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Research Article

A COMPARATIVE STUDY BETWEEN ONDANSETRON VS GRANISETRON FOR PREVENTION OF NAUSEA VOMITING FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY AND COMPARISON WITH CONTROL GROUP

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ABSTRACT

Background: Laparoscopic surgeries are associated with an appreciably high rate of post-operative nausea and vomiting. This study was designed to compare the effectiveness of Ondansetron with that of Granisetron for prevention of post operative nausea vomiting after laparoscopic surgery with control group.

Objectives: The aim and objective of our study is to investigate and compare incidence of postoperative nausea vomiting following laparoscopic cholecystectomy among Ondansetron, Granisetron and Control Group in interval of (0-9) hours, (9-16) hours and (16-24) hours. This study also compares and finds association of socio-demographic variables and hemodynamic values between groups. It also explores the need of rescue anti-emetic dose among three groups and measure significant association between them.

Methods: In a randomized, prospective study, 63 adult patients of both sexes of ASA grade I and II categorized into three groups. The Ondansteron group patients received 15mcg/kg Inj. Ondansetron and Granisetron group patients received 40mcg/kg Inj. Granisetron over period of 30 seconds at the end of surgery .The control group did not receive anything. Perioperative anaesthetic care was standardized in all patients. Patients were then observed 24 hours for post operative nausea vomiting after administration of the study drug.

Results: Female gender has been associated with higher incidence of post operative nausea vomiting. Incidence of nausea and retching was higher in control group than in Ondasteron andGranisetrongroup,while higher in Ondasteron than in Granisetron group. The incidence of postoperative nausea vomiting was reduced to 9.5% in Ondasteron group whereas no incidence of postoperative nausea vomiting in Granisetron group as compared to 90.5% with control group experiencing more incidence during first 9 hours (p=0.000).

Complete response (no nausea and vomiting) was found among 100% of patients who received Granisetron, 90.5% who received Ondasteron and 9.5% among control group during 0-9 hours.

Conclusion: Granisetron is not superior to Ondasteron in the prevention of postoperative nausea and vomiting as there was not significant differences found between these two groups. Granisetron and Ondansetron both are superior to control group for prophylactic therapy for PONV. We can say antiemetic plays major role in reducing PONV after laparoscopic cholecystectomy.

Keywords: Cholecystectomy**,** Control, Granisetron, Laparoscopic, Ondansetron, Postoperative nausea and vomiting

INTRODUCTION

Laparoscopic surgeries have many advantages compared to an open procedure like less surgical trauma, less intraoperative and postoperative pain, early discharge, and also cosmetic benefit. A laparoscopic surgery requires the creation of a pneumoperitoneum.

Laparoscopic surgeries are known to be associated with a higher incidence of postoperative nausea and vomiting.[1] Despite various advances in anesthetic and surgical techniques, postoperative nausea and vomiting still remain the most common distressing factor after surgery.[2]Postoperative nausea vomiting (PONV) is one of the most common causes of patient dissatisfaction after anesthesia, with reported incidences of 30% in all post-surgical patients and up to 80% in high-risk patients. In addition, PONV is regularly rated in preoperative surveys, as the anesthesia outcome the patient would most like to avoid.

The mechanism of activation of the vomiting system is dependent on stimulation of gastrointestinal (mechanoreceptors and chemoreceptors) and/or central pathways which activate the chemoreceptor trigger zone in the area postrema. Postoperative emesis is activated by a range of factors before, during and after anesthesia.[3]

Nausea and vomiting is an unpleasant and all-too-common postoperative morbidity that can delay patient discharge from the post-anesthesia care unit and increase unanticipated hospital admissions in outpatients. The consequences of PONV may be surgical such as wound dehiscence, disruption of vascular anastomosis, aspiration pneumonitis and electrolyte imbalance.[4]

A number of pharmacological agents like antihistamines, butyro-phenones, and dopamine receptor antagonist were used for PONV but they were found to be associated with undesirable side effects such as excessive sedation, hypertension, dry mouth, dysphoria, hallucinations and extra pyramidal symptoms.[5]

5HT3 receptor antagonist was introduced in 1991. It belongs to the cys-loop superfamily of ligand-gated ion channels and is first-line therapy in the prevention of PONV.[6] Currently available 5-HT3 receptor antagonists are ondansetron and granisetron. Ondansetron was the first 5HT3 receptor antagonist with a relatively short half-life of three to five hours. Other drugs of this group such as tropisetron, polanosetron, dolasetron, alosetron are still not available in our country.

Granisetron, as compared to ondansetron, has a stronger 5HT3 binding, a longer half-life of 8-9

hours, is more potent and longer acting and has also been found to be very effective for preventing PONV after laparoscopic surgery with less incidence of side effects.[7,8]

ETIOLOGY OF POSTOPERATIVE NAUSEA AND VOMITING[1]:

Post-operative nausea and vomiting have a complex and multifactorial etiology, but there are a number of recognized contributing factors. These include patient, anesthetic, surgical and postoperative conditions.

I. Patient Related Factors:

A. **Pregnancy** Vomiting commonly occurs in the first 14 to 16 weeks of pregnancy; nausea occurs in 50% to 90% of pregnancies and vomiting 25% to 55%. Nausea and vomiting are more frequent in primigravidas, younger women, nonsmokers, the obese, and those with a prior history of nausea and vomiting.

B. **Uremia**: It is not clearly known that how uremia causes nausea and Vomiting, but it appears to act through the CTZ because ablation of this area eliminates uremia vomiting, some have suggested that the inciting agent is elevated the level of vasopressin seen in uremic patients. Several other disorders of fluid balance, such as water intoxication, intracranial hypertension, and acute severe hyponatremia, also elevate vasopressin levels.

C. **Intracranial Hypertension**: The vomiting associated with raised intracranial pressure typically occurs in the morning, without preceding nausea, and can be projectile. It presumably results from direct pressure on the vomiting center but also may be related to high level of vasopressin. One treats it by relieving intracranial hypertension.

D. **Diabetes Mellitus**: Impaired gastric motility without anatomic obstruction can lead to nausea and vomiting. This commonly occurs in the diabetics who have an autonomic neuropathy involving visceral as well as cardiac fibers. The visceral neuropathy can lead to delay in gastric emptying, early satiety, and nausea and vomiting, and it can predispose diabetic patients to aspiration after induction of anesthesia.

E. **Abdominal Disorders**: Irritation or distension of viscera can lead to emesis; this is soon in multiple abdominal disorders including peritonitis, bowel or gastric outlet obstruction, and viral gastroenteritis. Distension of the ureter by renal calculi, testicular pain, or cervical dilatation will also induce nausea and vomiting. These stimuli are carried by splanchnic and vagal afferents to the area postrema and the vomiting center. Vagotomy eliminates vomiting caused by these stimuli; ablation of the area postrema does not.

F. **Motion Sickness**: Motion sickness is caused by excitation of vestibular afferents by movement and is eliminated by destruction of the vestibular apparatus or the CTZ. Opiates predispose humans to PONV by sensitizing the vestibular apparatus to movement. A history of motion sickness increases the likelihood of PONV. The timing of PONV indicates that the vestibular component may be significant, a great proportion occurs during transport out of the recovery room.

G. **Perioperative Pain**: Clinical studies show that pain is a stimulus to nausea and vomiting and that pain relief, regardless of analgesic used, can decrease nausea and vomiting. In a study of 104 postoperative

patients, complete cessation of pain relieved nausea in 80% of episodes and only 10% of patients experienced nausea without pain.

H. **Medications**: Medications commonly associated with nausea and vomiting are L-Dopa, Bromocriptine, Opiates, Chemotherapeutic agents, cardiac glycosides, Alcohol, Non- steroidal anti-inflammatory drugs and Antibiotics.

I. **Gender**: Adult women are 2-4 times more likely to suffer PONV than men, and their symptoms may be more severe. The greater incidence of PONV in women may be linked to female hormones, as it has been found that most PONV occurs in the luteal phase of the menstrual cycle. There is no gender difference in the risk of PONV in pre- pubertal children or in the elderly.

J. **Obesity**: While obesity appears to increase the risk of PONV, results of studies in this area are conflicting. Fat-soluble anesthetics may accumulate in the larger amounts of adipose tissue found in the obese and then be released slowly, leading to prolonged side effects, including PONV.

K. **Delayed Gastric emptying**: Decreased gastric motility and emptying increases the likelihood of PONV. Conditions associated with delayed gastric emptying include gastrointestinal obstruction, pyloric stenosis, diabetes and pregnancy.

L. **Miscellaneous risk factors**: In the general population there are people who will vomit at the slightest exposure to provocative stimuli. Although this may be psychosomatic, it is also possible that the vomiting reflex is variably developed. Even the skill of the anesthesiologist has been known to influence the incidence of vomiting.

Ii. Anaesthesia and Effects on Nausea and Vomiting:

A. Pre-medication:

Current anesthetic agents and techniques have helped to eliminate the need for routine premedication. In addition, the high frequency of outpatient surgery has reduced opportunities for premedication. However, the goal of a relaxed but not overly sedated preoperative patient is still desirable.

1. Barbiturates: Barbiturates have been used for a long period as premedicants. The incidence of nausea and vomiting after barbiturate anesthesia is less than after inhalational anesthetics, ketamine and etomidate. The incidence is even lower with midazolam or propofol.
2. Tranquilizers: Proponents of tranquilzers as premedicantssite their sedative, antiemetic, and antihistaminic properties, Phenothiazine derivatives such as promethazine are considered to be good for sedation in addition to having antiemetic and antihistaminic capabilities. Hydroxyzine is considered to be an excellent anxiolytic and has antiemetic,bronchodilatory, anticholinergic, and antihistaminic effects. Droperidol, a butyrophenone, was commonly used as a premedicant when administered in a fixed combination with fentanyl. Although droperidol is an effective antiemetic, in larger dosages it is long acting, may produce dysphoria and extrapyramidal symptoms, and it is a weak alpha-adrenergic receptor blocking agent. Diazepam, lorazepam, and midazolam, produce minimal cardiovascular depression, have anticonvulsant activity, and do not contribute to PONV.

3. Opioids: The routine use of opioids as premedicants, despite the absence of preoperative pain, is based largely on tradition. Opioids are associated with a high incidence of nausea and vomiting. It is difficult to assess the relative emetogenicities of different opioids. In human volunteer studies, incidence of nausea and vomiting were similar between alfentanil and fentanyl and greater following buprenorphine compared with morphine or pethidine.
4. Anticholinergies They are administered intravenously to prevent the oculo-cardiac reflex or before a second dose of succinylcholine in children. Hyoscine and atropine are believed to 21have antiemetic actions. Although these drugs may decrease gastric secretions and increase gastric pH, they may also produce unpleasant CNS effects such as hallucinations, restlessness. Glycopyrrolate is the preferred agent for drying of secretions as it does not cross the blood brain barrier and has no CNS effects.

B. General Anesthesia:

1. Nitrous-Oxide: The literature concerning the emetic effects of nitrous oxide (N2O) contains controversial findings. Several properties of N2O could contribute to PONV; sympathetic stimulation, opioid-like effects, and closed space expansion. Alphaadrenergic receptor agonism has been shown to cause nausea and vomiting in animals, and the sympathomimetic effects of N2O have been postulated to the same. Changes in middle ear pressure and bowel gas volume can also cause nausea and vomiting. Studies by Eger have shown that 75% N2O can increase the volume of bowel gas by 80% to 100% after hours. Since intestinal distension is a known stimulus to vomiting, this can contribute to PONV after long surgical procedures. Even 30 minutes of 80% N2O can rise middle ear pressure to a range that cause emesis. On the other hand, during the recovery period from N2O inhalation, middle ear pressure can reach negative values if the Eustachian tube is not functioning. This irritates the vestibular system by producing traction on the round window and could lead to nausea and vomiting.
2. Potent Inhalation anesthetics: Historically the potent inhalation agents were notorious for prolonged emetic action. The advent of halothane, enflurane, and isoflurane has reversed the notoriety of the 22potent agents, and in fact, animal work indicates that halothane may have an antiemetic effect. Most studies comparing the three newer agents have shown no difference between them in inducing PONV and they seem to cause less PONV than anesthesia involving narcotics.
3. Intravenous Anesthetics: Intravenous agents have variable emetic effects. PONV does not commonly occur after administration of ultrashort-acting barbiturates when used for induction or maintenance of anesthesia for brief, painless procedures. Thiopental is probably the most commonly used and least associated with PONV. Ketamine may cause PONV more frequently than other intravenous anesthetic agents, though not to the extent that would require the routine preoperative administration of antiemetic. When intravenous narcotics are used in large doses as the sole or major anesthetic agents, it has the clinical impression that postoperative emetic problems are very uncommon. It has been postulated that large doses of narcotics directly depress the vomiting center in the brain. One of the characteristics of neuroleptic analgesia, which combines an intravenously administered sedative with an

analgesic, is having a lower incidence of PONV.

4. Anticholinesterase: There is significant relationship between PONV and the antagonism of muscle relaxants by neostigmine and atropine. The incidence of vomiting was 47% in those patients in whom muscle relaxation was reversed versus only 11% in those in whom the neuromuscular block was allowed to wear off. All patients has joint replacement procedures, and determinations were made 24 hours postoperatively. It was concluded 23that the neostigmine, through an increase in gastrointestinal peristalsis and spasm, could contribute to PONV. The addition of atropine or glycopyrrolate to neostigmine failed to reduce the incidence of PONV after administration of anaesthesia using halothane and pancuronium.

III Surgical Factor:

Certain types of surgery carry a greater risk of PONV. In adults, high incidences of PONV are found in intra- abdominal surgery (70%), majorgynaecological surgery (58%), laparoscopic surgery (40-77%),orthopaedic surgery (40%) and ENT surgery (71%). The surgical procedure associated with the lowest incidence of PONV is peripheral and superficial extremity surgery. PONV after intra-abdominal surgery may be due to stimulation of vagal afferents during gut manipulation. Vagal afferents on the bowel and peritoneum may also be triggered when the peritoneal cavity is insufflated with carbon dioxide during laparoscopy.

Middle ear operations are most associated with PONV in adult ENT surgery. Stimulation of the auriculotemporal branch of the facial nerve during ear surgery may cause PONV, as could stimulation of the labyrinthine pathways during middle ear surgery.

In children, the surgical procedure associated with the highest incidence of PONV is strabismus surgery with figures from the literature of up to 85%. The emetogenicity of this procedure is caused by stimulation of the oculo-emetic reflex during traction of the extra-ocular muscles, or as a result of visual image distortion secondary to acute correction of visual axis alignment.

The incidence of PONV after adeno-tonsillectomy in children is 58%. This high incidence is probably due to the irritant effect of blood on chemoreceptors and nociceptors in the esophagus, and stimulation of the trigeminal nerve during surgery. As in adults, peripheral and superficial extremity surgery in children carries a low incidence of PONV.

IV Postoperative Factors:

Postoperative pain, particularly visceral and pelvic pain, is associated with PONV. The treatment of pain with opioids also causes PONV; in fact effective control of pain can be limited by PONV. This most often occurs when analgesia is self-administered as in patient-controlled analgesia (PCA). Movement is a common trigger of PONV. Use of opioids may sensitize the vestibular system and the combination of opioid pain control and postoperative movement is especially emetogenic. Postoperative hypotension and hypoxaemia can also result in PONV.

Laparoscopic Surgeries:

Laparoscopic surgeries are done very commonly nowadays in every part of the world. They have many advantages compared to an open procedure like less surgical trauma, less intraoperative and postoperative pain, early discharge, and above all the cosmetic benefit. It requires the creation of a pneumoperitonium. CO2 is used for gas insufflation via a VERESSS needle, at a rate of 1-6 liter /minute, to a pressure of 14- 20mmHg. Intraoperative problems during laparoscopic surgery can be cardiovascular, respiratory, gastrointestinal, renal or metabolic related. Hemodynamic changes, decrease in venous return, reflux tachycardia and arrhythmias due to gas insufflation are the main cardiovascular problems. Respiratory problems are mainly due to pneumoperitonium, which may cause cephalad displacement of diaphragm. This leads to reduction in lung volumes including tidal volume, functional residual capacity, decreased pulmonary compliance, increased airway resistance, and also the risk of barotraumas during IPPV. Restriction in diaphragmatic mobility promotes uneven distribution of ventilation to the nondependent part of the lung, which can lead to ventilation- perfusion mismatch with hypoxemia and hypercarbia. (CO2 absorption from pneumo- peritoneum may also cause hypercarbia). For this reason, ETCO2 (End tidal CO2) monitoring is very much desirable during laparoscopic surgeries. Increased intra-abdominal pressure may predispose to regurgitation and aspiration in those who susceptible. Gastrointestinal considerations during laparoscopic surgeries are mainly regarding injuries to the visceral organs that can be caused by the laparoscopic instruments. Trochar insertion can damage viscera; particularly a stomach distended by hand ventilation. There is increased incidence of nausea and vomiting after laparoscopic surgeries (Incidence of up to 70% has been reported in some studies). Though the exact cause for this is not known residual pneumoperitonium is considered the main etiology.

Intra-abdominal pressure >20mmHg adversely affects renal function and urine output. Renal blood flow and glomerular filtration rate decrease because of increase in renal vascular resistance, reduction in glomerular filtration gradient and decrease in cardiac output. Complications of gas insufflation can be arrhythmias, subcutaneous emphysema, pneumomediastinum, pneumopericardium, pneumothorax and venous gas embolism.

In the preanesthetic checkup, cardiac and respiratory function is assessed carefully. General anesthesia with muscle paralysis intubation and IPPV is the most common method. If appropriate, general anesthesia with spontaneous ventilation by using laryngeal mask airway can also be considered for ASA 1 or 2 patients with no other contraindications. Ventilatory pattern is adjusted according to respiratory and hemodynamic response of the patient. Large tidal volumes (12-15ml/kg) prevent progressive microatelectasis and hypoxemia and allows for more effective alveolar ventilation and CO2 elimination. However peak airway pressure is monitored to check excessive increase.

Postoperative recovery is usually very rapid. PONV can be particularly troublesome after laparoscopic surgeries. Pain consists of an early transient vague abdominal and shoulder discomfort. Pain

from trochar-puncture wounds is usually mild. Use of opioids should be accompanied by an antiemetic. Pulmonary function is better preserved following laparoscopic surgeries than in open abdominal surgeries.

REVIEW OF LITERATURE

FujiiY et al. revealed that during the 24 hour after recovery from anesthesia, the frequencies of postoperative retching and vomiting in patients who had received Granisetron were lower than those who had received placebo and the severity of postoperative vomiting was reduced with the administration of granisetron.[9]

According to **Sniadach MS et al** postoperative nausea and vomiting is a common complication of laparoscopic procedures. Those most at risk are patients who are young, female, and nonsmokers, patients with less co-morbidity, and those undergoing laparoscopic gynecologic procedures. The most frequently reported side effects of Ondansertron include constipation and headache.[12]

Bhattcharya D et al concluded that in comparison to Granisetron,Ondansetron& placebo, Granisetron is more potent..[13]

Kanwalpreet B et al. concluded that prophylactic use of Granisetron-dexamethasone combination significantly decreases the incidence of both postoperative nausea and vomiting. Further, the use of Granisetron-dexamethasone combination is more effective than either drug alone for prophylaxis against PONV in breast surgery patients. [14]

Gauchan S et al. revealed that Ondansetron and Granisetron had a similar antiemetic effect in the first 3 hours period (P>0.05). Between 4–12 hours also the episodes of nausea, retching as well as vomiting did not show statistically significant in both the groups. In the last 12 hours, episodes of nausea, retching and vomiting were significantly higher in Ondansetron group.[2]

Makker R et al. concluded that in the early postoperative period both Ondansetron and Granisetron are equally effective in preventing postoperative nausea and vomiting in patients undergoing gynecological surgery under spinal anesthesia. Granisetron is better than Ondansetron in the late postoperative period of up to 24 hrs. [15]

Chaudhari SA concluded Ondansetron effectively reduces postoperative nausea and vomiting as Granisetron in early post-operative period but Granisetron prevents PONV for longer period upto 24 hours postoperative without any significant side effects.[16]

In a prospective, randomized, double blind, comparative study conducted by **Rao Mekala et al.** in 2019 in order to compare the efficacy of Granisetron, Ondansetron and Palonosetron to prevent PONV after laparoscopic surgeries, it was found that prophylactic therapy with Palonosetron was more effective than prophylactic therapy with Ondasteron and Granisetron for the long-term prevention of PONV with minimal side effects.[17]

A randomized, cross-sectional study was done by **Taneja K et al.** in 2021 to compare the efficacy of Ondansetron and Granisetron in patients undergoing laparoscopic cholecystectomy. Thus, the incidence of

vomiting as compared to nausea and PONV were less in subjects who have received Granisetron. Data showed that Granisetron is a better antinausea drug. [18]

A prospective, randomized, double blind, comparative study was conducted by **Rao M et al.** in 2021 to compare Ondansetron, Granisetron and Granisetron with Dexamethasone for prevention of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic cholecystectomy. The findings were combination therapy with Granisetron and Dexamethasone IV used as prophylactic antiemetic was better than Granisetron or Ondansetron given IV alone. IV Granisetron and Dexamethasone combination had fewer side effects compared to Ondansetron or Granisetron. This was seen in all three time periods of 2-6 hours, 6-12 hours and 12-24 hours postoperatively. Need for the rescue antiemetic was least in the patients receiving Granisetron and Dexamethasone combination as compared to in patient receiving Ondansetron and Granisetron alone.[19]

In a randomized double-blind study done by **Ommid et al.** in 2013, it was concluded that prophylactic administration of Granisetron is more effective than Ondansetron, in reducing in incidence of PONV with prolonged effects.[20]

In a study done by **Esmael et al.** to evaluate and compare the antiemetic efficacy of Granisetron, Ondansetron and placebo for prevention of postoperative nausea and vomiting (PONV) in patient undergoing laparoscopic cholecystectomy (LC), the results revealed that prophylactic antiemetic reduce the incidence of PONV in patients undergoing elective laparoscopic cholecystectomy. The incidence of PONV was 37%, 32%, and 65% in Ondansetron, Granisetron, and placebo group, respectively, during first 48 hours after anesthesia. There were no significant differences in the incidence of PONV and the use of rescue antiemetic between Ondansetron and Granisetron groups; however, in both groups these incidences were significantly lower than that in placebo group. In Ondansetron and Granisetron groups, nausea scores were significantly lower than that in placebo group up to 6 hours postoperatively. Ondansetron (4 mg) is as effective as Granisetron (3 mg); however, Ondansetron is preferred for routine antiemetic prophylaxis as it is less expensive.[21]

A randomized prospective study was conducted by **Chidambaram et al.** in 2010 to compare the effectiveness of Ondansetron with that of Granisetron for prevention of PONV after laparoscopic surgery and their effect on clinical recovery and recovery time. Patients received either Ondansetron 4mg or Granisetron 2mg intravenously at the end of surgery. Perioperative anesthetic care was standardized in all patients. Patients were then observed 24 hours after administration of the study drug. The results found that a complete response (defined as no PONV and no need for another rescue antiemetic) was achieved in 75% of the patients given Ondansetron and 86% of the patients given Granisetron. This study concluded that the prophylactic intravenous administration of Granisetron is more effective drug than Ondansetron for controlling postoperative nausea and vomiting with fewer incidences of side effects [22]

The randomized study was done by **Gupta et al.** in 2008 in order to compare the antiemetic effect of intravenous Granisetron, Ondansetron & Metoclopramide for prophylaxis of post-operative nausea and vomiting (PONV) in patients undergoing laparoscopic cholecystectomy under general anesthesia. 60 patients

(ASA I & II) undergoing laparoscopic cholecystectomy under general anesthesia were randomly allocated into three equal groups Group A (Granisetron 3mg), Group-B(Ondansetron 4mg) or Group-C (metoclopramide 10mg)(n=20).. Minimal emetic episodes were observed in early post-operative period (1-12hrs) in patients who had received intravenous Granisetron in comparison to Ondansetron and Metoclopramide. However, after 12 hours emesis free periods were statistically insignificant between group A and B while patients in group C had no antiemetic effect.[23]

This prospective, double-blind study was conducted by **Kathuria et al.**[24] in 2020 in order to compare the prophylactic effects of intravenously administered Ondansetron, Palonosetron, and Granisetron in prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery under general anesthesia. Patients were randomized into three equal groups. Group P received inj. Palonosetron (0.075 mg), group O received inj. Ondansetron (8 mg), and group G received inj. Granisetron (2.5 mg) intravenously five minutes before induction of anesthesia. The episodes of postoperative nausea and vomiting, severity of nausea, need for rescue antiemetic, side effects and patient satisfaction were observed in the study groups for 24 hours in the postoperative period. Results revealed that the incidence of PONV was significantly less in the Palonosetron group (95.6%) as compared to the Ondansetron group (80%) and Granisetron group (73.3%), with a lesser need for rescue antiemetic in the Palonosetron group. All the three study groups did not have significant adverse effects reflecting that all the three drugs were well-tolerated. Patient satisfaction score was also more with Palonosetron.

A randomized, prospective and comparative study was done by **SahaA et al** in 2014 to compare the effectiveness of Ondansetron with that of Granisetron for prevention of PONV after laparoscopic cholecystectomy. Group one received Ondansetron 4mg intravenously and group two received 2mg Granisetron intravenously before induction. Perioperative anesthetic care was standardized in all patients. In 24 hours after administration of the study drug, a complete response (defined as no PONV and no need for another rescue antiemetic) was achieved in 66% of the patients given Ondansetron and 82% of the patients given Granisetron. Increased incidence of side effects was seen in Ondansetron group than Granisetron group. Thus, it is concluded from this study that Granisetron is slightly more effective than Ondansetron as prophylactic antiemetic in laparoscopic cholecystectomy.[25]

A prospective, randomized double-blind placebo-controlled study was conducted by **Bhashyam et al.**[26] in 2015 to study the efficacy of ODF of Ondansetron in the prophylaxis of PONV and to compare it with intravenous Granisetron and placebo in patients undergoing Laparoscopic cholecystectomy. Sample were randomized into 3 groups of 40 patients each as Placebo, intravenous Granisetron 2mg and ODF of Ondansetron 8mg (ODF8) groups. Study drugs were administered just before induction of anesthesia. The results revealed that the incidence and severity of nausea and vomiting at different time intervals in Group G and ODF Group was significantly lower when compared with Placebo Group (p=0.000). But there was no significant difference in between the ODF and intravenous groups. There was no significant difference in the incidence of side effects in between the three groups. Study found that orally disintegrating film of

Ondansetron is a safe, simple and cost-effective, novel formulation, equally effective to intravenous Granisetron in preventing PONV in patients undergoing laparoscopic cholecystectomy.

A comparative study was carried out by**Yeasmeen et al.** in 2006 to compare the efficacy of Granisetron with that of Ondasteron and Metoclopramide in the treatment and prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Sample were divided into three groups as Group I received injOndasteron (1 mg), Group II received injOndasteron (8mg) and Group III received injMetoclopromide(10mg). The incidence of emesis free was significantly higher in patients who received Granisetron(90%)than those who received Ondasteron(66.7%) or Metoclopramide(40%).

The incidence of vomiting free was significantly higher in patients who received Granisetron(93.3%) than those who received Ondasteron(73.3%) or Metoclopromide (46.7%). Granisetron was associated with greater patients' satisfaction than ondasteron and metoclopramide 40%, 20% and 10% respectively. The results conclude that Granisetron is more effective than Ondasteron and metoclopramide in the prevention and treatment of postoperative nausea and vomiting after laparoscopic cholecystectomy. [27]

The randomized double blind study was conducted by **Rajendra et al.** in 2015 to compare the efficacy of intravenously administered 5-HT3 receptor antagonists namely Ondansetron, Palonosetron and Granisetron given as prophylaxis for postoperative nausea and vomiting in patients undergoing laparoscopic surgeries under general anesthesia. The incidence of PONV (nausea, retching and vomiting) after 24 hours was 34% in the Ondansetron group, which was higher than in Palonosetron group and Granisetron group which had 6% and 20% incidence respectively. Hencethe results concluded that a single dose of Palonosetron (0.75 µg) when given prophylactically results in a significantly lower incidence of PONV after laparoscopic surgeries than Ondansetron (4mg) and Granisetron (2.5mg) during the first 24 hours.[28]

In a comparative study conducted by **Nanjundaswamy et al** in 2018 in order to compare the efficacy of combination of antiemetic: Ondansetron 4mg+Dexamethasone 8mg and Granisetron 1mg+Dexamethasone 8mg in prevention of post-operative nausea and vomiting, the results revealed that Granisetron 1mg and Ondansetron 4mg in combination with dexamethasone 8mg are equally effective and safe in decreasing the incidence of post-operative nausea and vomiting in laparoscopic cholecystectomies under general anesthesia.[29]

A prospective, randomized, double-blind study was carried out by **Naguib et al**. in 1997 in order to compare the antiemetic activity of the prophylactic administration of Ondansetron 4 mg, Tropisetron 5 mg and Granisetron 3 mg with that of metoclopramide 10 mg and placebo in 132 patients undergoing laparoscopic cholecystectomy. All study drugs and placebo were given as a short IV infusion ten minutes before the induction of anesthesia. The findings of the study showed that for the 24-hr recovery period after surgery, the percentages of emesis-free patients were 65.5%, 52%, 48%, 29.2% and 27.6% in the Ondansetron, Granisetron, Tropisetron, metoclopramide and placebo groups, respectively. Prophylactic antiemetic treatment with Ondansetron resulted in a lower incidence ($P = 0.02$) of PONV than with metoclopramide or placebo. The times at which rescue antiemetic was first received were longer ($P < 0.01$) in

Ondansetron group than in the placebo and metoclopramide groups. There were no statistical differences between Ondansetron, Tropisetron and Granisetron groups.[30]

A comparative study was conducted by **Sharma et al.** in 2017 to compare the efficacy of Granisetron with that of Ondansetron as antiemetic is compared in 90 patients undergoing laparoscopic surgeries. The patients were divided into three groups of 30 patients each. In group-G, patients received 40 mcg/kg Granisetron intravenously 3 min before induction. Group-O patients received 80 mcg/kg Ondansetron intravenously 3 min prior to induction while group-C patients received 3 ml of 0.9% normal saline as control. All the patients were selected for general anesthesia and observed for pulse rate, blood pressure, nausea, vomiting and side effects of the drugs under study up to 12 hours postoperatively. The frequency of nausea was 10%, 30% and 40% in group-G, group-O and group-C respectively. The results showed that Granisetron is better for prevention of post-operative nausea and vomiting (PONV) in comparison to Ondansetron and is highly significant in comparison to control group. As far as the side effects of the drugs are concerned, postoperative headache, dizziness, diplopia and shivering was significantly higher in Ondansetron groups.[31]

A comparative study was carried out by **Chandra et al.** in 2015 to compare the efficacy of Ondansetron, Granisetron andRamosetron to prevent nausea & vomiting after general anesthesia .Total 120 patients undergoing general anesthesia were randomly divided in four groups of 30 patients each as Group 1: Ondansetron 0.15mg/kg IV, Group 2: Granisetron 10mcg/kg IV, Group 3: Ramosetron 0.3mg/kg IV, Group 4: Normal saline 2ml IV. Result revealed that Granisetron is more effective to control nausea and vomiting after general anesthesia.[32]

In a comparative study conducted by **Sharma et al.** in 2015 in order to compare the efficacy of Ondansetron with Granisetron in preventing post-operative nausea and vomiting (PONV) after general anesthesia, 60 patients of American Society of Anesthesiologists (ASA) status I and II were randomly divided into two groups as Group 1(n=30) Inj. Ondansetron 0.15 mg/kg and Group 2(n=30) InjGranisetron 10 mcg/kg.

Incidence of nausea and vomiting was observed upto 24 hours post operatively after extubation. The findings of the result revealed that the number (percentage) of patients with mild nausea not requiring rescue antiemetic in group 1 was 10(33.3%) and in group 2 was 2(6.6%). The number (percentage) of patients with severe nausea or vomiting requiring rescue antiemetic in group 1 was 12(40%) and in group 2 was 5(16.6%).The number (percentage) of patients with no nausea or vomiting in group 1 was 8(26.6%) and in group 2 was 23(76.6%). Hence it was concluded that Granisetron is the better drug for prevention of postoperative nausea and vomiting than Ondansetron.[33]

A metanalysis was performed by **Wu et al.** in 2013 to assess the prophylactic antiemetic effects of Ondansetron versus Granisetron for laparoscopic cholecystectomy. Results revealed that the merged early incidence of postoperative nausea and vomiting (PONV) in Ondansetron group (42.9%) was higher than Granisetron group (34.3%). The merged total incidence of PONV in Ondansetron group (38.7%) was higher than Granisetron group although these differences were not statistically significant. Thus, the study

concluded that Ondansetron is equivalent to Granisetron for preventing early and total incidence of PONV after laparoscopic cholecystectomy. [34]

A randomized, double blind, placebo-controlled study was conducted by **Erhan et al.** in 2008 to compare the effectiveness of Ondansetron, Granisetron, and Dexamethasone for the prevention of PONV in patients after laparoscopic cholecystectomy. Patients were randomly divided into four groups (n = 20 each). Group 1, consisting of control patients, received 0.9% NaCl; group 2 patients received Ondansetron 4 mg iv; group 3 patients received Granisetron 3 mg iv; and group 4 patients received dexamethasone 8 mg iv, all before the induction of anesthesia. Both nausea and vomiting were assessed during the first 24 h after the procedure. Result revealed that the total incidence of PONV was 75% with placebo, 35% with Ondansetron, 30% with Granisetron, and 25% with dexamethasone. Thus, the study found that Dexamethasone 8 mg was as effective as Ondansetron 4 mg and Granisetron 3 mg, and it was more effective than placebo.[35]

A randomized, double-blind study was carried out by **Oksuz et al.** in 2007 to compare the antiemetic activity of different 5-hydroxytryptamine-3 receptor antagonists with that of Metoclopramide. 75 patients received the following: Group M, 10 mg Metoclopramide; Group K, 40 mcg/kg, Granisetron; and Group Z, 15 mcg/kg Ondansetron intravenously (IV) diluted in 20 cc 0.9% NaCl (n = 25 of each) i.v. immediately before the induction of anesthesia. The findings of the result wereGranisetron, when given prophylactically, resulted in a significantly lower incidence of PONV than metoclopramide and Ondansetron, whereas Metoclopramide was ineffective. Garnisetron may be an effective treatment in the prophylaxis of PONV. [36]

Network meta-analysis of randomized clinical trials and trial sequential analysis was performed by **Sridharan et al** in 2019 to evaluate drugs reducing PONV in LC. Ninety clinical trials were included. Results revealed that dexamethasone and Ondansetron have the best evidence as stand-alone options and the combination is preferred in high-risk category.[37]

A randomized, single blind study was conducted by **Bhattarai et al.** in 2017 to compare the antiemetic efficacyof two different 5-hydroxytryptamine-3 (5HT3) receptor antagonists, Ondansetron and Granisetron when given prophylactically to patients undergoing laparoscopic cholecystectomy. 75 patients were divided into two groups: Group O and Group G. Patients in group O were given 0.1 mg/kg Ondansetron intravenously (IV) and patients in Group G were given 0.04 mg/kg Granisetron. The standard general anesthetic technique was administered to all the patients. Episodes of nausea, retching and vomiting were assessed during the first 24 hours after anesthesia. The findings of the result showed that both drugs were similarly effective in first four hours (P>0.05). Between 4–12 hours and 12-24 hours, episodes of nausea and vomiting were higher in Ondansetron group. The incidence of PONV was significantly high in Ondansetron than in Granisetron given prophylactically in laparoscopic cholecystectomy. [38]

A comparative study conducted by **Agarwal et al** in 2018 to assess if there is any effect of Granisetron and ondansetron with dexamethasone in prevention of PONV after general anesthesia for laparoscopic cholecystectomy. Group I (n=50), group II (n=50) and group III (n=50) were introduced Ondansetron (4mg) andDexamethasone 8mg, Granisetron (1mg) andDexamethasone 8mg and Normal

saline&Dexamethasone 8mg respectively. The results revealed that there was no statistical difference observed between group I and II in first 24 hours but significant difference was observed between group I, group II and control group III. Complete response scored 96%, 98% and 56% respectively for group I, group II and group III correspondingly after at 6 to 12 hours. Findings of the study strongly suggested that combination of dexamethasone either with ondansetron or granisetron are equally effective in decreasing incidence of PONV in laparoscopic cholecystectomy patients as prophylaxis.[42]

Bhatrai B et al did randomized control trial to compare Ondansetron and combination of Ondansetron and dexamethasone as a prophylasis for PONV. Incidence of PONV in Ondansetron group was 24% while PONV in Ondansetron and Dexamethasone group was 8% (p=0.029)[43]

Ehlkim M et al did a randomized double blind, dose ranging study . The incidence of PONV in patient who did not receive prophylactic antiemetic was 83%while patient who received Ondansetron 4mg Ondansetron 8mg , Ondansetron 16mg was 50%,16% and 16% respectively [44]

METHODOLOGY (DATA COLLECTION PROCEDURE)

After approval from the institutional and ethical clearance committee and informed written consent from patients, sixty-three patients of ASA I or II of age between 20-60 years were selected for the study from routine list of Laparoscopic cholecystectomy. Detail History and Examination was done preoperatively. They were pre-medicated with 150 mg of ranitidine orally 12 hours before giving general anesthesia (to allay gastric reflux). Patients were kept NPO for 6 hours for solid food and 2 hours for clear water before surgery.

On the day of surgery, in the preoperative room, Intravenous line was secured by 18G of cannula. In the operation theatre routine monitoring devices pulse oximetry, Noninvasive Blood pressure (NIBP), Electro-Cardiography (ECG) monitors were attached, and baseline Blood pressure, heart rate, O2 saturation and values were recorded.

The anesthetic regimen and surgical procedures were standardized for all patients.

The patients were induced with Fentanyl (1-1.5 mg/kg) and Propofol (1-2mg/kg) with Vecuronium (0.1mg/kg) as a muscle relaxant. Endotracheal intubation was done by Anesthesiologist or Resident doctors.

Anesthesia was maintained with Isoflurane 1.2-1.5%, oxygen 2L/min and intermittent doses of Vecuronium Bromide was used.

Ventilation was controlled mechanically and adjusted so as to keep the end tidal Carbon dioxide 35-40 mm of Hg. Laparoscopic surgery was performed.

During surgery the patients were placed in trendelenberg position wherever required and the abdomen was insufflated with carbon dioxide with an intra-abdominal pressure of 12-15 mm of Hg via a VERES needle, at a rate of 1-6 liter /minute. During the port site closer, Group A patients received 15mcg/kg injOndansetron and Group B patients received 40mcg/kg inj. Granisetron was administered slow iv over period of 30 seconds. Group C did not receive anything.

Subcostal TAP block was given at the end of surgery with 20ml of 0.25% of Ropivacaine on each side.

Residual neuromuscular block was routinely reversed with inj Glycopyrrolate 0.001mg/kg and Neostigmine 0.05mg/kg and then patient was extubated. In post anesthesia care unit Blood pressure and Heart rate was recorded every 5 min for 30 mins.

We assessed postoperative nausea and vomiting by using PONV score[39]as: -

Score	Symptoms
0	No nausea
1	Nausea only
2	Nausea with retching
3	Vomiting

Table 1: Postoperative Nausea vomiting (PONV) score

Rescue dose of emetics was given to patients if patient develops PONV Score of 1 or more. Ondensatron was given for those who received Ondensetron initially and Granisetron for those who received Granisetron initially.

Total Doses of antiemetic, frequency of antiemetic and time for rescues dose of antiemetic drugs was noted.

During postoperative hospital stay, Patient was managed with Analgesics, (Inj Paracetamol 1gm IV TDS and Inj. Ketorolac 30mg IV sos) Inj. Pantoprazole 40mg IV and Maintainace fluid till patient was kept NPO.

Patient was observed for 24 hours and recorded if there is presence of PONV or not in during time interval of (0-9) hours, (9-16) hours, (16-24) hours.

If patient develope PONV repeatedly despite giving rescue emetics, patient is excluded from the study and further evaluated for other causes.

DISCUSSION

Post-operative nausea and vomiting (PONV) is amongst the most common complications following anesthesia and surgery with a selectively high incidence after laparoscopic cholecystectomy.

In our study, the incidence of PONV without antiemetic prophylaxis is 90.48%. Naguib et al demonstrated that the incidence of PONV after laparoscopic surgeries in their placebo group was remarkably high (72%) [11.] In our study the factors that would have contributed to nausea and vomiting may be laparoscopic cholecystectomy, use of Isoflurane, use of Fentanyl, and more female patients. The incidence of PONV is 20-30% in general anesthesia[29.]

Numerous drugs have been used in the past for the prevention of postoperative nausea and vomiting, but were associated with undesirable side effects. The 5-HT3 antagonists are found to be effective in preventing post-operative nausea and vomiting without any significant side effects.[24]

The incidence of PONV in our study in Ondansetron group was 14.28% whereas there was no incidence of PONV in Granisetron group. Bhatrai B et al did similar study in our hospital and the incidence of

PONV was 24% in Ondansetron group and 8% in Ondansetron and Dexamethasone group.[43] Incidence of PONV in patient receiving prophylactic Ondansetron is similar in their study as compared to us.

61.07% did not developed any symptoms ie No nausea (PONVscore-0).The incidence of Nausea only (PONV score-1) was 31.75% where as the incidence of Nausea with retching (PONV score -2) was 3.17%. There was no incidence of vomiting (PONV score -3).

The incidence of PONV among three groups was found to be statically significant (p=0.000). This demonstrates that Ondansetron and Granisteron significantly reduce incidence of PONV.

The incidence of PONV in early post operative period (0-9) hrs was 90.47% in control group and 9.52% in Ondansetron group. There was no incidence of PONV in Granisteron group. Patient who had developed PONV symptoms received rescue antiemetic and none of them developed symptoms of PONV. 4.76%patients developed new PONV symptoms in Ondansetron group during (9-16) hrs postoperatively

Majority of PONV develop in (0-9) hrs postoperatively. 30.12% patients had Nausea only (PONV score-1) whereas 3.17% had Nausea with retching (PONVscore-2). 66.67% developed No nausea (PONVscore-0)

Bhattacharya et al[13] in his study reported that Granisetron is superior to Ondasteron for the prevention of PONV and found that there was lower incidence of PONV in first 6 hours. The result is quite similar to our study though there was not much significant difference

Complete response (No nausea, PONVscore-0) was found among 100% of patients who received Granisetron, 90.48% who received Ondasteron and 9.52% among control group during 0-9 hours. Although the difference between Ondasteron and Granisetron against control groups was significant during 0-9 hrs interval (p=0.000), there was no any significant difference found between Ondasteron and Granisetron. In the study done by Ommid et al[20] there was statically significant difference between two groups in which 4% of patients in Granisteron group and 30% in Ondasteron group required rescue antiemetic medication. The factors that would have contributed for statically significant difference in Ommid et al[20] would be gender similarity (female patient only), drug administration during induction of anesthesia, use of halothane and use of morphine and paracetamol for postoperative analgesia.

In our research, our patient developed PONV in early post operative period. We continued our observation for up to 24hrs to observe for delay onset and reoccurrence of PONV symptoms. There was no incidence of PONV after 16hrs postoperatively in all 3 groups

Ondansetron of 15mcg/kg dose was similar to study done by Pearman M.H in which he concluded that 15mcg/kg dose is enough for preventing PONV in laparoscopy procedure.[10]

Granisetron of 40mcg/kg dose was similar to study done by Fuji et al in which they concluded that prophylactic use of Granisetron in a minimum dose of 40 micrograms/kg is effective for preventing nausea and vomiting.[9]

The drug was administered during closure of laparoscopic port. As per study done by Gauchan et al, a higher percentage of satisfied patients when Ondansetron was administered near the end of surgery. It is

stated that this makes the drug to be effective for longer time.[2]

Regarding demographical variance, all three groups were compared in terms of Age with p value of 0.52. So we concluded that there was no statically significant difference in age in among three groups

We noticed that there was a predominance of females undergoing laparoscopic cholecystectomy in all groups though there was not statistically significant difference between groups in terms of gender (p val= 0.49).In our study we discovered the statically significant incidence of PONV between female and male gender (p value:0.023) Female gender has been associated with higher incidence of PONV compared to male patients in previous studies which is consistent with our study.[2,20,22]

Most of the patient was of ASA grade I and the p value was 0.88. There was no any significant association in ASA grade between the groups.

We also concluded that there was no statically significant difference in weight in among three groups (p=0.141).

It has been recommended that in cases of breakthrough PONV, repeat anti-emetic should be of the different class that the one used in prophylaxis [24]. In our study, 9.5% of patients who received antiemetic Ondasteron and 90.5% of the patients in control group who did not receive anything initially were given Granisetron as rescue dose while patients who received Granisetron did not need any rescue dose at all. So we can say, the result is quiet similar to the study done by Ommid et at in which complete response was achieved initially after drug administration in Granisetron group.[20]

It was observed that there was no incidence of PONV in Granisetron group whereas incidence in ondansetron and control group was 14.28%and 90.48% respectively. Kushwaha et al in 2007 in their study concluded that PONV was controlled better with granisetron (incidence of PONV=16%) than with ondansetron (incidence of PONV=28%).[23] Similar was the findings in study done by Oksuz et alin 2007.[36] This result is also in accordance with our study. Overall results in our study shows that Granisetron is slightly more effective drug as compared to Ondasteron as nausea was not found in patients receiving Granisetron but statistically there is no significant difference between these drugs.

CONCLUSION

The incidence of postoperative nausea vomiting is high in patient undergoing laparoscopic cholecystectomy. Prophylactic antiemetic, both Onadnsetron and Granisetron significantly reduce incidence of PONV. But from our study, Granisetron was not found to be superior to Ondansetron in prevention of PONV, as there were not significant differences found between these two groups. There was no incidence of PONV symptoms who received Granisetron . We can say antiemetic plays major role in reducing PONV after laparoscopic cholecystectomy**.**

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