EFFICACY OF GRANISETRON AND GRANISETRON PLUS DEXAMETHASONE AS PRE-EMPTIVE ANTI-EMETIC THERAPY FOR PONV IN PATIENTS UNDERGOING GENERAL ANESTHESIA FOR ABDOMINAL SURGERY: A CONTROLLED, PROSPECTIVE & RANDOMIZED STUDY
Rashmi Pal¹, K. K. Arora²

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ABSTRACT: BACKGROUND: Abdominal surgeries are associated with a very high rate of postoperative nausea and vomiting (PONV), which can lead to dehydration, electrolyte-imbalance, aspiration-pneumonitis and wound-dehiscence, thereby delaying patient's recovery and prolonging hospital stay. OBJECTIVES: This study was designed to compare the effectiveness of granisetron alone and in combination with dexamethasone for prevention of PONV in patients undergoing general anesthesia for abdominal surgeries as well as recognizing the limitations of routine anti-emetic prophylaxis with a multimodal approach to anti-emesis. MATERIALS & METHODS: In this prospective, randomized and controlled study 75 patients undergoing general anesthesia for abdominal surgeries were randomly allocated to one of the three groups of 25 patients each. Group G received granisetron 40μg/kg, group G+D received granisetron 40μg/kg+dexamethasone 0.1mg/kg and group C received normal saline intravenously, before induction of anesthesia. Perioperative anesthetic protocol was standardized in all patients. Patients were observed for 24 hours postoperatively and all episodes of nausea and vomiting were recorded. RESULTS: The incidence of PONV was 20% with granisetron alone, 16% with granisetron and dexamethasone and 76% in the control group (p<.001). CONCLUSION: Granisetron is effective and safe drug for reducing the incidence of PONV in patients undergoing general anesthesia for abdominal surgeries and becomes more effective when combined with dexamethasone. KEYWORDS: Postoperative nausea and vomiting, Granisetron, Dexamethasone.

INTRODUCTION: Postoperative nausea and vomiting are the most common adverse events after anesthesia and surgery. They are associated with patient dissatisfaction during the postoperative period. Patients report that avoidance of PONV is of greater concern than avoidance of postoperative pain.[1] Among high risk patients, the incidence of PONV can be as frequent as 70-80%.[2] The consequences of PONV are physical, surgical and anesthetic complications for patients, as well as financial implications for the hospital or institutions.[3,4,5]

Many treatments are available for PONV, but none has been proved 100% effective.[6] Anti-emetics acting on dopamine, cholinergic, histamine, 5HT and NK1 receptors have been tried. Combinations of anti-emetic drugs with different mechanism of action are being studied for the prophylaxis of PONV with variable results. Multimodal approach may improve the outcome and should be recommended for patients at high risk for PONV.[7]

This prospective, controlled and randomized study was conducted to compare the efficacy of Granisetron alone and granisetron+Dexamethasone to the control as pre-emptive anti-emetic therapy for PONV in patients receiving general anesthesia for abdominal surgeries.
MATERIALS AND METHODS: The study protocol was approved by institutional ethical committee and informed consent was taken by every patient. Seventy five male and female patients of American Society of Anesthesiologists (ASA) grade 1 & 2 undergoing general anesthesia for abdominal surgery were included in the study. Patients with ASA grade 3 & 4, those who refused to give consent, were pregnant or had a history of motion-sickness, had acute narrow angle glaucoma, had received opioids, non-steroidal anti-inflammatory drugs (NSAIDS), steroids, anti-emetic agents or cytotoxic drugs in previous month or with a history of hypersensitivity to the study drugs were excluded from the study.

Pre-operative evaluation was carried out in all the patients with detailed history, general physical examination. Vital parameters (Pulse rate, blood pressure, respiratory rates and oxygen saturation of the patients on room-air were noted and systemic examination was performed. The routine examination and any specific investigations, if required were done. The patients were randomly allocated in three groups of 25 each using a random number table, to receive either granisetron-40mcg/kg in 5ml normal saline (Group G) or granisetron-40mcg/kg & dexamethasone 0.1mg/kg in 5 ml normal saline (Group G+D) and only normal saline, all intravenously over 30 seconds (Group-C).

The study medications were prepared by personnel not involved in the study and was administered intravenously five minute before induction of anesthesia. All patients received alprazolam 0.25mg and ranitidine 150 mg/kg orally, previous night and were fasted at least 8 hours before surgery. A standardized protocol for general anesthesia was followed for all the patients. On arrival to the operation theatre, a baseline heart rate, noninvasive blood pressure, arterial oxygen saturation was recorded. The patients were given injection glycopyrrolate 0.2mg intravenous just before induction of anesthesia. Anesthesia was induced with fentanyl 2mcg/kg and thiopentone 5mg/kg intravenously, after pre-oxygenation for 3 minutes. Tracheal intubation was facilitated with atracurium 0.5mg/kg intravenous. Anesthesia was maintained with halothane 0.5%-1.0% and nitrous-oxide 60% in oxygen with controlled ventilation. Supplemental doses of atracurium and fentanyl were given as and when required.

A baseline emptying of the stomach of air and gastric contents was ensured by placing a nasogastric tube. Intraoperative monitoring of vital parameters was done throughout the surgery. At the completion of the surgery residual neuromuscular block was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.01mg/kg both intravenous. The trachea was extubated when the patient was awake with a regular respiration and clinically adequate tidal volume. No other sedative, analgesic or anti-emetic was administered. The duration of anesthesia and surgery was noted. The postoperative analgesia was standard for all and was provided with tramadol 50 mg plus diclofenac sodium 75.0 mg intramuscular (i/m) 15-20 minutes after extubation and thereafter diclofenac i/m 8 hourly. All patients were observed in the recovery room for 24 hours and received supplementation of oxygen (3 liters/min) by a face mask for 6 hours and were also observed closely for any adverse effect and drug reactions. Episodes of PONV were recorded immediately after extubation (0 hour) and thereafter at the intervals of 4 hours for next 24 hours.

Nausea was defined as unpleasant sensation associated with awareness of urge to vomit, retching was defined as a labored, spasmodic rhythmic contraction of respiratory and abdominal muscles without expulsion of gastric contents through mouth and vomiting was defined as a forceful expulsion of gastric contents. Complete response to prophylactic anti-emetic was defined as no
postoperative nausea and vomiting and no need for rescue anti-emetic medication in postoperative period of 24 hours.

Rescue antiemetic treatment was given with metoclopramide 10 mg i/v only when patient experienced nausea for 3 minutes or more than one emetic episode in 15 minutes. Incidence of PONV was noted as whether patient had vomiting or retching or nausea only on a three point ordinal scale (TPOS), defined as 0=none, 1=nausea, 2=vomiting/retching (Retching was considered as a vomiting event). Frequency of PONV was noted as number of times, each event occurred. Associated adverse events were recorded either by general questions or spontaneous complaints made by the patients.

RESULTS: The groups were comparable in terms of patient’s demographics, risk factors of PONV, type of operations performed and duration of anesthesia. [Table-1] There was significant difference in the incidence of nausea and vomiting among the three groups (p<.001). During the first 24 hour after anesthesia, the incidence of PONV was 20% with granisetron, 16% with the combination of granisetron and dexamethasone and 76% in the control group (p<.001). Although, the incidence of PONV reduced further with the addition of dexamethasone the difference was not statistically significant. [Table-2]. The incidence was more in females but the difference was statistically insignificant (p>.05). [Table-3] Although there was no statistically significant difference in the PONV scores of group G and group G+D, but on their comparison with control group both groups had the scores which were statistically significant (p value=.000 upto 16 hours for both the groups, p=.003 and p=.001 in 16-20 hours respectively). Again the significance level was similar for granisetron and combination group in 20-24 hours (p=.002). [Table 4] The vitals remained stable throughout the surgery in all the groups. Headache, dizziness and dry mouth were the side effects associated with granisetron, which were statistically insignificant.

DISCUSSION: Post-operative nausea and vomiting are common complications following surgery. General anesthesia carries a higher risk of postoperative nausea and vomiting than does regional anesthesia, major conduction anesthesia (Sub-arachnoid or epidural block) or monitored anesthesia care. Neither of them, however, has resulted in a zero incidence of postoperative nausea and vomiting. Various factors associated with administration of general anesthesia have been implicated as causative factors for this.

Various postoperative factors have also been implicated in the development of postoperative nausea and vomiting including pain, dizziness, ambulation and intake and the use of opioid analgesics. Paradoxically, the administration of opioids in post anaesthesia care unit with the subsequent decrease in pain actually resulted in a decrease in the incidence of nausea. In patients who complained of both pain and nausea, 68.5% experienced relief of their nausea when pain was relieved after administration of an opioid analgesic.[8] Patients fear PONV more than postoperative pain.[1] Consequences of PONV range from patient discomfort and dissatisfaction to clinically significant events such as wound-dehiscence and bleeding, dehydration and electrolyte-imbalance and aspiration pneumonitis. The occurrence of intractable vomiting can prolong the hospital stay.[5] and hence the economic implications also assume greater significance.
The strategies for the prevention of early and late PONV have changed considerably over the last decade, the combination anti-emetic therapy or balanced anti-emesis being preferred over single drug therapy. The first evidence that such combination anti-emetic therapy is of superior benefit came in.\[9\] Since then, several combinations have been tried and many of them have proved to be more efficacious than single drug therapy.\[6\] More recently, multimodal management strategies incorporating changes in anesthetic technique, aggressive fluid management and pain-relief strategies have produced even better results.\[10\]

The 5HT3 receptor antagonists are highly specific and selective for nausea and vomiting.\[11\] Members of this group exert their effects by binding to the serotonin 5HT3 receptor in the chemoreceptor trigger zone (CTZ) and vagal afferents in the gastrointestinal tracts.\[11\] Granisetron is highly selective in its ability to bind the 5HT3 receptors 1000:1 to other receptors or α-1 and α-2 adrenergic, benzodiazepines, β- adrenergic and opioid receptors.

Dexamethasone is a glucocorticoid that produces strong anti-emetic effect by mechanism that is still not understood. It may act through prostaglandin antagonism, serotonin inhibition in the gut and by releasing endorphins. There are no reports of dexamethasone related adverse effects in the doses used for management of PONV, although even meta-analysis and systemic reviews may have insufficient power to detect rare complications.\[9,12\] When dexamethasone is used alone, late efficacy seems to be most pronounced.\[13\] A review of the role of dexamethasone for prevention of postoperative nausea and vomiting compared to placebo shows that dexamethasone treatment reduced early PONV by 35% and late PONV by 50%.\[9\]

The present study was designed to compare the effectiveness of granisetron alone and its combination with dexamethasone for prevention of postoperative nausea and vomiting in abdominal surgeries. In present study, the incidence of PONV was 16%, 20% and 76% (p<.001) and the complete response was found to be 84%, 80% and 24% (p<.001) in group G+D, group G and control group respectively. This is very well comparable to 82% and 78% response found in the combination and granisetron alone group respectively in a study done by Janknegt et al.\[14\]

A similar study was undertaken by Fujii et al,\[15\] to evaluate the efficacy of granisetron alone and its combination with dexamethasone for preventing post-operative nausea and vomiting in abdominal surgeries. In a prospective study, 120 patients received granisetron 40μg/kg or granisetron and dexamethasone 8 mg (n=60 each) intravenously, immediately before induction of anaesthesia. A complete response during next 24 hours was 83% with granisetron and 98% with granisetron plus dexamethasone respectively (p = 0.008). The complete anti-emetic response of 80% (p<.001) in the granisetron group in our study is quite comparable to 83% (p<.001) whereas 84% response in combination group of our study is lower than 98% response found in their study, the difference could be because of 0.1mg/kg dose of dexamethasone used in our study. In the present study the incidence of nausea, vomiting and retching in group-G was significantly decreased (20%) with granisetron as prophylactic anti-emetic before induction of anaesthesia. The higher anti-emetic efficacy of granisetron may possibly be explained by its known pharmacological properties. Granisetron is highly selective 5HT3 receptor antagonist, which blocks both central and peripheral 5HT3 receptors in its combined mode of action.\[16\]

The role of granisetron in pre-emptive anti-emetic prophylaxis was further proved by Fujii and Tanaka et al,\[17\] when they carried out one more study comparing granisetron 40μg/kg, droperidol 20μg/kg or metoclopramide 0.2 mg/kg (n=40 per group), intravenously in 120 patients undergoing laparoscopic cholecystectomy. The complete response noted after 24 hours of
anaesthesia was 88% in patients who had received granisetron (p< 0.05) and this is again comparable to 80% response in group G of present study. The higher number of females (16 out of 25) included in this group might be the responsible factor for a little lower response (80%) in the present study, as higher incidences of nausea and vomiting in females have been reported by Bellville et al,[18] and White and Shafer et al.[19]

Fujii and Saitoh et al,[20] conducted dose ranging study in children undergoing anaesthesia for surgery to determine the minimum effective dose of granisetron. 120 children, ASA-I and II, aged 4–0 years received normal saline (Placebo) and granisetron 20μg/kg, 40μg/kg and 100μg/kg and complete response was noted to be 57% with placebo, 67% with granisetron 20μg/kg, 90% with granisetron 40μg/kg and 90% with granisetron 100μg/kg respectively (p<0.05). It was concluded that granisetron 40μg/kg is the minimum effective (Optimal) dose for prevention of emesis after paediatric surgery. The dose of granisetron used in this study was based on the previous study and 80% response in our study is lower than 90% response seen with 40μg/kg in the mentioned study is possibly because of the type of surgical procedures done (Hernia and phimosis), where PONV is not so common. In present study the effectiveness of drug was 80%, this difference could be because of high-incidence of postoperative nausea and vomiting in abdominal surgeries included in the present study.

Fujii and Saitoh et al,[21] did another comparative study to see the efficacy of granisetron plus dexamethasone with that of granisetron alone for preventing postoperative nausea and vomiting in patients undergoing caesarean section under spinal anaesthesia. In a randomized double blind manner, 120 patients received either granisetron 3 mg (group-I; n= 60) or granisetron 3 mg plus dexamethasone 8 mg (Group-II; n=60) intravenously immediately after clamping of the fetal cord. A complete response was 83% in group-I and 98% in group-II (P=0.008). The corresponding responses of 80% and 84% in the present study were slightly lower, probably because of many other factors included in general anaesthesia, which increased the risk of postoperative nausea and vomiting.

Although Granisetron plus dexamethasone further reduced the incidence of nausea and vomiting in group-G+D (60% less than control group), which is statistically significant, the reduction in incidence of postoperative nausea and vomiting in group-G+D (16%) from group-G (20%) was not significant. With respect to PONV score as well, there was no significant difference between group G an group G+D over the duration of 24 hours. The difference in PONV scores of control group and the combination group was more significant (p=.001) than that of granisetron group (p=.003) at 16-20 hour interval. Two patients in control group required rescue treatment at 12-16 hour. Although the PONV score of group G+D had been lower than that of group G for 24 hours, it was found to be lowest at 0-4 hour in group G and 4-8 hour in group G+D [Table-4].

It should be noted that pre-emptive drugs were administered before induction of anesthesia in our study. The episodes of nausea decreased more in group G+D than group G, in later phase of our observation. Increased efficacy of granisetron could be because of augmentation by dexamethasone. Dexamethasone seems to control late episodes better than early episodes and nausea more than vomiting. The precise mechanism of augmentation by dexamethasone remains unclear, but as granisetron antagonism of 5HT3 receptor is associated with anti-emetic activity,[16] dexamethasone may also inhibit stimulation of 5HT3 receptors.[22] Dexamethasone did not increase the incidence of adverse effect when added to granisetron. Dexamethasone may inhibit synthesis of prostaglandins related to trigger of emesis.
As at higher doses, dexamethasone itself exerts emetic action, we have chosen its minimum effective dose to be 0.1mg/kg body weight. The dose of dexamethasone in present study (0.1mg/kg) was lower than that used in the other studies. This may have contributed to the relatively minor difference in the efficacy of mono drug-therapy and the combination drug therapy in the present study.

The present study did not show any significant alteration in pulse rate, blood pressure and hemodynamic stability was maintained in all the groups. This was in co-relation with the studies of Milne et al.[23] and Scuderi et al.[24] Hemodynamic stability is well maintained with dexamethasone. Granisetron also does not produce significant haemodynamic change and is well tolerated by most of the patients.[25,26]

None of the available agents is entirely effective for preventing PONV. As there is different major receptor systems involved in the aetiology of PONV, a combination of agents that act on different receptors results in better prophylaxis. Prophylactic administration of combination of granisetron with dexamethasone is safe and more effective than granisetron alone in reducing the incidence of PONV in its patients undergoing general anesthesia for abdominal surgeries. Further studies are required to make PONV a rare occurrence.

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### Variables

| Variables                  | Group- C | Group-G | Group- G+D |
|----------------------------|----------|---------|------------|
| Total no. of patients      | 25       | 25      | 25         |
| Age (years)                | 37.267±8.221 | 39.533±8.835 | 39.121±9.789 |
| Weight (kg.)               | 52.433±4.224 | 52.258±4.28 | 52.968±3.943 |
| Sex                        |          |         |            |
| Male                       | 12       | 9       | 13         |
| Female                     | 13       | 16      | 12         |
| Duration of anesthesia (min.)| 130.50±25.50 | 135.00±36.50 | 131.50±23.49 |

Table 1: Demographic Data

Values are expressed as mean ± standard deviation.

### Table 2: Comparison of incidence of PONV among groups

| Total no. of patients | C (%) | G (%) | G+D (%) | C/G | C/G+D | G/G+D |
|-----------------------|-------|-------|---------|-----|-------|-------|
|                       |       |       |         | X²  | P value | X²  | P value | X²  | P value |
| 25                    | 19(76%) | 5(20%) | 4(16%)  | 13.520 | <.001 | 16.320 | <.001 | 0.225 | >.05 |

### Table 3: Comparison of incidence of PONV according to sex in groups

| Group | Total no. of patients | Sex | No. of patient | Incidence of PONV (%) | P value |
|-------|-----------------------|-----|---------------|------------------------|---------|
| C     | 25                    | M   | 12            | 7(58%)                 |         |
|       |                       | F   | 13            | 12(92.30%)             |         |
| G     | 25                    | M   | 9             | 1(011.11%)             |         |
|       |                       | F   | 16            | 4(25.00%)              |         |
| G+D   | 25                    | M   | 13            | 1(7.60%)               |         |
|       |                       | F   | 12            | 3(75.00%)              |         |

Table 3: Comparison of incidence of PONV according to sex in groups

X² =3.14 P =.077
Time-interval | PONV Score | C (25) | G (25) | G+D (25) | C/G (P value) | C/C+G (P value) | G/G+D (P value) |
|--------------|------------|--------|--------|---------|---------------|----------------|----------------|
| 0-4          | 0          | 4      | 22     | 22      | .000          | .000           | .959           |
|              | 1          | 8      | 1      | 2       |               |                |                |
|              | 2          | 13     | 2      | 1       |               |                |                |
| 4-8          | 0          | 5      | 21     | 23      |               | .000           | .000           |
|              | 1          | 9      | 2      | 2       |               |                |                |
|              | 2          | 11     | 2      | 0       |               |                |                |
| 8-12         | 0          | 6      | 21     | 22      |               | .000           | .000           |
|              | 1          | 8      | 2      | 1       |               |                |                |
|              | 2          | 11     | 2      | 2       |               |                |                |
| 12-16        | 0          | 6      | 20     | 21      |               | .000           | .000           |
|              | 1          | 9      | 2      | 1       |               |                |                |
|              | 2          | 10     | 3      | 3       |               |                |                |
| 16-20        | 0          | 7      | 18     | 19      |               | .003           | .001           |
|              | 1          | 9      | 3      | 4       |               |                |                |
|              | 2          | 7      | 3      | 3       |               |                |                |
| 20-24        | 0          | 8      | 18     | 19      |               | .002           | .002           |
|              | 1          | 8      | 4      | 4       |               |                |                |
|              | 2          | 7      | 3      | 2       |               |                |                |

Table 4: Comparison of PONV Score among groups

PONV = Post-operative nausea vomiting.

Three Point Ordinal Scale (TPOS): 0 = None (Complete Response), 1 = nausea, 2 = retching/vomiting.