ORIGINAL ARTICLE

Comparison of Granisetron and Granisetron plus Dexamethasone for the Prevention of Post-operative Nausea and Vomiting (PONV)

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Abstract:

There is a high incidence of post-operative nausea and vomiting (PONV) in patients undergoing surgery and anaesthesia. Many factors are claimed to be responsible for PONV. This study was designed to compare the effectiveness of granisetron plus dexamethasone with granisetron alone to prevent post-operative nausea and vomiting. In this randomised double blind study, sixty patients were divided into two equal groups (n=30 each). Patients in Group A received granisetron 40 μgm per kg before induction of anaesthesia and those in Group B received granisetron 40 μgm per kg plus dexamethasone 8 mg before induction of anaesthesia. All the patients were observed for post-operative nausea and vomiting for 24 hours (0-6 hours in the recovery room and 18 hours in ward or cabin). A significant difference was found in complete response, defined as no post-operative nausea and vomiting, between patients of granisetron alone group and those of granisetron plus dexamethasone combination group. The combination of granisetron plus dexamethasone is considered to be more effective for prevention of post-operative nausea and vomiting.

Introduction:

Post-operative nausea and vomiting (PONV) is frequently experienced by the patient in the post-operative room. PONV is rarely fatal but is a most unwanted and unpleasant symptom; even mild PONV is sometimes more distressful than post-operative pain. The incidence of PONV was reported to be as high as 60-70% with older inhalational anaesthetics such as ether and cyclopropane[1,2]. But in today's practice with better anaesthetic technique, shorter acting anaesthetic drugs and with newer generation of anti-emetics the overall incidence of PONV is reduced to 25-30%[3], although severe intractable PONV is estimated to occur in approximately 0.18% of all patients undergoing surgery. PONV still occurs with an incidence as high as 60-70% in some high risk patients[4,5] leading to delay in recovery room discharge and/or unanticipated hospital admission, thereby increasing medical costs. In adults, high incidences of PONV are found in laparoscopic surgery, intra-abdominal surgery, major gynaecological surgery, breast surgery, neurological surgery, eye and otorhinolaryngology surgery. Paediatric operations that are at high risk for PONV include strabismus, adenotonsillectomy, hernia repair, orchidopexy, penile surgery and middle ear procedures[6,7]. The aetiology of PONV is

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multi-factorial. Commonly used older traditional anti-emetics have adverse effects on the patients. Newer anti-emetics do not have side effects like older ones. Granisetron is one of the newer group of anti-emetics used either alone or in combination with dexamethasone for the prevention of PONV. Granisetron, as well as ondansetron, are selective antagonists of 5-hydroxytryptamine type 3 (5HT3) receptors and are effective in the treatment of nausea and vomiting in patients receiving cytotoxic drugs[8]. Ganisetron has a more potent and longer acting activity against cisplatin-induced emesis than ondansetron[9].

It is recently demonstrated that prophylactic therapy with granisetron is efficacious against post-operative vomiting after paediatric strabismus surgery[10]. Even mild post-operative nausea and vomiting may result in delaying post-operative room discharge, increased worry and anxiety, decreased patients satisfaction and increased use of resources, including medical and nursing care and other supplies[11]. Avoiding PONV is very important for high-risk patients. Many authors rated avoiding PONV more important than avoiding pain post-operatively[12].

This prospective, randomised, double blind study was designed to compare the effectiveness of granisetron alone with the combination of granisetron and dexamethasone to prevent PONV in high risk patients.

Materials and method:

This was done during April 2004 to September 2005 in the Department of Anaethesiology, Holy Family Red Crescent Medical College and Hospital. Necessary permission to coduct the study was taken from the hospital authority. Informed written consent from the eligible patients was obtained during sample recruitment. Eligible patients were those who had higher chances of post-operative nausea and vomiting. Sixty patients of ASA grade I and/or II were included in this double blind randomized study. The patients were divided equally into two groups, A and B. Patients of both sex, aged 18-60 years scheduled for surgery were included. Patients with motion sickness, gastrointestinal diseases, smoking habits and previous history of PONV were not included in the study. Patients were randomly distributed to receive intravenously one of the two treatment regimens. Group A (n-30) received granisetron (kytril) 40 µgm per kg and Group B (n-30) received granisetron 40 µgm per kg plus dexamethasone 8 mg. The drug granisetron was diluted with 5 ml of normal saline. The drug was administered intravenously immediately before induction of anaesthesia. All the patients were kept on overnight fasting, and all of them received 10 mg diazepam orally two hours before anaesthesia with sips of water. Anaesthesia was induced with fentanyl 1 µgm per kg body weight intravenously, thiopenton sadium 4-5 mg per kg and suxamethonium 1.5 mg per kg i.v. to facilitate orotracheal intubation. Anaesthesia was maintained with nitrous oxide 60%, oxygen 40% and halothane 0.5-1%. Muscle relaxation was achieved with non-depolarising muscle relaxant norcuron, as required for mechanically controlled ventilation. Patients were monitored during anaesthesia by NIBP, pulse oxymeter and ECG. Stomach was emptied before extubation of the endotracheal tube by suction catheter. Action of the non-depolarising muscle relaxant was antagonized with atropine 0.120

mg and neostigmine 2.5 mg intravenously. Extubation was done when the patient was awake. Post-operative analgesia was maintained with intramuscular ketorolac 30 mg and pethidine 1.5 mg per kg. The incidences of nausea and vomiting were recorded for 0-6 hours in the recovery room and 6-24 hours in the ward or cabin. Episodes of nausea and vomiting were recorded by resident doctors and/or by senior staff nurses. Episodes were identified by spontaneous complaint by the patients or by direct questioning. At the end of the observation period, the patients were evaluated for the severity of nausea with a linear numerical scale ranging from 0 (no nausea) to 10 (severe nausea). The details of the adverse effects of both the groups were also recorded by the resident doctors.

Statistical differences between the groups in discrete and continuous variables were tested using $\chi 2$ and student's t-test respectively. A p-value of <0.05 was considered significant. All values were expressed as mean ±SD range or percentage. Power analysis was used to determine the number of patients needed in the study group based on the assumption that (i) no post-operative nausea and vomiting in patients receiving granisetron alone would be observed in 80%, and (ii) an improvement from 80 to 95% can be expected based on previous data. Based on these assumptions, 30 patients per group were required.

Results:

Patients profile, and information on the surgery and anaesthesia are summarized in Table-I. During 0-6 hrs staying in the post-operative room immediately after completion of surgery and anaesthesia there was no PONV in 90% patients who received granisetron plus dexamethsone but it was 83.3% in case of patients receiving granisetron alone. In next 18 hours 93.3% patients did not have PONV in the earlier group and 86.7% in the latter. Thus a complete response during the first 24 hours after anaesthesia was significantly more in the patients who received granisetron plus dexamethasone than those who received granisetron alone ($p<.05$) (Table-II). In both the groups, a few adverse events were observed as shown in Table-III, which do not have clinical importance.

Table–I: Distribution of patient in two groups according to their personal profile and surgery related factors

Parameters	Granistron group (n=30)	Combination group (n=30)
Mean age (years)	37.47	31.83
Mean weight (Kg)	52.47	50.30
Sex (male/female)	16/14	14/16
Mean duration of surgery (minutes)	52.15 ± 10.9	63.07 ± 24.9
Mean duration of anaesthesia (minutes)	65.92 ± 11.2	77.69 ± 26.6

Table–II: Distribution of patients according to their response and rescue anti-emetic requirement at different post-operative period

	Granisetron group (n=30)	Combination group (n=30)	p
0-6 hours after anaesthesia	Number (%)	Number (%)	
Complete response (no PONV, no rescue)	25 (83.3%)	27 (90%)	<0.05
Nausea	03 (10%)	02 (6.7%)	
Vomiting	02 (6.7%)	01 (3.3%)	
Rescue anti-emetic	02 (6.7%)	01 (3.3%)	
Severity of nausea	00 (0-5)	00 (0-3)	
6-24 hours after anaesthesia			
Complete response (no PONV, no rescue)	26 (86.7%)	28 (93.3%)	<0.05
Nausea	02 (6.7%)	02 (6.7%)	
Vomiting	02 (6.7%)	00	
Rescue antiemetic	01 (3.3%)	00	
Severity of nausea	00 (0-5)	00 (0-3)	
Overall cumulative incidences of PONV (0-24h)	06 (20%)	02 (6.7%)	<0.05

Table–III: Distribution of the patients of two groups according to adverse effects they developed during the course of trial

	Granisetron (n=30)	Combination (n=30)
0-6 hours after anaesthesia	Number (%)	Number (%)
Headache	04 (13.3%)	03 (10%)
Dry mouth/lip	02 (6.7%)	02 (6.7%)
Dizziness	02 (6.7%)	02 (6.7%)
Others(myalgia)	01 (3.3%)	02 (6.7%)
Total	09 (30%)	09 (30%)
6-24 hours after anaesthesia		
Headache	02 (6.7%)	02 (6.7%)
Dry mouth/lip	02 (6.7%)	02 (6.7%)
Dizziness	01 (3.3%)	02 (6.7%)
Others(constipation, myalgia)	01 (3.3%)	01 (3.3%)
Total	06 (20%)	07 (23.3%)

Discussion:

Post-operative nausea and vomiting is among the most common complications following anaesthesia and surgery but there is a remarkably high incidences of PONV following certain operations and anaesthesia. Nausea is defined as a subjective unpleasant sensation associated with awareness of the urge to vomit and vomiting is defined as the forceful expulsion of gastric contents from the mouth. Complete response is defined as no PONV. The vomiting centre coordinates the

process of nausea and vomiting. Stimulation can be initiated from the periphery (oropharynx, mediastinum, GI tract, renal pelvis, peritoneum and genitalia) and centrally from the CNS (cerebral cortex, labyrinthine, otic or vestibular apparatus). Peripheral stimuli are relayed to the vomiting centre by the autonomic nervous system through afferent fibres of vagus. Central cerebral sensory stimuli occur directly and are transmitted by the chemoreceptor trigger zone (CTZ), area post rema and nucleus of the solitary tract in the lateral reticular formation of the medulla oblongata to the vomiting centre[13,14,15]. A number of factors including anaesthetic technique, duration and type of surgery, sex, pain, care in the post-operative period and patient's demographics are considered to influence the incidence of emesis[16]. Morbidity and mortality are reduced in laparoscopic cholecystectomy than open cholecystectomy but PONV is significantly higher when no prophylactic anti-emetic is given. The aetiology of PONV following laparoscopic cholecystectomy are multi-factorial and complex. In this clinical study, the treatment groups were similar in respect to patients' demographics and operative management. Patients with a history of motion sickness and previous history of PONV, and smokers were not included because they had relatively high incidence of emetic symptoms[17,18]. Patients of both the groups were anaesthetized and operated by same group of anaesthesiologists and surgeons. Duration of anaesthesia and surgery were almost same in both the groups.

It has been demonstrated by Fuji et al that granisetron 40 µgm/kg is the minimum effective dose for reducing the incidence of PONV after laparascopic cholecystectomy. Dexamethasone has been found to have a prophylectic anti-emetic effect in patients undergoing surgery under general anaesthesia[19,20]. The dose of dexamethasone was fixed 8 mg based on other study reports. Mataruski et al in a retrospective study showed that patients who received intraoperative steroids were less likely to experience post-operative nausea and vomiting than those who did not. The exact mechanism by which dexamethasone increases the effectiveness of granisetron is not known[21]. Granisetron produces its anti-emetic effect by blocking 5HT3 receptors[22]. The effectiveness of intravenous granisetron for prevention of PONV has been determined[23]. Corticosteroids have been evaluated for their usefulness in preventing PONV after they were found to be effective in preventing chemotherapy-induced nausea and vomiting. An anti-inflamitory and/or membrane stabilizing effect may play a role in the anti-emitic action of corticosteroids. Dexamethasone may inhibit stimulation of 5HT3 receptor and may also potentiate the other pharmacological receptors[24]. In the post-operative room, patients of both the groups have consumed similar amounts of pethedine according to body weight as analgesic. Therefore, the differences in the incidences of PONV among the groups can be attributed to the study drug. The results of this study suggest that a complete response was more marked in patients who received granisetron plus dexamethasone combination than in those who received granisetron alone ($p<0.05$). The adverse effects like headache, dizziness and myalgia were noted in patients of both the groups and difference in their occurrence was not significant.

It is therefore concluded that the prophylactic anti-emetic therapy with combination of granisetron plus dexamethsone is more effective than granisetron alone for the prevention of PONV in high risk group patients undergoing surgery and anaesthesia.

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