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RESEARCH ARTICLE

The Effects of Glycopyrrolate as Premedication on Post-Operative Nausea and Vomiting: A Propensity Score Matching Analysis

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Abstract:

Background:

Glycopyrrolate is often used as a premedication for anesthesia as it has anti-sialogogue and vagolytic effect. Patients undergoing laparoscopic gynecologic surgery have high-risk of Post-Operative Nausea and Vomiting (PONV).

Objectives:

This retrospective study investigates the effect of glycopyrrolate as a premedication for PONV in patients receiving fentanyl-based Intravenous (IV) Patient-Controlled Analgesia (PCA) after laparoscopic gynecological surgery.

Methods:

We reviewed the medical records of adult patients who received fentanyl-based IV-PCA after laparoscopic gynecological surgery at Chung-Ang University Hospital between January 1, 2010, and June 30, 2016. We classified patients into two groups on the basis of glycopyrrolate premedication: non-premedicated group (Group N; n = 316) and glycopyrrolate premedicated group (Group P; n = 434). The Propensity Score Matching Method (PSM) was used to select 157 subjects in Group N and P, on the basis of their covariates which were matched with a counterpart in the other group.

Results:

Prior to PSM, the necessities for rescue anti-emetics were lower on Postoperative Day (POD) 0 (58[18.4%] *vs.* 45[10.4%], $P = 0.002$) and POD1 (60[19.0%] *vs.* 59[13.6%], $P = 0.046$), and Visual Analogue Scale (VAS) of pain on POD 1 (2.86 ± 1.49 *vs.* 3.13 ± 1.53, $P = 0.017$) was higher in group P. After PSM, the Numerical Rating Scale (NRS) score for nausea (0.38 ± 0.75 *vs.* 0.21 ± 0.62, $P = 0.027$) and rescue anti-emetics (27 [17.2%] *vs.* 15 [9.6%], $P = 0.047$) on POD 0 were both lower in the group P.

Conclusion:

In patients receiving fentanyl-based IV-PCA after laparoscopic gynecological surgery, the severity of nausea and necessity for rescue ant-emetic was lower in the glycopyrrolate premedication group.

Keywords: Analgesia, Patient-controlled, Gynecologic surgical procedures, Laparoscopy, Postoperative nausea and vomiting, Glycopyrrolate.

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1. INTRODUCTION

Postoperative Nausea and Vomiting (PONV), with the incidence reported to be 18-80%, is a common side effect in patients who undergo operation under general anesthesia [1 - 3] PONV causes a lot of discomfort to patients undergoing surgery, and can increase the length of hospital stay and overall medical cost [4].

The risk factors of PONV can be divided into three main categories. Firstly, there are surgical factors such as the duration of operation and kinds of surgeries performed (laparoscopic surgery, gynecologic surgery, breast surgery, thyroid surgery, *etc.*). Secondly, there are anesthetic factors,

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such as the duration of anesthesia, types of anesthetics used (N_2O, desflurane, sevoflurane, propofol), use of opioids and neostigmine during surgery, and postoperative analgesic use. Lastly, there are factors related to patients, such as female, non-smoker, and history of PONV or motion sickness [2, 3, 5].

Patients undergoing laparoscopic abdominal surgery have a high risk for PONV due to pneumoperitoneum and residual gas effect after surgery [6]. PONV risk in laparoscopic gynecologic surgery is especially increased because patients are all females [5]. Because opioid containing Intravenous (IV) Patient-Controlled Analgesia (PCA) is often used for pain control after laparoscopic gynecologic surgeries, it can also increase the incidence of PONV.

PONV is related to various receptors in vomiting center including histaminergic, cholinergic, dopaminergic, neurokininergic and serotonergic receptors that mediate these signals. Thus, agents that block these signal-related receptors are used to prevent PONV [7 - 10].

Anti-cholinergic agents, commonly used as premedication for general anesthesia as it has anti-sialogogue and vagolytic effect, also have the potential to prevent PONV. Among anti-cholinergic agents, scopolamine showed an effect to prevent PONV after surgery.

Glycopyrrolate is a commonly used drug because it has more anti-sialogogue effect and less effect on the heart rate and rhythm than atropine. Although glycopyrrolate has the potential to prevent PONV, its effects have not been investigated. Therefore, we retrospectively investigated the effect of glycopyrrolate on the incidence and severity of nausea and vomiting after laparoscopic gynecologic surgery.

2. METHODS

2.1. Study Design

Following Institutional Review Board approval [IRB No. C2016199], medical records of adult patients were reviewed who underwent laparoscopic gynecological surgery at Chung-Ang University Hospital between January 1, 2010, and June 30, 2016, from a prospectively collected database. In this database, all the patients used IV-PCA devices for postoperative pain control. Patient information was correctly anonymized and de-identified prior to analysis. The need for informed consent was waived for this study. Exclusion criteria were as follows: 1) patients who received re-operation on the same site, 2) patients who participated in other randomized controlled trials, 3) patients who received sugammadex as reversal agents, and 4) missing data. Patients who used sugammadex as a reversal agent were excluded due to the potential effect of sugammadex on PONV which was discussed in a study by Lee *et al.* [11].

Patients were classified into two groups on the basis of premedication used: non-premedicated group (Group N; n = 316) and glycopyrrolate premedicated group (Group P; n =434). In Group P, 0.2 mg of glycopyrrolate was injected intramuscularly within 30 minutes before the operation. This manuscript was prepared and written according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [12].

2.2. The Protocol of Postoperative Pain Management

In our institution, all the patients who request PCA following laparoscopic gynecologic surgery undergo a standardized pain management procedure. Accordingly, patients in the current study were instructed on how to use the Visual Analogue Scale (VAS) scoring system and PCA device during their preoperative visit. Specifically, patients were instructed to press PCA button when they wanted more analgesics.

The protocol of PCA is standardized according to the type of surgery and the expected degree of post-operative pain. In minor laparoscopic gynecologic surgeries or surgeries expected to cause mild post-operative pain, fentanyl 1000 mcg mixed with ketorolac 180 mg (or nefopam 120 mg) and granisetron 3 mg (or ramosetron 0.3 mg or palonosetron 0.25 mg) were added to normal saline to make a 100 mL solution. In major laparoscopic gynecologic surgeries or surgeries expected to cause moderate or severe post-operative pain, fentanyl 1400 mcg mixed with ketorolac 180 mg (or nefopam 120 mg) and granisetron 3 mg (or ramosetron 0.3 mg or palonosetron 0.25 mg) were added to normal saline to make a 100 mL solution. The continuous infusion rate was 1 mL/hour, bolus dose was 1 mL, and lockout interval was 15 minutes. PCA was started just after induction of anesthesia.

In the general ward, a highly experienced nurse was in charge of PCA management. This nurse evaluated the severity of postoperative pain using a 10 point VAS (0 = no pain, 10 = worst pain imaginable) and the severity of nausea using a numerical rating scale (NRS; 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = worst nausea imaginable). She also recorded the incidence of vomiting, headache, dizziness, and clamping of the PCA device.

For persistent pain with VAS >3, an additional 50 mcg of fentanyl as rescue analgesic was administered with 15 min interval until the pain subsided to VAS ≤3. Rescue anti-emetic was offered for persistent nausea with NRS ≥2, or when requested. Metoclopramide 10 mg was administered as the initial anti-emetic. Ondansetron 4 mg was administered as a second anti-emetic, at the discretion of the physician in charge.

2.3. Data Collection

Using the data recorded by a nurse dedicated to the management of patients with PCA, demographic, anesthetic, surgical and perioperative factors were noted that were related to PONV. The nurse only undertook tasks related to PCA, and she made the rounds at least once a day to investigate issues related to PCA, including PONV. She had 5 years' clinical experience, and she collected data after being trained in the standardized protocols of pain and PONV investigation. Furthermore, we excluded the data collected during the first 2 years of her PCA rounds. Specifically, we collected data on age, gender, weight, height, history of smoking, PONV or motion sickness, type of anesthetic agents used (remifentanil, propofol, desflurane, sevoflurane, and N_2O), use of anti-cholinergics (glycopyrrolate) as a premedication, use of nefopam, ketorolac, granisetron, ramosetron, or palonosetron in PCA, dosage of fentanyl in PCA, laparoscopic surgery, and

operation time. Furthermore, the postoperative variables collected were severity of nausea, frequency of vomiting, use of rescue anti-emetics, and Complete Response (CR). These variables were measured on postoperative days 0 and 1; CR was defined as no nausea, no vomiting, and no requirement for anti-emetics during postoperative days 0.

2.4. Statistics

As this was a retrospective cohort study, not a randomized clinical trial, potential confounding factors were caused by non-randomization and biased covariates; thus, comparability between group N and P was problematic [13]. For this reason, Propensity Score Matching (PSM) was conducted to decrease potential confounding [14]. The propensity score was calculated using logistic regression analysis; the following covariates were used [15]: age, gender, height, weight, history of smoking, PONV or motion sickness, type of anesthetic agents used.

Propensity score similarities were selected using the nearest-available match between the groups with the caliper radius 0.001. To evaluate the balance between the matched groups, Standardized Differences (STDs) we tested for each of the covariates mentioned above. Specifically, STD is the difference in means between the groups in units of Standard Deviation (SD) [16]. Comparability between the groups is usually considered to be good when the standardized difference is less than 20%. For continuous variables, the data distribution was first evaluated for normality using the Shapiro-Wilk test. Normally distributed data were then compared using parametric methods; non-normally distributed data were analyzed using non-parametric methods.

Continuous variables were analyzed using Student's *t*-test or the Mann-Whitney U test before propensity score matching, and the paired *t*-test or Wilcoxon signed-rank test after propensity score matching.

Descriptive variables were analyzed using Fisher's exact tests or χ^2 analyses before propensity score matching and McNemar test after propensity score matching. The $P < 0.05$ was considered statistically significant. All the statistical analyses were performed using SPSS for Windows (version 23; IBM Corp, Armonk, NY).

3. RESULT

The basic demographic and clinical characteristics of patient population are detailed in Table **1**. Out of the 849 adult patients who used fentanyl-based IV-PCA after laparoscopic gynecologic surgery at Chung-Ang University Hospital between January 2010 and June 30, 2016, ninety-nine patients were excluded due to missing data (n = 26), participation in other studies (n = 60), use of sugammadex as a reversal agents (n = 10), and re-operation on the same site (n = 3). Therefore, a total of 750 patients were included in this study: non-premedicated group (group N; n = 316) and glycopyrrolate premedicated group (group P; n = 434).

Table 1. Patient characteristics in total and matched cohorts.

Characteristic	Total Set				Matched Set			
Patients Characteristics	**Group N (*n* =316)**	**Group P (*n* =434)**	***STD(%)***	***P-value***	**Group N (*n* =157)**	**Group P (*n* =157)**	***STD(%)***	***P-value***
Age (yrs)	44.73 ± 24.66	39.92 ± 11.87	26.18	<0.001	41.12 ± 14.24	41.03 ± 11.93	0.69	0.949
Height (cm)	159.26 ± 5.43	159.31 ± 8.60	-0.67	0.914	159.22 ± 5.48	159.71 ± 5.64	-8.81	0.434
Weight (kg)	57.39 ± 9.23	57.79 ± 9.16	-4.35	0.557	57.07 ± 9.52	57.68 ± 8.54	-6.75	0.555
Smoking history(n)	17(5.4)	37(8.5)	-44.60	0.100	9(5.7)	10(6.4)	-12.28	0.886
PONV History (n)	19(6.0)	24(5.5)	8.70	0.779	7(4.5)	8(5.1)	-13.33	0.791
Anesthetic Factors								
OP time (min)	144.49 ± 120.17	142.44 ± 130.89	1.62	0.826	136.61 ± 89.23	137.01 ± 90.99	-0.44	0.891
Sevoflurane (n)	132(41.8)	143(32.9)	23.83	0.013	55(35.0)	54(34.4)	1.71	0.906
Desflurane (n)	184(58.2)	291(67.1)	-14.21	0.013	102(65.0)	103(65.6)	-0.92	0.906
N_2O (n)	224(70.9)	387(89.2)	-22.86	<0.001	134(85.4)	134(85.4)	0.0	1.000
Remifentanil (n)	37(11.7)	20(4.6)	87.12	0.652	9(5.7)	10(6.4)	-12.28	0.813
Pre intubation opioid (n)	187(59.2)	349(80.4)	-30.37	<0.001	116(73.9)	113(72.0)	2.57	0.703
PCA Related Factors								
PCA Fentanyl(mcg)	1064.60 ± 192.51	1049.69 ± 134.05	9.25	0.022	1049.80 ± 150.56	1052.87 ± 123.81	-2.23	0.844
Nefopam	168(53.2)	175(40.3)	27.59	<0.001	75(47.8)	63(40.1)	16.11	0.172
Ketorolac	126(39.9)	212(48.8)	-20.07	0.015	66(42.0)	79(50.3)	-19.76	0.141
Ramosetron	229(72.5)	382(88.0)	-19.31	<0.001	137(87.3)	135(86.0)	1.49	0.892
Palonosetron	7(2.2)	9(2.1)	4.65	0.895	4(2.5)	4(2.5)	0	0.702
Granisetron	80(25.3)	43(9.9)	87.5	<0.001	16(8.9)	18(11.5)	-12.75	0.656

Values are expressed as mean ± SD or absolute number (percentages). OP; Operation, STD: Standardized Difference, PONV: Postoperative Nausea and Vomiting, PCA: Patient-Controlled Analgesia

Table 2. Perioperative variables before matching.

Variables	Group N (*n* =316)	Group P (*n* =434)	STD(%)	*P*-value
Pain VAS at day	6.14 ± 1.95	6.37± 1.82	-12.26	0.100
Pain VAS at day 1	2.86 ± 1.49	3.13± 1.53	-17.84	0.017
Nausea NRS at day 0	0.31 ± 0.71	0.22 ± 0.66	13.06	0.061
Nausea NRS at day 1	0.07 ± 0.30	0.06 ± 0.29	3.40	0.701
Rescue anti-emetics at day0	58(18.4)	45(10.4)	55.56	0.002
Rescue anti-emetics at day1	60(19.0)	59(13.6)	33.12	0.046
CR at day 0	227(71.8)	313(72.1)	-0.42	0.932
CR at day 1	242(76.6)	355(81.8)	-6.57	0.080
Number of vomiting at day 0	0.06 ± 0.49	0.03 ± 0.22	7.51	0.222
Number of vomiting at day 1	0.00 ± 0.00	0.00 ± 0.07	0.0	0.227
Dizziness at day 0	5(1.6)	11(2.5)	-43.90	0.373
Dizziness at day 1	8(2.5)	8(1.8)	32.56	0.519
Headache at day 0	1(0.3)	1(0.2)	40	0.822
Headache at day 1	2(0.6)	1(0.2)	100	0.389

Values are expressed as mean ± SD, absolute number(percentages) or absolute number. STD: Standardized Difference, VAS: Visual Analogue Scale, NRS: Numerical Rating Scale, CR: Complete Responder. * $P < 0.05$ between group comparison

Table 3. Perioperative variables after matching.

Variables	Group N (*n* =157)	Group P (*n* =157)	STD(%)	*P*-value
Pain VAS at day	6.13 ± 2.05	6.32 ± 1.73	-10.02	0.375
Pain VAS at day 1	3.01 ± 1.48	3.08 ± 1.53	-4.65	0.794
Nausea NRS at day 0	0.38 ± 0.75	0.21 ± 0.62	24.71	0.027
Nausea NRS at day 1	0.07 ± 0.26	0.05 ± 0.22	8.30	0.479
Rescue Anti-emetics at day 0	27 (17.2)	15(9.6)	44.19	0.047
Rescue Anti-emetics at day 1	33(21.0)	22(14.0)	33.33	0.803
CR at day 0	103(65.6)	115(73.2)	-11.59	0.088
CR at day 1	118(75.2)	129(82.2)	-9.31	0.130
Number of vomiting at day 0	0.08 ± 0.44	0.04± 0.28	10.85	0.281
Number of vomiting at day 1	0.01 ± 0.08	0.00 ± 0.00	17.68	0.318
Dizziness at day 0	0(0.0)	0(0.0)	0.0	NA
Dizziness at day 1	0(0.0)	0(0.0)	0.0	NA
Headache at day 0	0(0.0)	0(0.0)	0.0	NA
Headache at day 1	2(1.3)	0(0.0)	100	0.156

Values are expressed as mean ± SD, absolute number (percentages) or absolute number. STD: Standardized Difference, VAS: Visual Analogue Scale, NRS: Numerical Rating Scale, CR: Complete Responder. * $P < 0.05$ between group comparison

3.1. Group N *vs.* Group P in the Total Set

Out of the 17 individual and composite predictors for confounding variables, 9 had poor standardized difference scores prior to propensity score matching. These variables were as follows: age, smoking history, use of sevoflurane, N_2O, remifentanil, preintubation use of opioid and use of nefopam, ketorolac, granisetron in PCA regimen. Compared with Group N, subjects in Group P were younger, received less sevoflurane, used less fentanyl, nefopam, and granisetron in PCA. They received more desflurane, N_2O, preintubation opioid, and ketorolac, ramosetron in PCA regimen (Table **1**).

Except for VAS of pain on POD 1, the rescue anti-emetics on POD day 0, and day 1, there was no significant difference in variables between the two groups. Differences in incidences of dizziness and headache were insignificant between two groups before PSM (Table **2**).

3.2. Group N *vs.* Group P in the Matched Set

After matching, there were 157 patients in each group. All 15 confounding variables showed acceptable STDs (<20%), confirming that the matching procedure was efficient in creating a balance between the two groups (Table **1**). The NRS score of nausea (0.38 ± 0.75 *vs.* 0.21 ± 0.62, P = 0.027) on POD 0 and rescue anti-emetics (27 [17.2%] *vs.* 15 [9.6%], P = 0.047) on POD 0 were both lower in group P. There was no case of dizziness after matching and difference in incidences of headache at POD 1 was insignificant (Table **3**).

4. DISCUSSION

In the present study, glycopyrrolate premedication was

found to be beneficial in terms of necessities for rescue anti-emetics at POD 0 as well as NRS score for nausea at POD 0 after PSM. Prior to PSM, the necessities for rescue anti-emetics was lower on POD 0 and POD1, and VAS of pain on POD 1 was higher in group P. However, these statistical differences between the two groups disappeared except for necessities for rescue anti-emetic at POD 0 after PSM. Nevertheless, tendencies of higher CR in group P than group N were observed after PSM.

These findings are consistent with previous studies that concluded that glycopyrrolate can prevent PONV in the cesarean section under spinal anesthesia. Ure *et al.* reported that 0.2 mg of intravenous glycopyrrolate before spinal anesthesia could prevent PONV in cesarean section under spinal anesthesia [17]. In this study, although the incidence of nausea was not significantly different, severity score and frequency of nausea were lower in the glycopyrrolate group, which suggested that glycopyrrolate can be considered a safe strategy to prevent PONV. Biswas *et al.*, also reported significantly decreased incidence of nausea and vomiting in glycopyrrolate group compared with normal saline group in the cesarean section under spinal anesthesia (3 [15%] *vs.* 11[55%], $p < 0.05$) [18]. In the study by Jain *et al.*, effect of glycopyrrolate on PONV after cesarean section was similar to ondansetron [19].

On the other hand, this result is different from that of other studies. Mirakhur et al. reported that the higher emetic sequela was observed in glycopyrrolate-morphine group compared with morphine only group in the minor gynecologic operation. Emetic sequela was significantly lower in morphine-hyoscine group at 0-1, 1-6, 0-6 hours (P <0.01), and morphine-atropine group at 0-1, 1-6 hours ($P < 0.01$) than morphine-glycopyrrolate group [20]. Salmenpera *et al*., compared the use of glycopyrrolate and atropine for post-anesthetic nausea, reporting that glycopyrrolate increased postoperative nausea compared to atropine (28% *vs*. 8%, $P = 0.017$) [21]. In Chisakuta *et al*., glycopyrrolate did not effectively prevent PONV in children undergoing strabismus surgery. (glycopyrrolate group; 25% *vs*. placebo group; 30%, $P > 0.0.5$) [22]. These discrepancies may be due to different kinds of surgeries (laparoscopy *vs*. laparotomy), co-administered analgesics, study population, and administration time of glycopyrrolate.

Some studies reported the relationship between PONV and mixture of neostigmine and glycopyrrolate which is used as a reversal agent complex for neuromuscular blocker. Lovstad *et al*., reported that post-operative 6-hour occurrence of nausea was significantly increased in the mixture of neostigmine and glycopyrrolate group compared with normal saline placebo group (13[30%] *vs*. 5[11%], $p = 0.03$) [9]. However, effect of the mixture of neostigmine and glycopyrrolate on the PONV is controversial. According to Nelskyla *et al*., the mixture did not increase the incidence or severity of PONV in patients who received gynecological laparoscopic surgery [23]. In another study, the complex by Girish *et al*. did not increase the incidence of PONV and neither did it require the need for anti-emetics in patients undergoing ambulatory surgery [24]. Also in the study by Hovorka *et al*., neostigmine and glycopyrrolate complex had no effect on the incidence of PONV [25]. The controversial outcome seems to be probably due to the effect of neostigmine on PONV tendency, not just the effect of glycopyrrolate alone.

As cholinergic receptors are also located outside the brain, blocking these receptors may play a role in anti-emetic effects of glycopyrrolate. Glycopyrrolate may attenuate the vagal stimulation induced by the peritoneal stretching and iatrogenic pneumoperitoneum in the laparoscopic surgery [26, 27], which reduced the vagal reflex mediated PONV. Increased heart rate and cardiac output may reduce hypotensive episodes, thus hypotension induced PONV [17]. As cholinergic receptors are distributed in the GI tract, as well as in the brain, glycopyrrolate may block cholinergic receptors in the GI tract, resulting in reduced gastric secretion and intestinal movement [11, 28]. These mechanisms of glycopyrrolate may decrease the incidence of PONV.

In the present study, the intensity of post-operative vomiting was lower in glycopyrrolate premedicated group than the non-premedicated group. The use of rescue anti-emetics on the day of surgery was also less in the glycopyrrolate premedicated group. As a result, the use of glycopyrrolate as a premedication was shown to have a preventive effect against PONV.

There are some limitations to this study. First, this is not a randomized controlled study but a retrospective cohort study, therefore confounding factors cannot be excluded. Although we tried to reduce the effect of known confounders by using propensity score matching method, there are still possibilities of confounding effect by unknown risk factors. Second, as this study was performed at a single medical center, the results of this study should be cautiously generalized into total population. Lastly, as with any retrospective study, missing or incomplete data were included in our data set. Recall bias could also be a problem because patients were asked to recall the severity or symptoms of nausea and vomiting in POD 0 or 1. Therefore, well-designed, large scale, multi-center, randomized controlled studies are needed to confirm the findings of this study in the future.

CONCLUSION

The severity and incidence of PONV in patients treated with fentanyl-based IV-PCA after laparoscopic gynecologic surgery under general anesthesia were lower in the glycopyrrolate premedicated group.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was done following Institutional Review Board approval [IRB No.C2016199].

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

The study involved the evaluation of pre-existing de-

identified electronic medical records of patients, the requirement for informed consent was waived.

STANDARD OF REPORTING

STROBE guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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