INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

COMPARISON OF INTRAOPERATIVE HIGH OXYGEN AND METOCLOPRAMIDE IN PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN ADULT FEMALE PATIENTS UNDERGOING ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY

Dr. Sonia Andleeb[1], Dr. Hameedullah Samiullah[2], Dr. Khalid Samad[2], Dr. Inam Gill[2]
[1]*Aziz Fatima Medical College & Hospital, Faisalabad, Pakistan.*
[2]*Aga Khan Medical College & Hospital, Karachi, Pakistan.*

ARTICLE INFO

Article history
Received 05/01/2019
Available online
31/01/2019

Keywords
Intraoperative High Fio_2,
Metoclopramide,
Laparoscopic
Cholecystectomy,
PONV.

ABSTRACT

INTRODUCTION: There are many benefits associated with the laparoscopic surgery including faster recovery, shorter hospital stays and prompt return to normal activities. Although laparoscopic surgery is minimally invasive in nature but high incidence of postoperative nausea and vomiting (PONV) remains a major cause of morbidity. To prevent PONV, multimodal techniques are helpful, but not any one technique is idea to deal with this problem. This study was carried out to compare the efficacy of intraoperative high oxygen concentration with metoclopramide in prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. OBJECTIVES: The objective of this study is to observe the effectiveness of high oxygen concentration as compared to metoclopramide in prevention of postoperative nausea and/ or vomiting in adult females undergoing elective laparoscopic cholecystectomy. METHODS AND MATERIAL: This prospective randomized clinical trial was conducted in the operating rooms of the Aga Khan University Hospital, Karachi. A total of 84 ASA I and II adult female patients undergoing elective laparoscopic cholecystectomy were included in this study. They were randomly divided into two equal groups to receive either FiO_2 intraoperatively or Metoclopramide. Postoperatively patients were observed for 24 hours for any episode of nausea, vomiting and antiemetic administration. RESULTS: There was a significant effect on incidence of PONV in adult female patients undergoing laparoscopic cholecystectomy and received high intraoperative oxygen concentration. During the 24 hr period, out of 84 patients, 12 patients (28.6%) in HO group experience PONV and required rescue antiemetic medication and 29 patients (69%) in Metoclopramide group experience PONV and so the rescue antiemetic medication. We can say high intraoperative oxygen concentration was effective in reduction of PONV as compared to metoclopramide. CONCLUSION: This study demonstrates that high intraoperative FiO2 was effective in prevention of postoperative nausea and vomiting in adult female patients undergoing elective laparoscopic surgery when compared to metoclopramide.

Corresponding author
Dr. Sonia Andleeb
MBBS, FCPS, Assistant Professor,
Aziz Fatima Medical College & Hospital,
Faisalabad, Pakistan.
03342915766 / 03018659185
drsonia.joseph@yahoo.com

*Please cite this article in press as **Sonia Andleeb** et al. Comparison of Intraoperative High Oxygen and Metoclopramide in Prevention of Postoperative Nausea and Vomiting in Adult Female Patients Undergoing Elective Laparoscopic Cholecystectomy . Indo American Journal of Pharmaceutical Research.2019:9(01).*

INTRODUCTION

Postoperative nausea and vomiting continues to be a therapeutic challenge for anesthesiologist particularly in ambulatory surgery. It affects approximately one third of the population undergoing general anesthesia whatever the procedure, with an average between 25% to 30% [1, 2]. PONV is multifactorial in nature with some risk factors and laparoscopic surgery is one of them. Incidence of PONV in laparoscopic surgery is between 53% to 72 %[3]. Significant research has focused on the use of different pharmacological agents and anesthesia techniques to prevent and treat PONV but none has been proved to be fully effective.

Antiemetic therapy itself is costly and associated with approximately 3% incidence of complications (Restlessness, dry mouth, sedation, hypotension & extra-pyramidal side effects) [4]. In literature review, there is no any recommendation for prophylactic use of antiemetic medications as there is little difference in the outcomes regarding time to discharge, unanticipated admission, patient satisfaction and time to return to normal activities when prophylactic antiemetic were used. Metoclopramide is among the most common antiemetic used [5]. It has an effect on chemoreceptor trigger zone, an anti-serotonin action at increase dose and increases the lower esophageal sphincter tone and gastric motility by its peripheral action.

Oxygen has been successfully used as antiemetic agent in many studies as is inexpensive and without side effect. However, there are different postulations regarding the action of oxygen as antiemetic but the exact mechanism of action is unknown. Intestinal tissues are thought to be highly metabolically active and so hypoxia or ischemia for even brief period is poorly tolerated by the intestinal tissue [4]. In laparoscopic cholecystectomy, pneumoperitoneum is created which leads to increased intraabdominal pressure and ultimately reduction of mesenteric and mucosal blood flow. Emetogenic substances are released due to gut ischemia and causes postoperative nausea and vomiting and intraoperative High FiO_2 reduces the postoperative nausea and vomiting by preventing the gut Ischemia.

We could not find any study in literature which compares metoclopramide with high oxygen supplementation in preventing PONV in adult female patients undergoing laparoscopic cholecystectomy, an abdominal surgery.

The rationale of this study is to evaluate the anti-emetic effects of high concentration of oxygen (70%) in adult female patients undergoing elective laparoscopic cholecystectomy. Since oxygen is cheap and without side effects [4, 6, 7], its use as an anti-emetic would enhance the anesthetist's armamentarium in dealing with PONV.

MATERIAL AND METHOD:

After obtaining approval from Ethics Review Committee of the Aga Khan University and informed written consent. This double blinded randomized clinical trial was carried out in the operating rooms of the Aga Khan University Hospital and 84 patients were enrolled. Female patients aged between 18 to 40 years' age, classified as ASA physical status I & II undergoing elective laparoscopic cholecystectomy were included. Patients having BMI > 30kg/m2, history of PONV or vestibule-cochlear disease, received aspiration prophylaxis or antiemetic of any duration, were excluded from the study. Randomization was done by opaque, sealed envelope method technique and patients were divided into two equal groups (Group C & Group HO). Group C (Metoclopramide) received 30% FiO_2 intraoperatively along with metoclopramide 10mg in 5mls on removal of gall bladder and Group HO (high intraoperative FiO_2) received 70% FiO_2 during intraoperative period and 5mls O.9% saline at removal of gall bladder. Blinding was done in a manner that neither the patient nor the primary investigators were aware of the group allocation. The syringe containing metoclopramide /Saline were prepared by anesthesiologist who was not providing anesthesia in the theatre and also not the investigator. In the operating room, the anesthesiologist who has given oxygen concentration and antiemetic according to the group allocation was not subsequently involved in the study. Primary investigator has collected the data in the postoperative period

Premedication was done with Tablet midazolam 7.5 mg to all patients one hour before surgery. In the operating room, routine preoperative anesthesia monitors including non-invasive blood pressure (NIBP), electrocardiogram (ECG) lead II and peripheral oxygen saturation (SpO2) was applied and baseline reading was obtained. Anesthesia was induced with morphine 0.1mg/kg and propofol 2mg/kg and muscle relaxation was achieved with atracurium 0.6mg/kg after maintaining a patent Intravenous (I/V) line. During the procedure, airway was maintained with size 7.0mm cuffed ETT and also for positive pressure ventilation (IPPV) during the procedure. Isoflurane in a concentration of 1 MAC was used to maintain anesthesia throughout the surgery. In the intraoperative period, FiO_2 was adjusted according to the group allocation with air.

If signs of light anesthesia (tachycardia, hypertension, sweating and lacrimation) or muscular movements were observed, additional bolus of atracurium 0.2-0.3mg/kg and morphine 1mg was given. In all the patients, orogastric tube was inserted to decompress the stomach and was removed at the end of surgery. The study drug was administered according to the group allocation at the time of removal of gall bladder. At the completion of surgery, Isoflurane was switched off and residual muscle relaxation was reversed with a mixture of neostigmine 0.04mg/kg and glycopyrrolate 0.01mg/kg and after fulfilling extubation criteria, trachea was extubated. All patients received half of fasting deficit of IV fluids in the first hour and half in the second hour intraoperatively. Patient was shifted to post anesthesia care unit (PACU) with O_2 4 l/min via face mask. Primary investigator has filled the predesigned proforma regarding the information of nausea and / or vomiting over 24 hours' period. All patients were prescribed metoclopramide 10 mg IV 8 hourly. Rescue antiemetic was given (Metoclopramide 10mg IV in Group HO and Ondansetron 4mg IV in Group C) if vomiting occurs by PACU nurse after enquiring from the anesthetist who had prepared the antiemetic at the time of group allocation

Sample size calculation was based on previous study [6]. A sample size of 84 (42 in each group) patients was required to achieve 80% power at 5% level of significance to detect a difference 26%. A study[6] showed that the incidence of PONV was 40% in those patients who treated with 30% oxygen in nitrous oxide and 14% in those treated with 70% oxygen in nitrous oxide.

All statistical analysis was performed using statistical packages for social science version 19 (SPSS Inc., Chicago, IL). Frequency and percentage was computed for categorical observation like ASA status and PONV. Mean and standard deviation was estimated for age, weight, BMI. Chi-square test was used to compare proportion difference among groups for PONV. $p \leq 0.05$ was considered level of significant. Stratification was done to control effect modifier like age, weight, height and ASA status to observe PONV

RESULT

During the conduct of this study, a total of 84 female patients who underwent elective laparoscopic cholecystectomy were studied.

Demographic and morphometric data are summarized in Table 1.

Duration of anesthesia was comparable in both groups, however duration of surgery was significantly higher in control group ($P < 0.05$) (Table 1)

Pain intensity and opioid consumption were similar in both groups and was not statistically significant.

Statistically significant result obtained in the reduction of PONV in the 1st and 6th hr.

In the 1st hr, 15 out of 42 patients (29%) in HO group and 29 out of 42 patients (69%) in C group experienced PONV (P=0.002) (table 2). Meanwhile in the 6th hr, 7 out of 42 patients (16.7 %) patients in HO group and 17 out of 42 patients (40.5 %) in C group experience PONV (p=0.016) (table 2). Although, there is no difference in the incidence of PONV in the 12th, 18th and 24 hr period (table 2).

There is significant reduction in the incidence of PONV in overall 24hr period. PONV was reported by 28.6% (n=12) in HO group and 69% (n=29) in metoclopramide group (p=0.005) and consequently require rescue antiemetic therapy (p=0.001) (table 3).

Table 1: Comparison of demographic and anesthetic measure between groups in adult females undergoing elective laparoscopic cholecystectomy.

Variables	Group HO n=42	Group C n=42	P-Values
Age (Years)#	40.69±9.95	42.05±10.87	0.55
Weight (kg)#	67.14±10.72	68.83±10.11	0.45
Height (cm)#	158.76±4.92	159.6±4.30	0.41
BMI (kg/m^2)#	26.61±3.92	26.96±3.45	0.65
ASA Status*			
ASA-I	21(50%)	19(45.2%)	0.66
ASA-II	21(50%)	23(54.8%)	
Co-Morbidity*			
Hypertension	8(19%)	9(21.4%)	0.78
Diabetic Mellitus	5(11.9%)	7(16.7%)	0.53
Anemia	7(16.7%)	7(16.7%)	0.99
Hypothyroid	2(4.8%)	1(2.4%)	0.55
Duration of Anesthesia (Min)#	96.43±16.32	94.05±20.72	0.56
Duration of surgery (Min)#	69.05±17.11	77.14±19.75	0.048†

Results are expressed as #mean ± standard deviation and * number (%). BMI= Body mass index

#Independent sample t test for mean comparison used *Chi-square test applied

Group HO=high oxygen; Group C= Control

Table 2: Comparison of nausea, vomiting and PONV among groups overtime in adult females undergoing elective laparoscopic cholecystectomy.

Follow-up Time	Group HO n=42	Group C n=42	P-Values
1st hours			
Nausea	12(28.6%)	27(64.3%)	0.001
Vomiting	13(31%)	26(61.9%)	0.004
PONV	15(29%)	29(69%)	0.002
6th hours			
Nausea	6(14.3%)	15(35.7%)	0.023
Vomiting	3(7.1%)	12(28.6%)	0.01
PONV	7(16.7%)	17(40.5%)	0.016
12th hours			
Nausea	0	2(4.8%)	0.15
Vomiting	0	1(2.4%)	0.999
PONV	0	3(7.1%)	0.24
18th hours			
Nausea	0	0	-
Vomiting	0	2(4.8%)	0.15
PONV	0	2(4.8%)	0.15
24th hours			
Nausea	0	0	-
Vomiting	1(2.4%)	1(2.4%)	0.999
PONV	1(2.4%)	1(2.4%)	0.999

Table 3: Comparison of nausea, vomiting and PONV, total dose of opioids and rescue Antiemetic among groups in adult females undergoing elective laparoscopic cholecystectomy.

	Group HO n=42	Group C n=42	P-Values
1 to 24h postoperative hours			
Nausea*	13(31%)	29(69%)ǂ	0.001
Vomiting*	14(33.3%)	26(61.9%)ǂ	0.009
PONV*	12(28.6%)	29(69%)ǂ	0.005
Rescue Antiemetic*	15(35.7%) (Metoclopramide)	30(71.4%)ǂ (Ondansetron)	0.001

#Independent sample t test for mean comparison used *Chi-square test applied
Group HO=high oxygen; Group C= Control

DISCUSSION

PONV is often documented by the patients as one of the worst complication of anesthesia and surgery and it has a major impact on patients particularly undergoing day care surgery. Although suture dehiscence, aspiration of gastric contents, esophageal rupture and other serious complications associated with PONV are rare, nausea and vomiting is still an unpleasant and all-too-common postoperative morbidity that can delay patient discharge from post anesthesia care unit and increase the unanticipated hospital admission in outpatients[12]. The incidence of intractable nausea and vomiting has been reported to be 0.18%[13]. It is not justifiable to use antiemetic medication for prophylaxis of PONV. Although, it is reasonable to use antiemetic for prophylaxis of PONV in high risk patients. The complication reported with use of antiemetic medication is 3% [4].

Much research on the control of PONV has been conducted during the last four decades. Many clinical trials focus on prophylaxis of PONV (i.e. patients receive an antiemetic at induction of anesthesia, during surgery or shortly before they wake up). However, with the prevention of PONV, several problems are encountered. First, in daily surgical settings (i.e. when the baseline risk for PONV is not particularly high), the efficacy of prophylactic antiemetic interventions is often disappointing. Second, the unanticipated admission risk decreases with prophylactic antiemetic is not evident[14]. Third, cost effectiveness is less with prophylactic antiemetic than to treatment of established symptoms[15]. Fourth, no single drug is without side effects and overall risk of adverse effects may not be different among various drug combinations[15].

And finally, prophylactic strategies exposed the patients unnecessarily who actually do not need it, and are thus put at risk of suffering from unnecessary adverse drug reactions[14]. It is not recommended to give prophylactic antiemetic medications to every patient, although PONV is a very unpleasant experience.

Generally, the incidence of PONV can be as high as 80% in high risk patients [16]. Among the multiple factors for PONV, including the type of surgery, high incidence of PONV (50-70%) has been reported in patients undergoing laparoscopic cholecystectomy [3].

However, the type of operation as a predictor of PONV provides questionable results (3,8,19, 20, 21).There are conflicting reports on type of operation and PONV because a high incidence of PONV after certain operations might be caused by the involvement of high-risk patients [19,21]. E.G. Multiple risk factors for PONV are present in patients undergoing day case gynaecological laparoscopy, as female gender, use of perioperative opioid, and a journey home which is likely to lower the threshold to motion-induced emesis[22]. This is not clear that the association is caused by the different anaesthetic agents, the different lengths of operation, or the operation itself[19]. The risk of PONV increases as the duration of surgery and anaesthesia increases because of greater accumulation of emetogenic anaesthetic agents [8,19]. The incidence of PONV increases from 2.8% in patients with a surgical duration of less than 30 minutes to 27.7% in patients with a surgical duration of between 151 to 180 minutes. The risk for PONV increases by 59% for each 30-minute increase in the duration of anesthesia [8,19].

There is still a continued search for an ideal antiemetic i.e. inexpensive, effective, few side effects and easily available. The concept of oxygen as antiemetic was first described by a German physician years ago, but this was not further investigated later on. In the literature, much of the information is present about the use of oxygen to reduce the incidence of PONV. However, clinicians are confused to use supplemental oxygen as a strategy to reduce the incidence of PONV because of the controversial results obtained in the literature.

The pathways involved in the pathophysiology of PONV are vestibular cochlear pathway, central chemoreceptor trigger zone and a local gastrointestinal pathway [4].

The rationale of administration of high intraoperative oxygen was that it minimizes the regional tissue hypoxia and thus release of emetogenic substances.

Metoclopramide and domperidone belong to benzamide group and it Blocks the effects of dopamine (a chemical that relays signals between cells) on the area of the brain containing the vomiting center. Metoclopramide is most widely used second line antiemetic among the benzamides. It has central and peripheral actions, centrally in the CTZ and in the area postrema, and peripherally in the GIT.

Metoclopramide hastens esophageal clearance, accelerating gastric emptying, and shortening bowel-transit time [5] .Adverse effects related to the metoclopramide are very much like that of the other D receptor antagonists and includes sedation, dizziness, and drowsiness. EPSs can occur, although they are rare. Patient can present with feelings of weakness, anxiety, agitation, and motor restlessness. Preoperative anxiolytic-sedative agent administration and slow intravenous administration of metoclopramide are important strategies for reducing the risk of akathisia from the administration of intravenous metoclopramide. Metoclopramide should be given at the end of surgery [23], as have a short duration of actions. It is established after a large randomized controlled multicenter trial of over 3000 patients led by Wallenborn in Germany that the most common side effects were hypotension and tachycardia immediately after the bolus administration, whereas the incidence of dystonia or extrapyramidal symptoms was less than 1%

Our study results are in accordance with previous studies conducted by Grief, Goll and Sadrsadat. Grief et al, found that 80% oxygen when given in colon resection surgery decreases the incidence of PONV from 30% to 17% as compared to 30% oxygen($p=0.027$) [4]. Although, operative procedure was different but we have also found that 70% oxygen reduces the incidence of PONV from 69 %(metoclopramide group) to 28.6 %(high oxygen group) ($p=0.005$). There was a standard rescue antiemetic in our study, although Grief has not standardized it.

Goll et al [24], in another study proved that 80% supplemental oxygen reduces the incidence of PONV from 44 % to 22 % as compared to 30% oxygen in accordance with our study results. Similarly, study done by Sadrsadat et al [5] concluded that there was a significant difference in postoperative nausea and vomiting in between two groups,14% in group treated with 70% oxygen and 40% in group treated with 30 % oxygen ($P=<0.00001$) which our study has also proved (28.6% PONV in HO group VS 69% in metoclopramide group)

Our study results are also in accordance of a study on the incidence of PONV by Jean and colleagues [25] and they concluded that the overall incidence of nausea during the first 24 postoperative hours was 48% in the patients given 30% oxygen, 46% in those given 80% oxygen, and 22% in those given droperidol.

Laparoscopic cholecystectomy is associated with highest incidence of PONV as compared to any other type of surgery. Purheonen et al in a study, concluded that supplemental perioperative FiO_2 of 80% could not be shown to reduce PONV as compared to 30% in patients undergoing gynecology laparoscopy (55 vs. 62) [7]

Overall incidence of PONV in 24hrs period in our study was high (69%) as compared to Grief (30%), Goll (44%) and Sadrsadat (40%), probably because some of the factors that are considered high risk for postoperative nausea and vomiting were included in our study that is laparoscopic cholecystectomy, female gender, intraoperative use of opioids and inhalational anesthetic agents.

Incidence of PONV is high in our study patients probably because of the laparoscopic surgery that is considered to be a risk factor for postoperative nausea and vomiting by creating increase intraabdominal pressure

One of the strongest risk factor for PONV is female gender with an odds ratio (OR) of 3,which indicates that female patients are on average three times more likely than men to suffer from PONV[12]. Female patients are at high risk probably because of high level of follicle-stimulating hormone (FSH) and estrogen and sensitization of the chemoreceptor trigger zone (CTZ) and vomiting center during menstruation and preovulatory phase of the menstrual cycle [7.26]. This is the reason for high incidence of nausea and vomiting in our study (40%).

Age as another risk factor, pediatric patients has been shown to be at high risk (34%) in the 6–10 year age group but considerably lower in younger patients, and the incidence decreases with the onset of puberty[21.27]. In adults, the incidence of PONV appears to decrease with age.

Recent meta-analysis demonstrated that an overall reduction in risk of PONV of 20% by avoiding nitrous oxide, the absolute difference in the incidence of PONV between the two groups is however small (33% with N2O and 27% without N2O)[28]. As nitrous oxide is a confounding factor and so it's not used in our study.

Risk of PONV increases two-fold by use of volatile anesthetics. Incidence of PONV increases in a dose dependent manner, and no significant difference in incidence with different volatile anesthetics. PONV increases by use of volatile anaesthetic agents by decreasing serum levels of anandamide, an endogenous cannabinoid neurotransmitter that acts on cannabinoid-1 and transient receptor potential vanilloid-1 receptors to suppress nausea and vomiting[19]. In our study, inhalational anesthetic was received by both groups of patients.

However, in a recent study it is concluded that PONV due to inhaled anesthetic is mainly in the early postoperative period and it seem not to be associated with the occurrence of the delayed PONV[29]

Although, Opioids are known to be the main triggers for PONV [23,29,30] but It is difficult to replace or at least minimize the use of Opioids [29]. All the patients in our study, received same opioids for analgesia.

There are some limitations of our study. First is that, results of our study may not be generalized to other population as they were obtained for only one type of surgery and from a single hospital. High oxygen was only administered during the intraoperative period and not in the post anesthesia care unit as it requires other apparatus.

CONCLUSION

This study has demonstrated that high intraoperative oxygen as compared to metoclopramide was effective in prevention of postoperative nausea and vomiting in adult female patients undergoing elective laparoscopic surgery

REFERENCES:

1. Shinn HK, et al. Post-operative nausea and vomiting after gynecologic laparoscopic surgery: comparison between propofol and sevoflurane. Korean journal of anesthesiology. 2011; 60(1):36-40.
2. Gupta P, et al. Role of pre-operative dexamethasone as prophylaxis for postoperative nausea and vomiting in laparoscopic surgery. Journal of minimal access surgery. 2006; 2(1):12-5.
3. Koivuranta M, et al. A survey of postoperative nausea and vomiting. Anaesthesia. 1997; 52(5):443-9.
4. Greif R, et al. Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. Anesthesiology. 1999; 91(5):1246-52.
5. Nelson PS, et al. Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam, and atropine for premedication in children. Anesthesiology. 1989; 70(4):616-21.
6. Sadrolsadat SH, et al. The effect of supplemental 70% oxygen on postoperative nausea and vomiting in patients undergoing inguinal hernia surgery. Hernia : the journal of hernias and abdominal wall surgery. 2008; 12(2):167-71.
7. Purhonen S, et al. Supplemental oxygen does not reduce the incidence of postoperative nausea and vomiting after ambulatory gynecologic laparoscopy. Anesthesia and analgesia. 2003; 96(1):91-6, table of contents.
8. Sinclair DR, et al. Can postoperative nausea and vomiting be predicted? Anesthesiology. 1999; 91(1):109-18.
9. Dodd M, et al. Advancing the science of symptom management. Journal of advanced nursing. 2001; 33 (5):668-76.
10. Kermode J, et al. Postoperative vomiting in children. Anaesthesia and intensive care. 1995; 23(2):196-9.
11. Kranke P, et al. An increased body mass index is no risk factor for postoperative nausea and vomiting. A systematic review and results of original data. Acta anaesthesiologica Scandinavica. 2001; 45(2):160-6.
12. Pierre S, Whelan R. Nausea and vomiting after surgery. Continuing Education in Anaesthesia, Critical Care & Pain. 2013; 13(1):28-32.
13. Kwekkeboom . The placebo effect in symptom management. Oncology nursing forum. 1997; 24(8):1393-9.
14. Kazemi-Kjellberg F, et al. Treatment of established postoperative nausea and vomiting: a quantitative systematic review. BMC anesthesiology. 2001; 1(1):2.
15. Norred . Antiemetic prophylaxis: pharmacology and therapeutics. AANA journal. 2003; 71(2):133-40.
16. Kappen TH, et al. Impact of risk assessments on prophylactic antiemetic prescription and the incidence of postoperative nausea and vomiting: a cluster-randomized trial. Anesthesiology. 2014; 120(2):343-54.
17. Chandrakantan , Glass PS. Multimodal therapies for postoperative nausea and vomiting, and pain. British journal of anaesthesia. 2011; 107 Suppl 1: 27-40.
18. Koivuranta M, et al. A survey of postoperative nausea and vomiting. Anaesthesia. 1997; 52(5):443-9.
19. Ku CM, Ong BC. Postoperative nausea and vomiting: a review of current literature. Singapore medical journal. 2003; 44(7):366-74.

20. Apfel CC, et al. A risk score to predict the probability of postoperative vomiting in adults. Acta anaesthesiologica Scandinavica. 1998; 42(5):495-501.
21. Apfel CC, et al. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999; 91(3):693-700.
22. Ahmed AB, et al. Randomized, placebo-controlled trial of combination antiemetic prophylaxis for day-case gynaecological laparoscopic surgery. British journal of anaesthesia. 2000; 85(5):678-82
23. Kovac AL. Prevention and treatment of postoperative nausea and vomiting. Drugs. 2000; 59(2):213-43.
24. Goll V, et al. Ondansetron is no more effective than supplemental intraoperative oxygen for prevention of postoperative nausea and vomiting. Anesthesia and analgesia. 2001; 92(1):112-7.
25. Joris JL, et al. Supplemental oxygen does not reduce postoperative nausea and vomiting after thyroidectomy. British journal of anaesthesia. 2003; 91(6):857-61.
26. Chatterjee S, et al. Current concepts in the management of postoperative nausea and vomiting. Anesthesiology research and practice. 2011; 2011:748031.
27. Stadler M, et al. Difference in risk factors for postoperative nausea and vomiting. Anesthesiology. 2003; 98(1):46-52.
28. Fernandez-Guisasola J, et al. Association between nitrous oxide and the incidence of postoperative nausea and vomiting in adults: a systematic review and meta-analysis. Anaesthesia. 2010; 65(4):379-87.
29. Apfel CC, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. British journal of anaesthesia. 2002; 88(5):659-68.
30. Watcha MF. Postoperative nausea and emesis. Anesthesiology clinics of North America. 2002; 20(3):709-22.

5487847845**1190109**