Prophylaxis of postoperative nausea and vomiting with ondansetron, metoclopramide, or placebo in total intravenous anesthesia patients undergoing laparoscopic cholecystectomy

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ABSTRACT

الأهداف: مقارنة تأثير التخدير الكلي (TIVA) المتجنب لأسباب الغثيان والقيئ (PONV)، بالعقاقير المعالجة للقيئ لدى المرضى في حالات استئصال المرارة عن طريق منظار البطن.

الطريقة: أجريت دراسة مستقبلية عشوائية مزدوجة العتمة في مستشفى جامعة الملك عبدالعزيز – جدة – المملكة العربية السعودية، في عام 2007م. شملت الدراسة 75 مريض مصاب بحصوات المرارة، واللذين ستجرى لهم عملية استئصال المرارة عن طريق منظار البطن. تم تقسيم المرضى إلى ثلاث مجموعات (25 مريض في كل مجموعة): المجموعة الأولى تخدر تخديرا كليا (TIVA) مع استبعاد مسببات الغثيان، المجموعة الثانية تعطى نفس التخدير مع عقار ميتوكلوبرمايد 10mg وريديا، والمجموعة الثالثة تعطى نفس التخدير مع عقار أوندنسيترون 4mg وريديا. تم تسجيل جميع حالات حدوث الغثيان والقيئ (PONV)، كان هناك حاجة إلى مسكنات للألم، واستخدام معالجات للغثيان وأي أعراض جانبية.

النتائج: عانا 19 مريضا من الغثيان (PONV). نسبة حدوث الغثيان (PONV) متساوية بين المجموعات (28%)، وكانت أقل عند مرضى عقار أوندنسيترون (20%) ($p>0.05$). لوحظ زيادة حدوث الغثيان (PONV) لدى السيدات مع زيادة مدة العملية الجراحية، وزيادة مدة البقاء في المستشفى، بغض النظر عن مجموعة الدراسة ($p<0.05$). مجموعة مرضى عقار أوندنسيترون كانوا أكثر رضا من غيرهم ($p>0.05$). لم يلاحظ أي فرق في الآلام المصاحبة للعمليات، أو في التغيرات الحيوية بين المجموعات الثلاثة.

خاتمة: لتفادي حصول أي غثيان أو قيئ مصاحب للعملية الجراحية، ينصح بتجنب مسببات الغثيان عند التخدير وكذلك إعطاء عقار معالج للغثيان.

Objective: To compare total intravenous anesthesia (TIVA) with ondansetron, and metoclopramide in preventing postoperative nausea and vomiting (PONV) in laparoscopic cholecystectomy patients.

Methods: A prospective randomized double-blinded study was performed at King Abdulaziz University Hospital, Jeddah, Saudi Arabia in 2007. Seventy-five patients scheduled for laparoscopic cholecystectomy under TIVA were randomized to receive either: metoclopramide 10 mg (n=25), 4 mg ondansetron (n=25), or placebo (n=25) at the end of surgery. Postoperative nausea and vomiting episodes, analgesic supply, rescue medication, adverse events, and patient satisfaction were collected over 24 hours.

Results: Nineteen patients developed PONV. The frequencies of PONV were equal for the 2 groups (28%), and lower among the ondansetron group (20%) ($p>0.05$). Female gender, lengthy surgery, and longer hospital stay were associated with more frequent PONV regardless of the study group ($p<0.05$). Patient's satisfaction was more frequent among the ondansetron group ($p>0.05$). Morphine consumption was associated with more PONV, but it was statistically significant only in the placebo group. There was no difference between the 3 groups with regard to the VAS pain score, cardiovascular parameters, or oxygen saturation.

Conclusion: It is unlikely that a single technique or drug will ever be effective in treating emesis under all surgical circumstances. Therefore, a multimodal regimen incorporating avoidance of emesis triggering factors, and administration of antiemetic medications is recommended.

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Laparoscopic cholecystectomy is commonly complicated by postoperative nausea and vomiting (PONV), with a relatively high incidence, from 45-72%.[1-5] The optimal strategy for the prevention and management of PONV remains disputed.[6-7] The use of prophylactic antiemetic treatment has been suggested to improve patients' satisfaction.[8] Meta-analysis has shown that the efficacy of prophylactic antiemetic strategies is limited.[9] Some studies have even suggested that antiemetic prophylaxis offers no advantage over timely symptomatic treatment.[6-8] A variety of drug regimes has been evaluated for prevention and treatment of PONV.[10] However, PONV continues to be a postoperative complication. The use of a multimodal approach incorporating both total intravenous anesthesia (TIVA), and a combination of antiemetic drugs was reported to be associated with lower incidence of PONV less than 10%.[11] This prospective double-blinded placebo-controlled trial was designed, to compare the use of an emesis non-triggering anesthetic technique with, or without antiemetic medications, either ondansetron or metoclopramide for the prevention of PONV in patients undergoing laparoscopic cholecystectomy.

Methods. With approval from the King Abdulaziz University Hospital ethics committee, 75 adult patients were enrolled in this study. An informed consent was obtained from all patients. They had to be classified as American Society of Anesthesiologists (ASA) physical status I or II, and had to be 18-50 years old. Exclusion criteria were ASA class III and IV, emergency surgery, pregnancy, morbid obesity, susceptibility to vomiting or retching, allergy to the study medicine, ongoing antiemetic or psychotropic medications use, mental retardation, and psychiatric illness.

The anesthetic technique was standardized for all patients. All patients were premedicated with intravenous midazolam (20 μg/kg) 15 mins prior to induction of anesthesia, and intravenously rehydrated with 30 ml/kg of ringer lactate solution. They were monitored using routine monitoring devices such as electrocardiogram (ECG) Lead II, heart rate, non-invasive arterial blood pressure, continuous pulse oxymetry, capnography, and peripheral nerve stimulator. General anesthesia was induced with intravenous (IV) Fentanyl 2-3 μg/kg, and propofol 1-2 mg/kg IV. Then, Rocuronium 0.6 mg/kg IV was given to facilitate tracheal intubation and maintain muscle relaxation. Anesthesia was maintained with continuous infusion of propofol 200-50 μg/kg/min, and Fentanyl 1-2 μg/kg/hour. End-tidal carbon dioxide was maintained at 35-40 mm Hg. A 50% oxygen in air was used throughout the procedure. A gastric tube was inserted orally, without any active suction, for the duration of the procedure, and was removed immediately before emerging from anesthesia following complete deflation of peritoneal gas. If needed, residual neuromuscular blockade was reversed with neostigmine 40 μg/kg IV, and glycopyrrolate 20 μg/kg IV before tracheal extubation. Ten minutes prior to the end of anesthesia, randomization was achieved by using a sealed envelope technique prepared by an independent personnel. Patients were randomly allocated into one of the 3 groups. The first group (group P, Placebo) was given 1 ml of normal saline, second group (group M) was given 10 mg/ml of metoclopramide, and the third group (group O) was given ondansetron 4 mg/ml. All groups received an equal volume of the study medicine. The anesthesia was performed by an anesthesiologist not involved in the before, or after operation patient care. All surgeries were performed by the same surgical team. The laparoscopic technique was controlled for all patients, and the anesthesia and operative times were documented. At the end of the procedure, patients were transferred to the post anesthesia care unit. Episodes of nausea (subjective unpleasant sensation with awareness of urge to vomit), retching (spasmodic contraction of the abdominal wall without forceful expulsion of gastric contents), and vomiting (forceful expulsion of gastric contents), oxygen saturation (SaO_2), heart rate (HR), mean arterial blood pressure (MAP), and any adverse effects were reported on an hourly basis for the first 4 hours, then every 4 hours, for the next 20 hours. An independent research assistant who was unaware of the patients' randomization collected all data. For any PONV episode, metoclopramide 10 mg IV was prescribed as a rescue medicine. Visual analogue scale for pain (VAS) was performed to assess postoperative pain, and VAS score >3 was treated with repeated doses of morphine 1-2 mg IV.

All patients were asked to rate the degree of after operation emesis according to a 3-point scale (0-no nausea and vomiting, 1-nausea, 2-retching or vomiting). Patients who experienced both nausea and vomiting were included in the vomiting category. Twenty-four hours postoperatively, the patients were interviewed to rate their satisfaction with the anesthetic management in a retrospective way, based on a 5 point scale (1-very satisfied, 2-satisfied, 3-neither satisfied nor dissatisfied, 4-dissatisfied, 5-very dissatisfied). The total duration of hospital stay in hours was recorded for each patient.

Statistical analyses. Data were analyzed using SPSS® statistical software version 10 for Windows (SPSS Inc., Chicago, Illinois, USA). All shown data were presented as mean, standard deviation (SD), standard error of the mean and range, unless otherwise specified.

Qualitative variables were compared using chi-square test. Whenever the expected values in one or more of the cells in a 2x2 tables was less than 5, Fisher exact test was used instead. Student t test was used to compare quantitative variable between the groups. While the comparison of changes in relation to time (MABP, mean SaO_2, mean HR and mean VAS) was skewed and showed high scatter, and on applying Levene's test for equality of variance showed significant results, multiple response test could not be applied, and Friedman test was used instead. Results were considered to be statistically significant at $p<0.05$.

Results. A total of 78 patients were enrolled in the study. Three patients were excluded from the study, one patient in group M, after the laparoscopic approach was changed to laparotomy for surgical reasons, and 2 patients; one in placebo group for after surgery complications (surgical), and one in group O, due to improper selection. There was no significant inter group difference in the patient demographic data, ASA classification, or surgical time (**Table 1**). In all the study groups, PONV was more common among female patients than males, the percentage ranged between 21.1% in group O, to 31.2% in group M, and 38.9% among group P, while in group O it was 16.7% among male patients, 22.2% in group M, and none in group P. However, the differences between males and females with regard to the occurrence of PONV within the 3 study groups were not statistically significant ($p>0.05$). **Table 2** shows that 19 patients developed PONV. The frequencies of PONV were equal for both group P and M, and lower among group O. The difference between the study groups regarding the occurrence of PONV was not statistically significant ($p>0.05$, df=2, $X^2=0.564$). The longer the duration of the surgery, the more likely the patient would complain of PONV regardless of the study group $p<0.05$. **Table 3** shows that the patients who got PONV had significantly longer stay in the hospital than those who did not ($p<0.05$). The level of patient satisfaction was higher among group O (68%) when compared to other groups. However, the difference in the levels of satisfaction between the study groups was not statistically significant ($p>0.05$, df=2, $X^2=2.3$) (**Table 4**). **Table 5** shows that patients who consumed morphine had more PONV than those who did not. It ranged from 27.8% in group O, to 46.7% for patients in group P. The difference was statistically significant for patients in group P ($p=0.013$), but not for those in groups M and O ($p>0.05$). There was no difference between the 3 groups with regard to the VAS pain score, cardiovascular parameters, or oxygen saturation.

Table 1 - Characteristics of the patients.

Characteristics	Group P (n=25)	Group M (n=25)	Group O (n=25)	*P*-value
Age (years)*	41.4±10.3	43.4±10.2	43.4±9.4	0.066
Gender (M/F)	7/18	9/16	6/19	0.675
ASA (I/II)	17/8	19/6	20/5	0.5

Group P - placebo group, Group M - metoclopramide group, Group O - ondansetron group, *mean±SD, M - male, F - female, ASA - American Society of Anesthesiology classification

Table 2 - Incidence of postoperative nausea and vomiting (PONV) among the study groups.

Study groups	Without PONV		With PONV	
	n	(%)	n	(%)
Placebo group (n=25)	18	(72)	7	(28)
Metoclopramide group (n=25)	18	(72)	7	(28)
Ondansetron group (n=25)	20	(80)	5	(20)
Total	**56**	(74)	**19**	(25.3)

Table 3 - Association of postoperative nausea and vomiting (PONV) with the surgical duration and hospital stay.

Study group /occurrence of PONV	Mean duration of surgery ± SD (min)	Mean duration of hospital stay ± SD (hrs)	*P*-value
Placebo group			0.003
No (n=18)	59.39 ± 8.30	18.11 ± 2.7	
Yes (n=7)	90.86 ± 4.26	22.00 ± 2.58	
Metoclopramide group			0.000
No (n=18)	56.11 ± 8.01	17.44 ± 2.26	
Yes (n=7)	83.29 ± 7.76	23.43 ± 1.51	
Ondansetron group			0.013
No (n=20)	57.5 ± 7.88	19.00 ± 3.15	
Yes (n=5)	87.6 ± 2.88	21.60 ± 2.61	

Table 4 - Postoperative patient's satisfaction according to the treatment group.

Groups	Satisfied		Not sure		Total	
	n	(%)	n	(%)	n	(%)
Placebo group	12	(48)	13	(52)	**25**	**(100)**
Metoclopramide group	13	(52)	12	(48)	**25**	**(100)**
Ondansetron group	17	(68)	8	(32)	**25**	**(100)**

Table 5 - Association of postoperative nausea and vomiting (PONV) with morphine consumption among the study groups.

Study group/morphine consumption	Occurrence of PONV				*P*-value
	Without PONV		With PONV		
	n	(%)	n	(%)	
Placebo group					0.013
No	10	(100)	-	-	
Yes	8	(53.3)	7	(46.7)	
Total	**18**	**(72)**	7	**(28)**	
Metoclopramide group					0.105
No	6	(100)	-	-	
Yes	12	(63.2)	7	(36.8)	
Total	**18**	**(72)**	7	**(28)**	
Ondansetron group					0.161
No	7	(100)	-	-	
Yes	13	(72.2)	5	(27.8)	
Total	**20**	**(80)**	**5**	**20**	

Discussion. This prospective, randomized, double-blind placebo-controlled clinical investigation has shown no difference among the study groups regarding the incidence of PONV in 24 hours. Postoperative nausea and vomiting that are distressing were the frequent adverse events of laparoscopic surgery. In laparoscopic cholecystectomy, the frequency without prophylactic antiemetic was reported to be 72% in one randomized controlled trial.[2] In the presence of prophylactic antiemetic, the frequency decreased, but remained significant, within the range of 30-60% depending on the type of study.[3-5] The efficacy of routine use of prophylactic anti-emetic medications remains controversial.[12] Measurable beneficial effects were observed in only 20% of patients receiving prophylactic ondansetron to prevent PONV.[13] Prophylactic anti-emetic administrations also increase the risk of adverse drug effects, and increase the cost of care.[14] Emesis non-triggering anesthesia was planned. Prophylactic intravenous midazolam premedication was provided to all patients. Midazolam was found effective in reducing the incidence and severity of PONV in many studies. The possible mechanisms for this effect may be GABA receptor antagonism, inhibition of dopamine release, or anxiolytic effects.[15-16] Before surgery correction of intravascular volume deficits effectively reduces PONV and postoperative pain in high risk patients presenting for ambulatory surgery.[17-18] In most meta-analyses, propofol was associated with a lower frequency of PONV when used for TIVA, and nitrous oxide (N_2O) was avoided.[19-22] In one meta-analysis, the rate of PONV was lower with the use of propofol when compared with sevoflurane.[23] Peri-operative oxygen administration and avoidance of hypotension after induction of anesthesia has been shown to decrease PONV, suggesting that tissue hypo-perfusion may be an important etiological factor of PONV.[24-27] Gastric distension resulting from vigorous positive-pressure ventilation through a facemask may also precipitate vomiting.[28] To reduce the risk of PONV, the current study utilized emesis non-triggering TIVA technique in a relatively homogenous surgical population. The difference among the 3 groups regarding incidence of PONV within 24-hrs was not statistically significant. In a double-blinded study involving 160 patients, Helmy[29] reported a lower incidence of PONV under TIVA with ondansetron in comparison to droperidol, metoclopramide, or placebo. Postoperative nausea and vomiting precipitating factors were not avoided in that study. In our study, the incidence of PONV among ondansetron receiving patients was lower than those in other groups, but statistical significant was not reported ($p>0.05$). The more effective antiemetic rule of ondansetron was noticed by many studies. In a meta-analysis involving 58 studies and conducted by Domino et al,[30] ondansetron and droperidol were more effective than metoclopramide in reducing postoperative vomiting. Although the overall risk of adverse effects was the same among the drugs. Similar to that, Naguib et al,[2] and Dabbous et al[31] found that ondansetron is more effective in the treatment of established PONV than metoclopramide, and the patients were satisfied best with ondansetron. However, many studies have found that prophylactic administration of metoclopramide or ondansetron resulted in an equal effect in reducing the incidence of postoperative vomiting for laparoscopic cholecystectomy.[32-34] Now the question is whether ondansetron is more effective than metoclopramide or not? Our decision was to use both agents, depending on the availability of the 2 agents. In adult patients undergoing general anesthesia female gender, surgical duration of >60 minutes, and use of postoperative opioids are predictive factors for PONV.[35-37] The same findings were reported in this study as PONV was more frequent with female gender, lengthy surgical procedure, and with postoperative morphine consumption. Similar to Doze et al [38] study patients who encountered higher incidence of vomiting stayed in the hospital significantly longer than the others. This was a common finding among the study groups.

This study has potential limitations. First, these data may not be applicable to different patient populations, lengthier or different surgical procedures, or various anesthetic techniques. Second, the absence of pre-study power analysis. Third, this present study was designed to determine whether an emesis non-triggering anesthesia is associated with less PONV. Thus, the failure of this technique to alter the incidence of PONV when compared with administration of antiemetic medications

may not represent a lack of effect, but rather reflects a defect in the used technique. Fourth, the use of opioids analgesic and anticholinesterase were not avoidable, thus, the precipitant for PONV remains speculative.

In conclusion, it is unlikely that one technique or the drug will ever be effective in treating emesis under all surgical circumstances. Therefore, a multimodal regimen incorporating avoidance of emesis triggering factors and antiemetic medications is being recommended.

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