COMBINATION OF GRANISETRON AND DEXAMETHASONE FOR PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

Postoperative nausea and vomiting (PONV) is the second most common complaint in postoperative period especially in high risk surgeries like laparoscopic cholecystectomy. Many pharmacological strategies have been used for its prevention as PONV may cause adverse effects. Drugs like granisetron and dexamethasone has been used alone and in combination for the prophylaxis of PONV. We observed the adequacy and safety of the combination of these drugs by injecting granisetron (40mcg/kg) with dexamethasone (6mg) after induction of anesthesia. The total number of cases enrolled was 115. During 0-2 hours postoperatively, nausea, retching or vomiting was not seen in 110 (95.7%) of patients. Four (3.5%) patients had nausea or retching and 1 (0.9%) had vomiting episode in 30 minutes duration. During 2-6 hours, no nausea, retching or vomiting was seen in 113 (98.3%) patients and an episode of nausea was present in 2 (1.7%) cases. There was no nausea, retching or vomiting in any patient during 6-12 and 12-24 hours. The prophylactic anti-emetic therapy with combination of granisetron and dexamethasone is effective and safe during the first 24 hours in the postoperative period after laparoscopic cholecystectomy.

KEYWORDS

Postoperative nausea and vomiting, laparoscopic cholecystectomy, granisetron, dexamethasone

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INTRODUCTION

Postoperative nausea and vomiting is one of the most distressing experiences associated with surgery[1] and is known to be the second most common complaint in the postoperative period after pain.[2] The incidence of postoperative nausea and vomiting without any prophylaxis ranges from 20-30%[2] which increases to 41-88.0% in high risk surgeries like strabismus,[3] laparoscopic,[4] breast[5] and middle ear surgery.

Laparoscopic surgeries have many advantages over open procedures such as less pain, smaller scar, early ambulation, shorter hospital stay and more rapid return to normal daily activities.[6] These advantages has led to increased preference to laparoscopic surgery even with high risk of post-operative nausea and vomiting.

The strategies for the prevention of early and late PONV have changed considerably over the last two decades, from the single drug therapy to combination antiemetic therapy, or balanced antiemesis.[7]

Laparoscopic cholecystectomy is a commonly done surgery in our hospital and various antiemetic drugs are being used for the prophylaxis of PONV like ondansetron, granisetron and dexamethasone. The purpose of this study was to evaluate the efficacy and safety of prophylaxis with combination of granisetron and dexamethasone for the prevention of nausea and vomiting after laparoscopic cholecystectomy.

MATERIALS AND METHODS

This is a hospital based observational study among all patients who were scheduled for elective laparoscopic cholecystectomy in Nepal Medical College Teaching Hospital within a period of six months (July 2022 to January 2023). Ethical approval was taken from the institutional review committee (Ref. No.: 082-078/079). Pre-anesthetic checkup was done on the previous day. All patients were kept fasting 6 hours for solid food and 2 hours for plain fluid. In the operation theatre, standard monitoring (electrocardiogram, pulse oximetry, non-invasive arterial blood pressure) was attached. Baseline pulse, blood pressure and SPO_2 was recorded. Intravenous line was opened with 18/20G intravenous cannula on left arm. The anesthesia regimen and surgery was followed according to the hospital protocol. After preoxygenation, induction of anesthesia was done with injection midazolam 2 mg, injection fentanyl 2 mcg/kg, injection propofol 2 mg/kg and rocuronium 0.8 mg/kg intravenously. Tracheal intubation was done and intermittent positive pressure ventilation was started. Patient received injection granisetron (40 mcg/kg) with dexamethasone (6 mg) after induction of anesthesia. Anesthesia was maintained with oxygen, isoflurane and supplemental doses of injection vecuronium (0.01 mg/kg intravenously). At the end of surgical procedure, residual neuromuscular block was adequately reversed using neostigmine (0.04 mg/kg) and injection glycopyrrolate (0.2 mg for every 1 mg of neostigmine). Patient was extubated after meeting extubation criteria and shifted to post anesthesia care unit. Post-operative analgesia was provided with injection paracetamol 1gm and injection ketorolac 30 mg intravenously 8 hourly. All the patients were observed for nausea, retching and emetic episodes along with other adverse events during 0-2 hours, 2-6 hours, 6-12 hours and 12-24 hours. Pulse, SPO_2 and blood pressure was recorded at PACU on shifting the patient, 2 hours, 6 hours, 12 hours and 24 hours.

Nausea was defined as a subjectively unpleasant sensation associated with an urge to vomit. Retching was defined as the laboured, spasmodic, rhythmic contraction of the respiratory muscles, including the diaphragm, chest wall and abdominal wall muscles without expulsion of gastric content. Vomiting was defined as the forceful expulsion of gastric contents from the mouth.[8]

Severity of nausea and vomiting will be assessed by following score:[9]

Score 0: No nausea, retching or vomiting

Score 1: Nausea or retching

Score 2: one vomiting episode in 30 minutes duration

Score 3: Persistant nausea (>30 minutes) or two or more vomiting episodes in 30 minutes duration

Any patient who had two or more episodes of vomiting postoperatively received rescue dose. Total number of vomiting episodes as well as complete response (no nausea or vomiting in 24 hours) was also noted.

Inclusion critera

1. Age between 20-65 years of either gender
2. ASA I and II
3. Patients scheduled for elective laparoscopic cholecystectomy

Exclusion critera

1. Age less than 20 or more than 65 years
2. ASA III or more

3. Previous history of motion sickness or PONV
4. Gastroesophageal reflux disease
5. Pregnant or menstruating women
6. Patient's receiving chemotherapy or radiotherapy
7. Who has taken antiemetic within 24 hours of surgery

RESULTS

The total number of cases enrolled was 115. None of the patients were excluded from the study. No conversion to open surgery was necessary for any patient and no major intraoperative complications were recorded. Total number of female cases was 86 (74.5%) and male cases was 29 (25.2%). Among 115 patients, 112 (97.4%) had the diagnosis of symptomatic cholelithiasis, 2 (1.7%) had gall bladder polyp and 1 (0.9%) had choledocholithiasis. During 0-2 hours postoperatively, nausea, retching

Table 1: Gender distribution

	n	%
Male	29	25.2
Female	86	74.8
Total	**115**	**100.0**

Table 2: Diagnosis distribution

	n	%	Cumulative %
Symptomatic Cholelithiasis	112	97.4	97.4
Gall bladder polyp	2	1.7	99.1
Choledocholithiasis	1	0.9	100.0
Total	**115**	**100.0**	

Table 3: Incidence of nausea, retching and vomiting at 0-2 hours

	n	%	Cumulative %
No nausea, retching or vomiting	110	95.7	95.7
Nausea or vomiting	4	3.5	99.1
One vomiting episode in 30 minutes duration	1	.9	100.0
Persistant nausea (>30 minutes) or two or more vomiting episodes in 30 minutes duration	-	-	-
Total	**115**	**100.0**	

Table 4: Incidence of nausea, retching and vomiting at 2-6 hours

	n	%	Cumulative %
No nausea, retching or vomiting	113	98.3	98.3
Nausea or vomiting	2	1.7	100.0
One vomiting episode in 30 minutes duration	-	-	-
Persistant nausea (>30 minutes) or two or more vomiting episodes in 30 minutes duration	-	-	-
Total	**115**	**100.0**	

Table 5: Incidence of nausea, retching and vomiting at 6-12 hours

	n	%	Cumulative %
No nausea, retching or vomiting	115	100.0	100.0
Nausea or vomiting	-	-	-
One vomiting episode in 30 minutes duration	-	-	-
Persistant nausea (>30 minutes) or two or more vomiting episodes in 30 minutes duration	-	-	-
Total	**115**	**100.0**	

Table 6: Incidence of nausea,retching and vomiting at 12-24 hours

	n	%	Cumulative %
No nausea, retching or vomiting	115	100.0	100.0
Nausea or vomiting	-	-	-
One vomiting episode in 30 minutes duration	-	-	-
Persistant nausea (>30 minutes) or two or more vomiting episodes in 30 minutes duration	-	-	-
Total	**115**	**100.0**	

or vomiting was not seen in 110 (95.7%) of patients. Four (3.5%) patients had nausea or retching and 1 (0.9%) patient had one vomiting episode in 30 minutes duration. During 2-6 hours, no nausea, retching or vomiting was seen in 113 (98.3%) patients and an episode of nausea was present in 2 (1.7%) cases. There was no nausea, retching or vomiting in any patient during 6-12 and 12-24 hours. During the period of our study, the patients did not require any rescue medication and the complications of the drugs were not seen.

DISCUSSION

Postoperative nausea and vomiting is one of the most distressing experiences associated with surgery[1] and is known to be the second most common complaint in the postoperative period after pain.[2] The incidence of postoperative nausea and vomiting without any prophylaxis ranges from 20-30%[2] which increases to 41-88% in high risk surgeries like strabismus,[3] laparoscopic,[4] breast[5] and middle ear surgery.

Laparoscopic surgeries have many advantages over open procedures such as less pain, smaller scar, early ambulation, shorter hospital stay and more rapid return to normal daily activities.[6] These advantages has led to increased preference to laparoscopic surgery even with high risk of post-operative nausea and vomiting. PONV remains a significant problem in modern anesthetic practice because of the adverse consequences of PONV such as delayed recovery, unexpected hospital admission, delayed return to work of ambulatory patients, pulmonary aspiration, wound dehiscence, and dehydration.[10]

The chemoreceptor trigger zone (CRTZ), which is located at the caudal end of the fourth ventricle in the area postrema, and the nucleus tractus solitarius (NTS), located in the area postrema and lower pons. The CRTZ receives input from vagal afferents in the gastrointestinal tract, and it can also detect emetogenic toxins, metabolites, and drugs circulating in the blood and cerebrospinal fluid due to its lack of the blood –brain barrier. The CRTZ projects neurones to the NTS, which receives input from vagal afferents and from the vestibular and limbic systems. The NTS triggers vomiting by stimulating the rostral nucleus, the nucleus ambiguous, the ventral respiratory group, and the dorsal motor nucleus of the vagus. Multiple neurotransmitter pathways are implicated in the physiology of nausea and vomiting. Enterochromaffin cells in the gastrointestinal tract release serotonin, and the vagus nerve communicates with the CRTZ via 5-HT3 receptors. The CRTZ communicates with the NTS primarily via dopamine-2 (D2) receptors.[11]

Many pharmacological approaches like antihistamines,[12] butyrophenones,[13] dopamine receptor anatagonists,[14] dexamethasone,[15-18] and $5HT_3$ antagonist[19-22] have been used successfully for prevention of postoperative nausea and vomiting. Granisetron is a selective $5\text{-}HT_3$ receptor antagonist. It is effective orally as well as intravenously. It blocks the $5\text{-}HT_3$ receptors at both the central and the peripheral sites. It acts on the vagal efferent nerves of the gut and produces blockade of $5\text{-}HT_3$ receptors. It has half-life of 8-9 hours. It is more selective and has longer duration of action than ondansetron.[23] Dexamethasone is a 21 carbon compound having a cyclopentanoperhydrophenanthrene (steroid) nucleus. It is potent and highly selective long acting (36-48 hours) drug after a single intravenous dose given before induction of anesthesia. It causes prostaglandin antagonism, serotonin inhibition in the gut and the release of endorphins. It augments the efficacy of other primary antiemetic drugs like metoclopramide, ondansetron and granisetron.[24]

In our study, we observed that 110 (95.7%) patients who received the combination of granisetron and dexamethasone did not have nausea, retching or vomiting in the first two hours of postoperative period. This result was similar to Gupta and Jain[1] who suggested that the incidence of complete response (no PONV, no rescue medication) was 96% with combination of granisetron and dexamethasone, as compared with 86% with granisetron and 4% with ondansetron during 0-3h after surgery which was clinically significant ($p < 0.05$). In their study, at 3-6 h, 24% (6) in ondansetron group and 8% (2) in granisetron group had nausea and retching. Episodes of vomiting were 20% (5) in ondansetron group and 16% (4) in granisetron group. None of the patients in group G+ D (granisetron and dexamethasone) complained of nausea, retching or vomiting during this time period ($p < 0.05$) which is statistically significant. But in our study, 2 (1.7%) patients had nausea and retching during 2-6 hours.

Erhan *et al*,[25] compared the effectiveness of granisetron 3mg and 8 mg dexamethasone in patients undergoing laparoscopic cholecystectomy. Incidence of vomiting was 10% in both the groups and was not significant. Opposed to that finding, in a study done by Sharma *et al*[2] incidence of vomiting was 43.3% for granisetron and 16.7% for dexamethasone

and was significant. When we used the combination of these two drugs in our study, we observed that the incidence of vomiting was only 0.9% (1) which was in accordance with Rudra *et al.*[27] They had compared granisetron and combination of granisetron and dexamethasone and found that complete response (no nausea, no vomiting) was 29 (96%) in combination group which was significant ($p < 0.05$).

During the period of our study, the patients did not require any rescue medication and the complications of the drugs were not seen which revealed the adequacy and safety of the drugs used in the combination.

Limitation: The limitation of our study was that we did not take in account the history of smoking in the patients and intraabdominal pressure during laparoscopy which can affect postoperative nausea vomiting in the patients.

In conclusion, our study suggest that the prophylactic anti-emetic therapy with combination of granisetron and dexamethasone is effective and safe during first 24 hours in the postoperative period after laparoscopic cholecystectomy. It is preferable to use this combination specially in patients who are at high risk for postoperative nausea and vomiting.

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