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RESEARCH ARTICLE

A RANDOMIZED, DOUBLE-BLIND TRIAL OF GRANISETRON COMPARED WITH DEXAMETHASONE IN PREVENTING POSTOPERATIVE NAUSEA AND VOMITING AFTER LAPAROSCOPIC ABDOMINAL SURGERY AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Granisetron is a highly selective and potent 5-HT receptor antagonist acting specifically at 5-HTreceptors on the vagal afferent nerves of the gut. Granisetron leads to irreversible block of 5-HT receptors. This may account for the long duration action of this drug.
Purpose: The present randomized, double-blind study was designed to evaluate and compare the effectiveness of long acting drug, Granisetron and Dexamethasone for preventing post-operative nausea and vomiting in patients undergoing laparoscopic abdominal surgery.
Methods: In a randomized, double-blind study, 80 inpatients in the age group of 20-60 years, weighing 40-75 kg, belonging to physical status of ASA I and ASA II (American Society of Anaesthesiologists) scheduled for elective laproscopic abdominal surgeries received Granisetron (2.5mg) and Dexamethasone (8 mg) i.v. (n=40 of each) before IV induction agent. The standardized anesthetic included isoflurane and nitrous oxide in oxygen. After surgery all patients were observed for forty-eight hours. The incidence of nausea and vomiting was recorded at 2, 6, 12, 24 and 48 hours after extubation for a period of 48 hours after the surgery by direct questioning to the patient or His/Her attendents. The PONV was defined as the subjective unpleasant sensation associated with awareness of urge to vomit (nausea, vomiting and retching was grouped together).
Results: With Granisetronthe incidence of overall PONV during first 24 hr (0-24 hr) was 30% (n=12) and Dexamethasone showed 40% (n=16). The corresponding incidence during the next 24 hr (24-48 hr) after anesthesia was 37.5% (n=15) in Granisetron and in Dexamethasone was 22.5% (n=9). Overall use of rescue medication was 22.5% (n=9) in Granisetron and 42.5% (n=17) in Dexamethasone. There was a significant difference in the use of rescue medications between the two groups (p value<0.05). No clinically important adverse events due to the study drug were observed in any of the groups.
Conclusion: In conclusion Granisetron (2.5mg) intravenous was a better agent in decreasing incidence of post-operative nausea and vomiting. The overall requirement of rescue antiemetic was also significantly less when compared with Dexamethasone group.

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INTRODUCTION

Post operative nausea and vomiting (PONV) includes distressing symptoms that commonly occur after surgery performed under general anaesthesia (Madej and Simpsom, 1986). Dehydration, electrolyte imbalance, disruption of surgical repair and increase in perception of pain may result due to vomiting (Jellish *et al.,* 2006). Despite improvements regarding the prevention and treatment of PONV in the 13 years since a prior review of PONV in Drugs (Kovac, 2000), the 'big little problem' of PONV has shown an improvement but continues to persist (Lichtor and Glass, 2009). An estimated overall incidence of approximately 25–30 % is seen in all surgical patients (Gan *et al.,* 2007). While nausea is estimated to occur about in 40–50 % and vomiting occurs in 25–30 % of the time depending on the specific surgical population studied (Cohen *et al.,* 1994). Many pharmacological agents (antihistamines, butyro-phenones, dopamine receptor antagonists) have been tried for the prevention and treatment of PONV. Adverse effects such as excessive sedation, hypertension, dry mouth, dysphoria, hallucinations and extra pyramidal symptoms have been noted (Watcha and White, 1992).

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But 5-hydroxytryptamine type 3(5HT3) receptor antagonists are devoid of such side effects and highly effective in prevention and treatment of PONV. Corticosteroids like dexamethasone are thought to exert antiemetic properties by inhibiting prostaglandin synthesis or the release of endogenous opioids with negligible side effects (Holte and Kehlet, 2002). Among the 5-hydroxytryptamine receptor 3 (5-HT3) antagonists, which are most frequently used for the prevention of PONV, granisetron is a drug with higher receptor affinity which is highly selective and longer duration of action than its congeners such as ondansetron (Blower, 1990). It acts specifically at 5-HTreceptors on the vagal afferent nerves of the gut and produces irreversible block of the 5-HT receptors (Newberry *et al.,* 1993; Elliott *et al.,* 1990). We designed and conducted this prospective randomized double blind trial to assess and compare the antiemetic efficacy of dexamethasone and granisetron as PONV prophylaxis in patients undergoing laparoscopic abdominal surgery.

PATIENTS AND METHODS

Patients

The study protocol was approved by the institution ethical committee and informed consent was obtained from every patient. This study enrolled 80 patients scheduled for elective laparoscopic abdominal surgery under general anesthesia. They ranged in age from 20-60 years (mean = 46 years). Patients were excluded from the study if they had one or more of the following: American Society of Anesthesiologists (ASA) physical status III–IV; administration of antiemetic medication within 24 h before surgery; administration of steroids within 24 h before surgery or during the 24 h after surgery; gastrointestinal, renal, or hepatic disease; insulin-dependent diabetes mellitus; and conversion to open cholecystectomy. Patients with vomiting or retching in the 24 h preceding surgery, those who had received cancer chemotherapy within 4 weeks or emetogenic radiotherapy within 8 weeks before study entry, and patients with ongoing vomiting from gastrointestinal disease were also excluded.

Study design and treatment

Through a computer generated randomization schedule patients were randomly allocated into two groups (n=40each) to receive one of the following regimens: dexamethasone 8 mg in 2.5 ml (0.9% saline was added to make the desired volume) (group D) or granisetron 2.5mg in 2.5 ml (group G). The study medication were administered immediately before the induction of anaesthesia. Trained anaesthesia technicians who did not participate in the study prepared the drugs according to manufacturer's instructions and placed them in numbered, sealed envelopes assigned by computer generated random numbers. The envelopes were opened before anesthetic induction by a physician not involved in the study. All patients were kept fasting after midnight and received Tab. Alprazolam 0.25 mg orally as premedication. On the operation table, routine monitoring (ECG, pulse oximetry, NIBP) were started and baseline vital parameters like heart rate (HR), blood pressure (systolic, diastolic and mean) and arterial oxygen saturation (SpO2) were recorded. An intravenous line was secured. Patients were premedicated with Inj. Rabeparazole-20 mg i.v and Inj. Midazolam 1 mg i.v Preoxygenation with 100% O_2 was done with a facemask. Subsequent induction was done with Inj. Propofol 2mg/kg body weight and relaxation and intubation was accomplished with Inj. Atracurium Besylate 0.5 mg/kg body weight. Anaesthesia was maintained with oxygen and nitrousoxide mixture (50:50). Isoflurane (0.7-1.3 MAC) and Inj. Atracuriumbesylate 0.1 mg/kg body weight was used as a muscle relaxant. Positive pressure ventilation was delivered with tidal volume and respiratory rate adjusted to maintain end tidal CO_2 between 30-40 mmHg. Inj. Tramadol Hcl 2mg/kg body weight and Inj. Paracetamol 20mg/kg body weight was administered intravenously for intraoperative analgesia. During surgery Ringer lactate was infused in accordance with maintenance of volume requirements.

A nasogastric tube was inserted to make the stomach empty of air and other contents. For laparoscopic surgical procedure, peritoneal cavity was insufflated with carbon dioxide to keep intra abdominal pressure <14mmHg. At the end of surgical procedure, residual neuromuscular block was adequately reversed using intravenous glycopyrrolate 0.02mg/kg body weight and neostigmine 0.05mg/kg body weight and. Before tracheal extubation, the nasogastric tube was suctioned and removed and patient subsequently extubated. For postoperative analgesia, diclofenac transdermal patch was applied on body surface. All patients were observed postoperatively by resident doctors who were unaware of the study drug.

Patient Monitoring

All episodes of PONV (nausea, retching and vomiting) were recorded for 0-2 hour in postanaesthesia care unit and from 2-48 hour in postoperative ward. The incidence of nausea and vomiting was recorded at 2, 6, 12, 24 and 48 hours after extubation by direct questioning to the patient or His/ Her attendents. The severity of PONV was graded as follows (Wilson's Score):

1) No PONV – Absence of any emesis or nausea.
2) Mild PONV – Patient having only mild nausea, or one emetic episode or nausea lasting for less than 10 minutes and where no antiemetic is required.
3) Moderate PONV – patient has 1-2 emetic episodes or moderate to severe nausea and antiemetic therapy is required.
4) Severe PONV – Patient has more than 2 emetic episodes or is nauseated more than twice and more than one antiemetic required. The use of rescue antiemetic drug use was monitored at 0--48 h post surgery.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit, where as an episode of vomiting was defined as vomiting (forceful expulsion of gastric contents from the mouth) or retching (laboured, spasmodic, rhythmic contractions of the respiratory muscles without expulsion of gastric contents). Metoclopramide (10 mg i.v.) was permitted as a rescue antiemetic when two episodes of PONV occurred.

If metoclopramide treatment was ineffective, ondansetron 4 mg i.v was permitted. A complete response was defined as the

absence of PONV and no use of rescue antiemetics. Details of any adverse effects (including headaches, dizziness, constipation and myalgia) were recorded. The primary outcome measure of this study was the incidence of nausea and vomiting during the first 48 h after anaesthesia. Secondary outcome measures were the severity of nausea, need for rescue medication, patient satisfaction and incidence of adverse effects.

Statistical Analyses

All statistical analyses were performed using SPSS® statistical package, version 17.0(SPSS Inc., Chicago, IL, USA) for Windows®. The Student's t-test was used to comp reinter group differences and the $\chi 2$ or Fisher's exact tests were used for categorical variables. The P-values were corrected by the Bonferroni method and a P-value < 0.05 was regarded as statistically significant.

RESULTS

In total, 80 patients were recruited, all of whom completed the study. There were no statistically significant differences between dexamethasone and granisetron treated groups in terms of patient characteristics, PONV risk factors or operative data (Table 1 and Table 2). The groups were comparable with respect to age, weight and duration of surgery (Table 1 and Table 2).

The incidence of PONV (Table 3) during 0-2 hour in the postoperative period was27.5% (n=11) with Group G (Granisetron) and 72.5% (n=29) with Group D (Dexamethasone) and the incidence during 2-6 hour postoperatively was32.5% (n=13) with Group G (Granisetron) and 64.5% (n=26) with Group D (Dexamethasone). The difference was statistically significant (p value<0.05). During 6-24 hour, the incidence was 30% (n=12) and 40% (n=16) respectively (Table 3). The difference was statistically insignificant (p value>0.05). During 24-48 hours the incidence of PONV in Group G (Granisetron) was37.5% (n=15) and in Group D (Dexamethasone) it was 22.5% (n=9).

Table 1. Patient characteristics

		Group D (n=40)	Group G (n=40)	p value
Age (Years)		43.9±14	39.6±15.3	0.533
Gender	Male	18	22	0.263
	Female	22	18	
Weight (Kgs)		61.75±9.5	59.09±8.8	0.627
Duration of surgery (minutes)		42.1±13.05	49±16.6	0.125

*p<0.05 is significant

Table 2. Risk distribution in the two study groups

	Group D (n=40)	Group G (n=40)	p value
Obesity n (%)	5(12.5)	9(22.5)	
Non obese n (%)	35(87.5)	31(77.5)	.23
Smokers n (%)	7(17.5)	7(17.5)	
Non smokers n (%)	33(82.5)	33(82.5)	1
H/O motion sickness n (%)	8(20)	5(12.5)	
No H/O motion sickness n (%)	32(80)	35(87.5)	.36

*p<0.05 is significant

Table 3. Groupwise incidence of post-operative nausea and vomiting (PONV) in patients undergoing elective abdominal laparoscopic surgery during 48 hours post operation who received Granisetron 2.5 mg (Group G) and Dexamethasone 8 mg (Group D) intravenously 10 seconds before induction of anesthesia

	Group G(n=40)	Group D (n=40)	p value
0 – 2 h			
Nausea n (%)	7 (17.5)	24 (60)	<.0001
Vomiting n (%)	4 (10)	5 (12.5)	.9999
Overall PONV n (%)	11 (27.5)	29 (72.5)	<0.0001
2 – 6 h			
Nausea n (%)	8 (20)	21 (52)	.0025
Vomiting n %)	5 (12.5)	5 (12.5)	1
Overall PONV n (%)	13 (32.5)	26 (64.5)	.0036
6 – 24 h			
Nausea n (%)	7 (17.5)	12 (30)	.1884
Vomiting n (%)	5 (12.5)	4 (10)	.4315
Overall PONV n (%)	12 (30)	16 (40)	.34
24– 48 h			
Nausea n (%)	9 (22.5)	8 (20)	.7913
Vomiting n (%)	6 (15)	1 (2.5)	.1084
Overall PONV n (%)	15 (37.5)	9 (22.5)	.1435
Rescue antiemetics n (%)	9 (22.5)	17 (42.5)	.0561

*p<0.05 is significant

Although the difference is statistically insignificant (p value<0.05), the antiemetic efficacy of dexamethasone shows an improvement as post operative hours increase. Overall use of rescue medication is 22.5% (n=9) in Group G (Granisetron) and 42.5% (n=17) in Group D (Dexamethasone). The use of rescue medication is about 50% less in the use of Granisetron as antiemetic than dexamethasone.

During late post operative period the antiemetic effect of dexamethasone shows an improvement. Thus a complete response during 0-48 hour in the postoperative period was significantly more patients who had received Granisetron than in those who had received dexamethasone. Headache, dizziness, drowsiness and constipation were the commonly observed adverse effects but those were not clinically serious or significant. Also, the incidence of adverse effects were statistically insignificant between the groups (Table 4).

Table 4. Groupwise incidence of adverse effects in patients undergoing elective abdominal laparoscopic surgery

Postoperative period	Group D (n=40)	Group G (n=40)	p value
0-2 hr			
Headache n (%)	6 (51)	8 (20)	.5541
Constipation n (%)	8 (20)	8 (20)	1
Drowsiness n (%)	1 (2.5)	1 (2.5)	1
2-6 hr			
Headache n (%)	3 (7.5)	3 (7.5)	1
Constipation n (%)	5 (12.5)	8 (20)	.3623
Drowsiness n (%)	1 (2.5)	1 (2.5)	1
6-24 hr			
Headache n (%)	1 (2.5)	3 (7.5)	.6153
Constipation n (%)	4 (10)	7 (16.67)	.5169
Drowsiness n (%)	1 (2.5)	1 (2.5)	
24-48 hr			
Headache n (%)	2 (5)	1 (2.5)	.9999
Constipation n (%)	0	0	1
Drowsiness n (%)	0	0	1

* $p<0.05$ is significant

DISCUSSION

In this prospective, randomized, and double-blind trial, administration of Granisetron provided an overall superior antiemetic efficacy than dexamethasone in terms of PONV scores at different intervals of time and the incidence of use rescue medications after laparoscopic abdominal surgery. Postoperative nausea and vomiting shows a variable incidence depending on the duration of surgery, the type of anaesthetic agents used (dose, inhalational drugs, opioids), smoking habit etc (Lerman, 1992). Primary event in the initiation of vomiting reflex is the 5-HT receptor stimulation which are situated on the nerve terminal of the vagus nerve in the periphery and centrally on the chemoreceptor trigger zone (CTZ) of the area postrema (Bunce and Tyers, 1992; Watcha and White, 1992).

The etiology of PONV after laparoscopic surgery is multifactorial, involving gender, age, obesity, a history of motion sickness and/or previous PONV, smoking habit, anesthetic technique, and postoperative use of opioids as the risk factors. In addition, the development of PONV is provoked by operative procedure such as CO2 insufflation, residual pneumoperitoneum after surgery, peritoneal distension, and diaphragm and visceral organ irritation (Feo *et al.,* 2006; Nesek-Adam *et al.,* 2007). However in this study both the groups were comparable with respect to patient demographics, types and duration of surgery and anesthesia and analgesics used postoperatively. Therefore the difference in PONV scores between the groups can be attributed to the study drug only. The incidence of PONV after laparoscopic abdominal surgery is up to 70% because not only do most patients have several patient-related risk factors for PONV, including female gender and not smoking, but there are also surgical risk factors (Gan *et al.,* 2007).

5-HT3antagonists are the most widely used and extensively studied drugs and include ramosetron, ondansetron, and granisetron. Granisetron is effective for the treatment of emesis induced by cancer chemotherapy (Bermudez *et al.,* 1988). The precise mechanism of granisetron for the prevention of PONV remains unclear, but it has been suggested that granisetron may act on sites containing 5-HT receptors with demonstrated antiemetic effects (Carmichel *et al.,* 1989).

40-80µg kg is the effective dose of granisetron for the treatment of cancer chemotherapy induced nausea and vomiting (Furue *et al.,* 1990). The dose of granisetron 2.5 mg (approximately 45µg kg) selected for this study was within its effective dose range (40-80µg kg). Dexamethasone, a corticosteroid, has been suggested to have antiemetic properties by inhibiting prostaglandin synthesis and endogenous opioid release (Holte and Kehlet, 2002). The dose of dexamethasone used was also chosen based on recommendations of previous studies that addressed its efficacy for treating PONV and postoperative pain (Karanicolas *et al.,* 2008; Fujii and Itakura, 2010). A single dose of dexamethasone administered perioperatively is rarely associated with significant side effects such as increased risk of infection, glucose intolerance, delayed wound healing, and adrenal suppression (Henzi *et al.,* 2000). In the current study, a single dose of dexamethasone 8 mg was not related to these adverse effects.

In the current study, granisetron 2.5 mg conferred significant antiemetic benefits compared todexamethasone8 mg. When comparing the antiemetic efficacy of the two groups, the benefits conferred by the granisetron 2.5 mg were more superior than those of dexamethasone 8 mg since it resulted in an improved emesis control, and a lower incidence of PONV for longer durations with a higher level of statistical significance at 0-2 hours, 2-6 hours and 24-48 hours when compared to dexamethasone alone.

Of particular interest, the overall need of rescue antiemtic was 9 (22.5) for group G compared to 17 (42.5) for groups D. We did not include a placebo group in our study. As per A spinall and Goodman if you have active drugs available, placebo controlled trials may be unethical because PONV are very much distressing after laparoscopic surgery (Aspinall and Goodman, 1995).

In conclusion prophylactic therapy with granisetron 2.5 mg appeared to be more effective than dexamethasone 8 mg for reducing PONV in patients who are at increased risk of developing PONV after laparoscopic abdominal surgery without apparent side effects.

Conflict of interest

Authors have no conflicts of interest or financial ties to disclose.

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