



# A Randomized Comparative Trial on the Efficacy and Safety of Generic Granisetron, Kytril and Metoclopramide in the Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Ophthalmic Surgery

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## ABSTRACT

**Background:** Post-operative nausea and vomiting (PONV) is commonly experienced by patients after surgical procedures. **Objectives:** The purpose of the present trial was to compare the antiemetic efficacy of three drugs (generic granisetron, metoclopramide and kytril) for the prevention of acute emesis induced by eye surgery.

**Patients and Methods:** One hundred and fifty-one patients undergoing ophthalmic surgery were randomized to receive generic granisetron (n = 51), metoclopramide (n = 50) or kytril (n = 50), intravenously. A standard general anaesthetic technique and postoperative analgesia was used. The PONV and adverse effects of study drugs were assessed during the early (0-6 hrs) and late (6-24 hrs) periods after administration of medications. **Results:** There was no significant difference between the groups regarding demographic characteristics. Complete protection from retching and vomiting was achieved in all patients receiving generic granisetron. Incidence of nausea, retching and vomiting was significantly higher in the metoclopramide group when compared with generic granisetron group. The most common adverse event in the three groups was headache. No significant difference in the incidence of adverse effects attributable to the study drug was observed between the groups. **Conclusions:** Generic granisetron was found to have favourable efficacy in the prevention of PONV after eye surgery and could be regarded as a safe and inexpensive alternative for kytril and metoclopramide.

## Introduction

Nausea and vomiting are among the most disturbing side effects of surgery, chemotherapy and radiotherapy. In spite of their high prevalence, effective measures for the prevention of nausea and vomiting are yet to be introduced. Postoperative nausea and vomiting (PONV) is among the most frequent complications of anaesthesia.<sup>1</sup> Findings arising from large-scale studies have indicated a rate of around 20-30% for the incidence of PONV,<sup>1,2</sup> while the reported frequencies in the earlier studies were even higher and around 75%.<sup>3,4</sup> PONV may itself result in several other adverse events such as dehydration, dehiscence, electrolyte imbalance, aspiration pneumonitis and delayed discharge especially in ambulatory surgery.<sup>5,6</sup> Therefore, it is

essential to identify effective strategies to decrease the incidence of PONV. Several factors including age, female gender, type of surgical procedure, pre-operative medications, anaesthesia type and duration, history of previous PONV, smoking status, and degree of postoperative pain are associated with PONV.<sup>1,7</sup> Antagonists of serotonin [5-hydroxytryptamine 3 (5-HT<sub>3</sub>)] receptors are among the most effective and widely administered antiemetic agents for the prevention of PONV.<sup>8,9</sup> Serotonin plays an important role in the emetogenic reflex and its effect is mainly exerted through 5-HT<sub>3</sub> receptors. 5-HT<sub>3</sub> receptors are present in vagus nerve terminals, nucleus tractus solitarius and chemoreceptor trigger zone, all places

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being critically involved in emesis.<sup>10</sup> Following an emetogenic stimuli, serotonin is released from the gut enterochromaffin cells and directly stimulates 5-HT<sub>3</sub> receptors on vagal afferents and starts a vomiting reflex.<sup>11</sup>

Currently, several 5-HT<sub>3</sub> receptor antagonists are available for the treatment of PONV. The frequency of severe adverse events such as extrapyramidal symptoms has been shown to be lower with 5-HT<sub>3</sub> antagonists compared with metoclopramide.<sup>12</sup> In spite of their efficacy, the most important factor that limits the application and availability of 5-HT<sub>3</sub> receptor antagonists is the relatively high cost of brand-name drugs. The present trial investigated the efficacy and safety of a recently developed generic granisetron, in comparison with those of kytril and metoclopramide (as drugs that are routinely administered for PONV) in the prevention of PONV in patients undergoing eye surgery. Comparison of generic granisetron with its brand-name counterpart (kytril) was performed to assess the equivalence of these two agents, and the importance of such a comparison lies in the substantially lower cost of generic agent versus the brand-name drug. Furthermore, equivalence of the clinical efficacy of generic granisetron and metoclopramide would be of high translational value owing to the better safety profile of generic granisetron and its lower cost.

### Materials and Methods

This study was performed as a pilot randomized controlled trial. After obtaining institutional review board approval and informed consent, we studied 151 patients (both male and female, aged from 15-87 year) undergoing eye surgery. All patients were scheduled for eye surgery under general anaesthesia. Patients who were pregnant or breast feeding, at risk of QT prolongation, or those who had a history of motion sickness or other movement disorders, previous postoperative vomiting, gastrointestinal disorders, or received an antiemetic within 24 hours before surgery were excluded from participation. Patients were not allowed to have solid food after midnight before surgery.

Subjects were randomly (using random number table) allocated to receive generic granisetron ( $n = 51$ ; 40 µg/kg), kytril ( $n = 50$ ; 40 µg/kg) or metoclopramide ( $n = 50$ ; 0.2 mg/kg), intravenously 2-5 min after induction of anaesthesia (prior to the start of surgery).

Anaesthesia was induced by increasing concentration of sevoflurane in 66% nitrous oxide (N<sub>2</sub>O) and oxygen (O<sub>2</sub>) via mask. After an inhalation induction of anaesthesia, atropine 0.01 mg/kg was given intravenously and tracheal intubation was facilitated with vecuronium 0.1 mg/kg intravenously. After tracheal intubation, anaesthesia was maintained with N<sub>2</sub>O/O<sub>2</sub> (2:1) and sevoflurane 1.0%–3.0% (inspired concentration). Muscle relaxation was achieved with vecuronium and was antagonized by a combination of

atropine 0.02 mg/kg and neostigmine 0.04 mg/kg intravenously at the end of surgery. Rectal temperature was monitored and maintained at 37±1 °C throughout surgery. If two or more episodes of vomiting occurred during the first 24h after anaesthesia, a rescue antiemetic was given.

After operation, all patients were admitted to the ward and remained for 6 hrs. Postoperative analgesia was provided by acetaminophen 15–20 mg/kg rectally for mild pain and by pentazocin 0.3 mg/kg intravenously for severe pain. Clear liquids were offered only if requested by the patient, and other oral intake was not allowed for 4 hrs after recovery from anaesthesia. All episodes of emetic symptoms (retching and vomiting) during 0–24 hours and 24–48 hours after anaesthesia were recorded by nursing staff. Moreover, details of any adverse effects such as headache, dizziness, diarrhea and constipation throughout the study were also recorded.

All data are reported as means ± SD. Categorical variables (e.g. frequencies of nausea, vomiting, retching and adverse events) were compared using Chi-square and Fisher's exact (between-group comparisons), or McNemar's (within-group comparisons) test. Continuous variables (e.g. age, blood pressure, duration of surgery and duration of anaesthesia) were analyzed using ANOVA with Bonferroni's adjustment for *post-hoc* multiple comparisons. A probability of less than 0.05 was considered as significant. Data were analyzed using SPSS, version 16.

### Results

Patients' demographic profile is summarized in Table 1. There was no statistically significant difference between the groups regarding most of their baseline characteristics in the study. The mean age of all patients in this study was 53.93±20.24 years. Of the 151 patients who entered the study, 68 (45%) were male and 83 (55%) were female. The mean duration of anaesthesia in the kytril group was significantly higher than those of biogeneric granisetron and metoclopramide groups ( $p < 0.01$ ). The median systolic and diastolic blood pressure, respiratory rate and pulse rate in the preoperative and postoperative periods were calculated in each group at specified time intervals of time and compared between the three groups. No statistically significant difference was observed in these latter parameters between the three groups.

Table 2 shows data on acute nausea, retching and vomiting during the first 6 hrs (0-6 h) and 6-24 hrs after anaesthesia. Generic granisetron was as effective as metoclopramide and kytril in controlling PONV and reducing the incidence of nausea, vomiting and retching. Complete protection from retching and vomiting was achieved in all patients receiving generic granisetron. Five patients had nausea in the generic granisetron group, 9 in metoclopramide group and 9 in kytril group, in the first 6 hrs post-anaesthesia. Within-

group comparisons revealed a significant reduction in the occurrence of nausea, vomiting and retching in the post-surgical 6-24 hrs interval compared with the 0-6

hrs interval in all studied groups, except for the cases in which the patients were symptom-free at both assessed intervals.

**Table 1.** Patient demographic characteristics

	<b>Generic granisetron</b>	<b>Metoclopramide</b>	<b>Kytril</b>	<b>p-value</b>
<b>Mean age (years)</b>	54.18±20.41	54.02±19.02	53.61±21.62	0.893
<b>Sex (no)</b>				
<b>Male</b>	28	20	20	0.64
<b>Female</b>	23	30	30	0.78
<b>Duration of surgery (min)</b>	22.85±9.43	25.41±12.62	21.48±10.98	0.53
<b>Duration of anaesthesia (min)</b>	32.55±12.25	31.60±13.11	43.67±23.29	<0.01
<b><u>Before surgery</u></b>				
Systolic BP (mmHg)	128.92±32.03	123.52±21.04	140.42±27.32	0.06
Diastolic BP (mmHg)	76.41±13.02	76.24±12.11	79.22±13.28	0.23
Respiratory rate (per min)	17.73±1.69	18.48±1.58	17.62±2.11	0.67
Pulse rate (per min)	79.45±15.78	85.96±13.88	88.56±16.84	0.54
<b><u>After surgery</u></b>				
Systolic BP (mmHg)	128.37±26.18	124.24±18.88	130.24± 19.87	0.66
Diastolic BP (mmHg)	74.75±13.60	76.86±10.21	72.82±10.52	0.51
Respiratory rate (per min)	17.88±1.99	18.76±2.07	16.82±2.16	0.12
Pulse rate (per min)	70.78±12.33	72.92±9.54	77.86±18.51	0.08

**Table 2.** Number (%) of patients having nausea, retching and vomiting during the first 6 hrs and 6-24 hrs after anaesthesia.

	<b>Generic granisetron</b>	<b>Metoclopramide</b>	<b>Kytril</b>	<b>p-value</b>
<b><u>Nausea</u></b>				
0-6 hrs after anaesthesia	5 (9.9%)	9 (18%)	9 (18%)	0.23
6-24 hrs after anaesthesia	0 (0%)	3 (6%)	0 (0%)	0.12
	<0.001	<0.001	<0.001	
<b><u>Retching</u></b>				
0-6 hrs after anaesthesia	0 (0%)	4 (8%)	2 (4%)	0.22
6-24 hrs after anaesthesia	0 (0%)	1 (2%)	0 (0%)	0.49
	-	<0.001	<0.001	
<b><u>Vomiting</u></b>				
0-6 hrs after anaesthesia	0 (0%)	4 (8%)	4 (8%)	0.05
6-24 hrs after anaesthesia	0 (0%)	0 (%)	0 (0%)	-
	-	<0.001	<0.001	

Table 3 shows the data on the frequency of adverse effects of three study drugs. No clinically relevant increase in the incidence of adverse events was noted between the three groups. The most common adverse

event in the three groups was headache. There was no difference in the incidence of these events during the first 6 and 24 h after anaesthesia among the three groups.

**Table 3.** Adverse effects attributable to the study drug

	Generic granisetron	Metoclopramide	Kytril	p-value
<b><u>0-6 hrs after anaesthesia</u></b>				
Headache	28 (54.9%)	23 (47.9%)	35 (70%)	0.31
Dizziness	0 (0%)	1 (2.1%)	0 (0%)	0.4
Diarrhea	0 (0%)	1 (2.1%)	0 (0%)	0.4
Constipation	0 (0%)	1 (2.1%)	0 (0%)	0.4
<b><u>6-24 hrs after anaesthesia</u></b>				
Headache	0 (0%)	1 (2.1%)	2 (4%)	0.31
Dizziness	0 (0%)	0 (0%)	0 (0%)	-
Diarrhea	0 (0%)	0 (0%)	0 (0%)	-
Constipation	0 (0%)	0 (0%)	0 (0%)	-

### Discussion

In spite of advances in antiemetic therapy in the last decades, incidence of PONV is still relatively high. Granisetron and metoclopramide are the most commonly prescribed medications for the prevention of PONV. However, 5-HT<sub>3</sub> antagonists are preferred owing to the lower incidence of adverse events such as extrapyramidal syndrome.<sup>12</sup> The present study was aimed at comparing the antiemetic efficacy of generic granisetron, metoclopramide and kytril in the prevention of PONV. In our study, the treatment groups were similar in terms of patient characteristics, surgical procedure, type of anaesthesia and analgesics used postoperatively. Therefore, the differences in scores can be attributed to the differences in the antiemetic activity of tested agents.

In this investigation, generic granisetron was shown to be an effective treatment for PONV in patients who had received eye surgery, and its efficacy was comparable with those of metoclopramide and kytril in preventing PONV. The number of subjects experiencing episodes of nausea, vomiting and retching was found to be significantly fewer at 6-24 hrs interval compared with the first 6 hrs interval.

Several studies have shown the high efficacy of granisetron in the prevention of PONV,<sup>13-15</sup> but the exact mechanism of action of granisetron in the prevention of PONV is not fully understood. It has been suggested that granisetron may act on sites containing 5-HT<sub>3</sub> receptors with demonstrated antiemetic effects.<sup>16</sup> Andrews *et al.* demonstrated that granisetron is more potent and long-acting than ondansetron against emesis associated with chemotherapy.<sup>17</sup> It has been that granisetron administration was superior to metoclopramide and placebo in the long-term prevention of PONV after anaesthesia.<sup>18</sup> There is also evidence indicating that granisetron reduces the incidence of PONV after thyroidectomy and that granisetron is more effective than other commonly used and well-established

antiemetics, such as droperidol and metoclopramide, in the prevention of PONV.<sup>16,19</sup> In another study, efficacy of granisetron, droperidol and metoclopramide in the treatment of PONV after laparoscopic cholecystectomy was evaluated. Complete control of established PONV was achieved in 88% of patients with granisetron, 60% with droperidol and 55% with metoclopramide.<sup>13</sup> In addition, comparison of the efficacy of granisetron versus droperidol in reducing the incidence and severity of PONV after laparoscopic cholecystectomy has shown that granisetron is more effective than droperidol and placebo in reducing the incidence and severity of PONV.<sup>20</sup> In another study, the antiemetic effect of granisetron on PONV was compared with placebo and metoclopramide in 60 patients undergoing general anaesthesia for major gynecological surgery. It was concluded that granisetron is superior to metoclopramide in the long-term prevention of nausea and vomiting after anaesthesia.<sup>21</sup> The two other studies found that granisetron was more effective and less toxic than dexamethasone combined with a phenothiazine.<sup>22,23</sup> Granisetron has also been the subject of comparison with another widely used member of the 5-HT<sub>3</sub> antagonist family, i.e. ondansetron. It has been shown that a single dose (10 or 40 µg/kg) of granisetron is as equally effective as three doses of ondansetron (0.15 mg/kg) in the prevention of cisplatin-induced nausea and vomiting.<sup>24</sup> Consistently, Poon and Chow showed equivalent activity of granisetron and ondansetron in controlling acute PONV, yet the impact of both drugs on chronic PONV was less satisfactory.<sup>25</sup> Concordant results on the equivalence of granisetron and ondansetron has also been reported in terms of preventing PONV after laparoscopic cholecystectomy.<sup>26</sup> Finally, the findings of two other studies indicated superior efficacy and better tolerability of granisetron versus ondansetron in reducing the incidence of PONV in patients undergoing middle ear surgery, and also in reducing chemotherapy-induced nausea and vomiting in children with acute

lymphoblastic leukemia.<sup>27</sup> Although the trend in findings is in favor of equivalency of granisetron and ondansetron, future studies are warranted to compare generic granisetron with ondansetron in terms of preventing PONV.

Adverse effects observed in the present study were not clinically serious and did not differ significantly in incidence between the groups. However, generic granisetron had lower postoperative adverse effects compared with other drugs. The most common adverse events of 5-HT<sub>3</sub> receptor antagonists have been reported to be headache, drowsiness, dizziness and itching.<sup>28,29</sup> At doses used for prevention of PONV, these side effects are usually mild. Falkson *et al.* reported that mild headache occurs in patients receiving granisetron.<sup>30</sup> In the current study, 28 patients (54.9%) in the granisetron, 23 patients (47.9%) in the metoclopramide and 35 patients (70%) in the kytril groups had mild headache. Despite this relatively high frequency of headache, 5-HT<sub>3</sub> receptors do not affect heart rate, blood pressure and respiratory rate.

### Conclusion

In light of the present findings, generic granisetron is well-tolerated and exerts favourable efficacy, which is at least as equal as those of the kytril and metoclopramide, in patients who have undergone eye surgery. This study was limited by its pilot nature, relatively small population size and short duration of follow-up, lack of registration in a clinical trial database, and lack of measurement of episodes of nausea, vomiting and retching as well as episodes of adverse events per patient. In spite of these limitations, the findings suggest that the generic granisetron could serve as an effective, safe, available and inexpensive alternative for kytril and metoclopramide. Nevertheless, larger trials with longer durations of follow-up are needed to confirm the efficacy of generic granisetron in other types of PONV.

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