay, and pain score. After discharge, patients' ability to return to normal function and whether they sought extra medical attention would be gathered by the researcher.

Statistical analysis

The sample size is calculated from estimate baseline 7-day risk of PDNV in female patients undergoing ambulatory anesthesia at 63.6% [2] and risk reduction of ondansetron at 0.56.[4] The calculated sample size is 49 samples per group with type I error = 0.05, and type II error = 0.2. We increased total sample size to 110 to prevent lost-of-follow-up data.

Statistical analysis was calculated via SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Demographic data was analyzed by T-test and Chi-square test. Perioperative data was analyzed by Chi-square test and Mann-Whitney U test for non-normal distribution data. Post-operative data was analyzed by Chi-square test. *P*-value < 0.05 is considered statistically significant.

Results

One-hundred and ten patients were included in this study. After follow-up period, 4 of the patients in controlled group and 5 in ondansetron group couldn't be contacted via telephone in 2 weeks, thus excluded from the study. So, there were 50 patients in controlled group and 51 patients in ondansetron group included in outcome analysis (Figure 1).

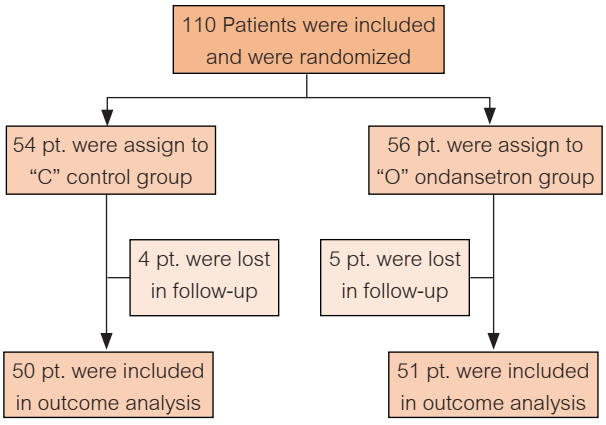

Figure 1 Flow diagram for patient enrollment

There was no statistical difference in demographic data between C and O groups, including age, ASA, BMI, and underlying disease (Table 1). More than 80% of patients have Apfel's simplified score at 2, which were prominently from female gender and non-smoker status as predicted for baseline risk (p=0.939) (Table 1). There was also no statistical difference in each risk factor. Noted that all patients received intra-operative opioid which contribute to the risk for nausea and vomiting.

Table 1 Demographic data

Variables	Control group (N=54)	Ondansetron group (N=56)
Age, mean±SD	38.91±9.84	39.25±9.22
ASA, N (%)		
I	40 (74.1%)	34 (60.7%)
II	14 (25.9%)	22 (39.3%)
BMI unit (kg/m^2)	22.61±3.68	22.14±3.29
Underlying disease		
Diabetes mellitus	0	0
Hypertension	3 (75.0%)	1 (25.0%)
Other (total)	5 (9.3%)	11 (19.6%)
Anemia	1 (1.9%)	5 (8.9%)
Apfel's score; n(%)		
1	1(1.9)	1(1.8)
2	46(85.2)	49(87.5)
3	6(11.2)	5(8.9)
4	1(1.9)	1(1.8)
Non-smoker	53 (98.1%)	55 (98.2%)
History of PONV	2 (3.7%)	3 (5.4%)
Motion sickness	3 (5.6%)	3 (5.4%)

Data are presented as total number and percent. PONV= Postoperative nausea and vomiting

In anesthetic period, there were no statistical differenced is duration of anesthesia or procedure, drug dosage, fluid infusion and amount of blood loss. Median duration of anesthesia is 45 minutes in both groups. Median total Propofol dosage is 380 and 390 mg in C group and O group, respectively. There was no statistic difference in time to awaken (median = 6 minutes in C group, 7 minutes in O group, *p*-value = 0.337). No nicardipine was given in this study. Median fentanyl dosage is 50 mcg in both groups.

In post-anesthetic care units, 4 patients were admitted due to insurance status, and 1 patient was admitted because of persistent dizziness but she denied any nausea symptom. Rescue drug usage and pain score did not have any statistical difference (Table 2).

Table 2 PACU data

Variables	Control group (N=50)	Ondansetron group (N=51)	*p*-value
	N (%)	N (%)	
Duration of PACU stay (minutes)	120 (90-160)	120 (60-195)	0.55
Inpatient admission	1 (2.0%)	4 (7.8%)	0.36
Pain (PADSS score)	-	-	0.68
Mild or tolerable pain	3 (6.0%)	2 (3.9%)	-
No pain	47 (94.0%)	49 (96.1%)	-

For PONV and PDNV outcomes, there were no statistically significant differences in the incidence of both PDNV and PONV between 2 groups. Furthermore, there was no incidence of vomiting at all. The overall incidence of PDNV in Control group was 14% and 5.9% in Ondansetron group (Table 3). No patients reported inability to return to normal function or seeking extra medical care.

Table 3 Incidence of PONV and PDNV

Variables	Control group (N=50) N(%)	Ondansetron group (N=51) N(%)	*p*-value
Nausea scores			
PACU	0	0	>0.999
Day0	4 (8.0%)	1 (2.0%)	0.205
Day1	4 (8.0%)	2 (3.9%)	0.44
Day2	1 (2.0%)	1 (2.0%)	>0.999
Vomiting scores			
PACU	0	0	>0.999
Day0	0	0	>0.999
Day1	0	0	>0.999
Day2	0	0	>0.999
Overall incidence (Day02-)	7 (14.0%)	3 (5.9%)	0.2

Discussion

PONV and PDNV affect substantial number of patients after ambulatory surgery. Even PONV is usually described as minor side effect, but it can cause distress to the patient. Besides patient related distress, PONV may result in prolong PACU stay and unanticipated hospital admission.[6] This increase interest in using antiemetic prophylaxis in ambulatory surgical patient.

The overall incidence of PONV and PDNV in Gynecological surgery is 26.8% and 42.9% respectively[7] but for minor gynecological procedure, PONV incidence is around 0-2.5%.[3] In our study, we found the overall incidence of PONV to be 0% and PDNV to be 14% and 5.9% in group C and O respectively. There was no statistical difference in PONV, PDNV, or any complications between two groups. Nausea is highest at post-operative day 0 (after hospital discharge) and day 1, which correlated with 7-day incidence by Odom-Forren et al.[2] The explanation for the overall lower incidence can be multifactorial. First, the TIVA technique used in our study usually resulted in lower incidence of nausea and vomiting. According to Gan et al. [6], TIVA with propofol reduced PONV up to 25% compare with using inhalation anesthesia. Besides, the ambulatory hysteroscopic procedures are typically shorter and less invasive than inpatient procedures, this also contribute to the lower risk for PONV and PDNV.[7]

Our study shows that adding ondansetron to propofol TIVA doesn't have additional benefit. This may be due to the overall low incidence of PONV from the TIVA based technique. Most patients in our study also had Apfel's simplified risk score around two, which would be categorized in moderate risk group.[4] Thus, adding antiemetic drug such as ondansetron might not significantly improve the overall incidence. Somehow antiemetic prophylaxis may be considered in higher risk patients such as those with more than 3 risk factors for PONV, which include: female sex, history of PONV or motion sickness, non-smoking status and post-operative opioid used. Moreover, ondansetron was shown to be more effective in reducing the incidence of PONV if general anesthesia is maintained with inhalation agents rather than TIVA.[8]

Our study is consistent with Alghanem et al., they suggested that ondansetron or dexamethasone added to propofol TIVA technique does not further reduce the incidence of PONV after laparoscopic cholecystectomy.[11] But in the study, the incidence of PONV was around 32%, which was higher than in our study. This may be due to the different type of operation and the higher average Apfel's score in their study group. The possible explanation was that the antiemetic mechanism of both propofol and ondansetron are similar. Both act by reducing the release of 5-HT3, therefore small benefit was obtained when ondansetron is added to TIVA. Apfel et al. also suggested that only little further benefit was gained when two interventions for antiemetic prophylaxis were used compared with one intervention.[9] However, in study by Habib et al., they showed that combination of 2 antiemetics (droperidol and ondansetron) was more effective in reducing PONV when incorporation TIVA with propofol than TIVA alone in ambulatory patient undergoing laparoscopic cholecystectomy.[10]

Limitations of this study were: the total opioid dosage was based on individual judgement, the post-discharge follow-up period (3 days) was shorter compared to other study (7 days)[2], one patient was accidentally given ondansetron and needed to be analyzed base on intention-to-treat, and lastly, we didn't monitor depth of anesthesia during the procedure.

Conclusion

In summary, ondansetron prophylaxis does not further reduce the incident of PONV and PDNV in patients undergoing hysteroscopy with propofol TIVA technique in ambulatory setting. Several factors may have contributed to the relatively low incidence of PONV and PDNV in this clinical setting, thus administering ondansetron prophylaxis is not mandatory. Further study is needed to find the additional benefit of ondansetron in higher risk group of patients undergoing TIVA for ambulatory hysteroscopic procedure.

Acknowledgements

The authors would like to thank the department of anesthesia Ramathibodi Hospital and the statisticians who involved with this study

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