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Comparative Study Between Intravenous Granisetron and Metoclopramide for the Prevention of Emesis After Gynaecological Surgery Under Subarachnoid Block

KEYWORDS: PONV; Granisetron; Metoclopramide; subarachnoid block;

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ABSTRACT **Back ground and objectives**

Nausea and vomiting after spinal anaesthesia for gynaecological surgery are distressing to the patient. Granisetron, a selective 5-HT3 antagonist, is more effective than the traditional antiemetic metoclopramide for the prevention of PONV. This study was undertaken to evaluate the efficacy and safety of granisetron, versus metoclopramide for the prevention of postoperative nausea and vomiting in patients undergoing major gynaecological surgery under subarachnoid block.

Methods

In this randomized, double–blind study hundred patients (age, 20-60 years) of ASA I-II received intravenous Granisetron 1mg, Metoclopramide 10mg (n = 50 of each) immediately before induction of anaesthesia. Postoperatively the incidences of nausea, vomiting and safety assessments were performed at 1, 2, 6 and 24hour during the first 24 hour after surgery.

Results

There were no differences between the groups with regard to patient demographics. The percentage of patients who had complete response was 68% (34/50) with granisetron and 40% (20/50) with metoclopramide (P < 0.05); the corresponding rates at 1, 2, 6 and 24 hour after anaesthesia were 80 and 74%; 78 and 60%; 100 and 84% (P < 0.05); 100 and 98% respectively. Safety profiles of the two drugs were comparable, as no clinically serious adverse effects caused by study drugs were observed in either of the groups.

Conclusion

The prophylactic therapy with Granisetron is highly efficacious and safe than Metoclopramide in preventing PONV in patients undergoing gynaecological surgery under subarachnoid block.

INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the most unpleasant and distressing symptoms which follow anaesthesia and surgery (1). Despite the advances in our understanding of PONV, the overall incidence of emetic sequelae after a balanced anaesthetic remains between 20 and 30%, approaching 70% in patients in certain high–risk categories (2). With the change in emphasis from an inpatient to outpatient hospital and office-based medical / surgical environment, there has been increased interest in the 'big little problem' of PONV (3).

PONV is a continuing concern in surgical patients and the management of this problem is still confusing(4), Patients often perceive PONV as one of the most bothersome anaesthesia – related adverse effects and may consider it as distressing as the pain associated with the surgical procedure (5). Development of effective antiemetic therapy has been hampered by the multifactorial nature of PONV (6). Patients undergoing major gynaecological surgery are especially prone to PONV, with reported incidences of 50-75% (7).

Presently, there is no single PONV antiemetic medication or technique that is 100% effective for all patients (3) and a search for better drug continues.

Metoclopramide, a dopamine receptor antagonist was discovered almost 40 years ago, and is still used widely in clinical practice (8). The management of nausea and vomiting has improved greatly in recent years, with the introduction of 5-Hydroxytryptamine (5-HT3)–receptor antagonists (Granisetron), and are widely regarded as the most efficacious antiemetics available today and are currently recommended as the agents of first choice to control nausea and vomiting in most instances (9).

OBJECTIVES OF STUDY

To evaluate the efficacy, safety, incidence of adverse effects and complications of prophylactic use of i.v. Granisetron 1mg versus i.v. Metoclopramide 10mg, in preventing / reducing the incidence of PONV after gynaecological surgery under subarachnoid block.

MATERIALS AND METHODS

After obtaining Institutional Ethics Committee approval and patient's written, informed consent, the present study was conducted in 100 ASA physical status I and II hospitalized female patients in the age group of 20 to 60 years who were scheduled for major gynaecological surgeries. Patients having gastrointestinal (GI) disease (e.g. hiatus hernia, gastro- esophageal regurgitation disorder, peptic ulcer disease, and autonomic dysfunction disorder), those who had received any antiemetic medication within 24 hours of surgery, were excluded.

patients were randomly allocated to receive the study drugs(Granisetron 1mg in group I patients

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(n=50),Metoclopramide 10mg in group II patients (n=50). The study drugs were provided in identical 5ml syringes, and administered according to randomization list; patients and data collectors were both blinded to the treatment. The standard anaesthetic and postoperative pain care procedures were followed in all the patients. Postoperatively, patients were observed for 24 hours, divided into 4 periods: 0 to 1, 1 to 2, 2 to 6, and 6 to 24 hour.

Postoperative vital score (PVS) - Heart rate, noninvasive blood pressure and respiratory rate were considered as the measures of postoperative vitals. Scores awarded as 2 - When all the three parameters were within 20% of the preoperative value, 1 - If any one or more of the three parameters ranged between 20-40% of the preoperative value, 0 - If atleast one of the three parameters was more than 40% of preoperative value. Numeric rating scale used for scoring PONV is as follows: Grade 0 (No nausea / vomiting), Grade 1 (Nausea only), Grade 2 (Vomiting once), Grade 3(Vomiting more than once). Complete response was defined as no nausea, vomiting, or retching, and no need for rescue antiemetic. Ondansetron 4mg i.v. was given as rescue antiemetic in case of vomiting episode more than once and in moderate-severe nausea.

Efficacy assessment

Repeated vomiting within 1 to 2 minutes period was recorded as single episode. No emesis =Complete control, 1 episode= Partial control, More than 1 episode or receipt of rescue antiemetic is considered as Failure. Nausea was graded as 0(no nausea), 1(mild), 2(moderate) and 3(severe). Intensity of nausea was assessed at 1, 2, 6 and 24th hours period by retrospective verbal rating scale (VRS). The total number of retching in 5 minutes was taken as one episode.

Adverse effects included are headache, dizziness, diarrhea, constipation, drowsiness, sedation, seizures, extra pyramidal symptoms (tremors, dystonia). Patients were questioned about any possible of these effects (1, 2, 6 and 24 hours after surgery). In the postoperative ward, blood pressure, pulse rate, respiratory rate and urine output were monitored for 24 hour. Patients were assessed for incidence of nausea, retching, vomiting and side–effects at 1, 2, 6 and 24 hr postoperatively.

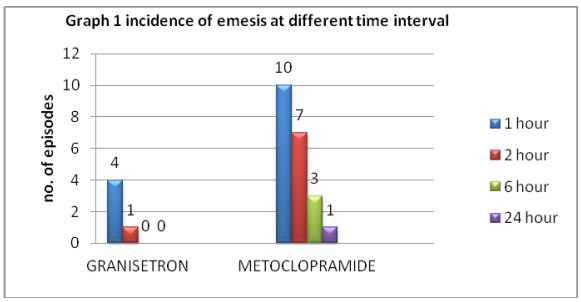
Statistical analysis

Continuous data, expressed as the mean ± SD, were compared using the 'Z' test. For qualitative data, X2 (Chi-square) test was applied.

RESULTS

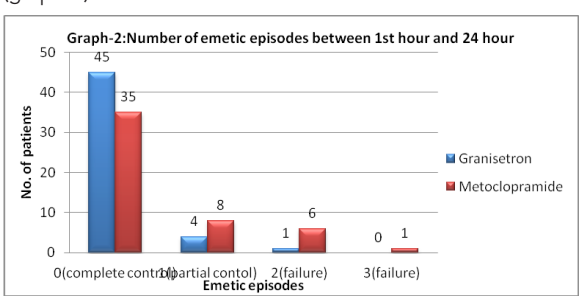
Patient's age, weight and duration of surgery, type of surgery and postoperative vital scores did not differ between the groups.

Incidence of emesis at different time intervals (graph 1)



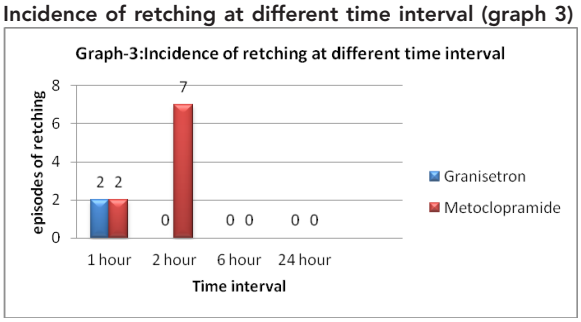
Incidence of emesis was more at 1st hour in group I, and 1st and 2nd hour in group II; emesis was significant at 2nd hr in group II.

Number of emetic episodes between 1st hour and 24 hour (graph 2)



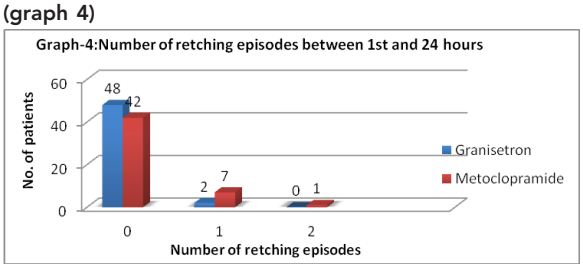
A complete control during the first 24 h after anaesthesia occurred in 90% and 70% of group I and group II patients respectively ($P < 0.05$). Incidence of emesis was highly significant in group II compared to group I ($P < 0.01$). Failure was more in group I than group II ($P<0.05$).

Incidence of retching at different time interval (graph 3)



Incidence of retching was more in the 1st hour in group I, and 2nd hour in group II. Incidence of retching was reduced significantly in group I patients at 2nd hour as compared to group II.

Number of retching episodes between 1st and 24 hours (graph 4)



96% of group I patients experienced no retching, while 84% of group II patients were free of retching. Incidence of retching was reduced significantly in group I patients as

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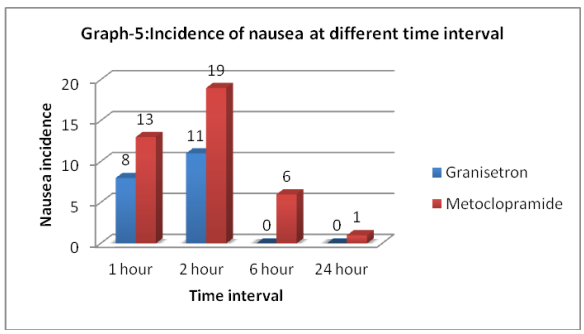
compared to group II

Incidence of nausea at different time interval (graph 5)



Incidence of nausea was more at 1st and 2nd hr in both the groups. Mean episode was not significant statistically at different time intervals.

There was highly significant reduction in the nausea incidence in group I compared to group II. 68% of Group I patients did not experience nausea, while, in group II this was 40%. When major nausea episodes were considered (score of 2 or more), significantly less number of patients in group I had major nausea (10% in group I and 42% in group II).

A complete response during 1-2 hour after anaesthesia occurred in 78% and 60% of patients who had received granisetron and metoclopramide respectively; Corresponding percentage of patients requiring rescue antiemetics at 1-2h were 10% and 22%. These results at 1 to 2 hour were significantly different among the groups, with granisetron being better than metoclopramide. Frequency of nausea and vomiting was low after 2 hour in both the groups. Observation of PONV score at 2-6 hours was significantly different among the groups. More patients required rescue antiemetics in metoclopramide group than in granisetron group at 0-1 hour.

Postoperative analgesic requirements were not significantly different at any point of time among the 2 treatment groups.The frequency of adverse effects was not significant statistically between the groups. In Group I four patients complained of headache and three complained of dizziness. In group II three patients had headache, three had dizziness and two were drowsy.

DISCUSSION

Severe post operative emesis may lead to dehydration, electrolyte imbalances, venous hypertension, bleeding, hematoma formation, suture dehiscence, esophageal rupture, aspiration pneumonitis, delayed post-anaesthesia care unit (PACU) discharge and unanticipated hospital admission, leading to increased health care costs.2

Studies comparing many of the drugs with granisetron have been carried out in the recent years (Since 1995). It was evident that granisetron was highly or equally effective in preventing PONV in some studies (10-13). The incidences of side effects were negligibly low or nil with granisetron. In our study all the factors were well balanced between the two groups, all patients underwent the same preoperative fasting, premedication and same standardized balanced anaesthesia and postoperative care. The groups were similar with respect to age, weight, duration of surgery, type of surgery and postoperative analgesia.

Mikawa K, et al. found that Changes in vital signs were similar and remained within the clinically acceptable ranges in both groups (14), tachycardia and hypertension are the reflection of pain which in turn can influence the incidence of emesis in early post operative period. In our study scoring system was used to quantify the haemodynamic changes during surgery and in postoperative period. There was no difference in haemodynamic changes between the two groups as compared preoperative value, both during intraoperative and postoperative period. The postoperative pain scores and requirement of analgesic were essentially comparable without any significant difference between the groups.

In a study by Wilson AJ et al. granisetron 1mg provided effective prophylaxis against vomiting in 63.4% of patients in the first 24 hr and 78.4% in the first 6 hr after surgery. Significantly more patients did not require rescue antiemetics in granisetron group than in placebo group (15). In PONV prevention study of patients undergoing major gynaecological surgery Fujii Y, et al (1998) found that the incidence of PONV was 20% with granisetron (2.5mg) and 60% with metoclopramide (10mg). No clinical adverse events were observed in any group (11).

Prophylactic therapy with granisetron in the prevention of vomiting after pediatric surgery by Fiji Y (1998) found complete response occurred in 68% and 88% of patients who had received metoclopramide and granisetron. Our study also agrees with these results, showing 70% [35/50] and 90% [45/50] in metoclopramide and granisetron group respectively ($P<0.01$) (16).

Efficacy of prophylactic granisetron in postoperative emesis by Hanaoka K, et al (2004). found the no-vomiting rates in granisetron (1mg) patients were significantly higher than that in the placebo group (83.7% and 57.9%). The severity of nausea was also less in granisetron–treated patients (11.5%) than placebo (25.2%). Fewer rescue medications were required in the granisetron group compared with those receiving placebo (17).

In our study 90% of granisetron group patients were emesis free while in metoclopramide group 70% patients experienced no emesis. The incidence of vomiting was more at 1 hour and 2 hour in both groups and incidence was less in granisetron group at both time intervals. Only 10% of patients in granisetron group had vomiting, compared to 20% of metoclopramide group at 1 hour, this finding was highly significant statistically ($P<0.01$). Severity of vomiting was also less in granisetron group than metoclopramide, only two patients of group I had one emetic episode, while 8 patients of group II had this, which was highly significant statistically. 26% of Group II patients had early emesis (with in 2h) and 6% had late (after 2h) emesis where as in group I corresponding values were 10% and 0% respectively. Difference in requirement of rescue antiemetic was statistically significant at 1 hour (4% Vs 16%).

We observed retching separately from vomiting: which has not been done in earlier studies. The incidence of retching was less in granisetron group than metoclopramide group. 96% of patients experienced no retching in group I while it was 84% in metoclopramide group. This observation was significant at 2 hour. Severity was also less in granisetron group.

Henzi et al (1999). The anti nausea effect with 10mg i.v. metoclopramide was not significantly different from pla-

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cebo in early (within 6 hour) events. They also stated that "knowing the doses of metoclopramide (10mg) used in anaesthesia are not really antiemetic begs the question as to whether these doses are too low (18).In our study 'no nausea' in metoclopramide group was 40% as compared to 68% in granisetron group. Postoperative nausea scores were lower in the granisetron group than the metoclopramide group at all the times till 24 hours but the scores did not achieve statistical significance. When the severity of nausea was compared between the two groups, they were found to be significantly less in granisetron group than in metoclopramide group. When major nausea episodes were considered (Score of 2 or more), significantly less number of patients in group I had major nausea (10% in group I and 38% in group II, [$P < 0.01$]).

Loewen PS, et al. in their quantitative systemic review study stated that "there was no difference between the 5HT3 antagonists and the metoclopramide in the overall rate of adverse reactions". Headache was the most common adverse experience occurring in 14.6% of patients in whom it was evaluated (12 trials) and was more in the 5HT3 group (17%) than in the traditional antiemetic (metoclopramide) group (13%). Sedation occurred in 9.6% of patients evaluated (11 trials) and was more common in the traditional antiemetic group (11.9%) than in the 5HT3 group. Finally, dizziness was found in 7.6% of patients evaluated (10 trials) and the incidence was not different between the groups (19).

There was no significant difference in the side effects between the two groups in our study. Though 7 patients in each group had side effects, they were mild and not worth considering. In granisetron group 4 patients complained of headache and 3 had dizziness. In metoclopramide group 2 patients had headache, 2 were drowsy and 3 had dizziness. Thus, the observations in our study confirmed the safety of the granisetron and metoclopramide.

CONCLUSION

- In this randomized, double–blind clinical study, we found that, i.v. granisetron 1mg, administered immediately before induction, significantly decreased the incidence and severity of nausea, retching and vomiting, and the need for rescue antiemetic therapy compared with i.v. metoclopramide. There was no significant difference in haemodynamic changes and incidence of side effects between the two groups (except for mild headache, dizziness, drowsiness). No serious complications were observed in either group, thus Prophylactic therapy with granisetron is highly efficacious and safe than metoclopramide in preventing PONV in patients undergoing gynaecological surgery under subarachnoid block.

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