A COMPARATIVE STUDY OF THE EFFICACY OF GRANISETRON AND ONDANSETRON IN THE PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING IN LSCS PATIENTS UNDER SPINAL ANAESTHESIA

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ABSTRACT: BACKGROUND: The most common and distressing symptoms that follow anaesthesia and surgery are pain and vomiting problems. Pain causes greater amount of suffering, but in some instances nausea and vomiting may be more distressing, particularly after minor surgery. Spinal anaesthesia has been shown to be easy, rapid and safe technique for caesarean section. Nevertheless, it has some minor side effects, including nausea and vomiting in more than 66% of the cases. (Ref (Chestnut D) H 1987). The abrupt diaphragmatic contractions, and protrusion of the abdominal viscera causes surgery more difficult, aspiration is a hazard. Hence we intended to compare the preventive and therapeutic effects of Granisetron and Ondansetron on the incidence of postoperative nausea and vomiting (PONV) in patients undergoing elective Lower segment caesarian section under spinal anaesthesia. OBJECTIVES: Post-operative nausea and vomiting (PONV) are commonly reported adverse events after surgery and can contribute to the development of aspiration, wound dehiscence, and increased bleeding. Prophylaxis with antiemetic has been shown to reduce the incidence of PONV as well as improve patient satisfaction. The main aim of this study is to compare the efficacy and safety of Granisetron with that of Ondansetron and placebo in the prevention of post-operative nausea and vomiting in patients undergoing lower segment caesarian section under spinal anaesthesia. This study is also intended to know the incidence of postoperative nausea and vomiting in this group of patients. Incidence of adverse effects of ondansetron and granisetron were also noted in this study. METHODS: With prior approval from the Institutional ethical committee and written informed consent, 75 patients of ASA grade I, aged between 20–30 years, body weight ranging from 45kg to 65 kg were studied. All the patients were subjected to elective caesarian section. RESULTS: We have studied 75 patients of ASA grade I, they were divided into three groups. 25 patients (group–P) received 10ml inj. Normal saline I.V, 25 patients (group–O) received inj. Ondansetron 4 mg diluted in 10ml normal saline I.V & 25 patients (group-G) inj. Granisetron 1mg I.V diluted in 10 ml normal saline. These drugs were administered 10 minutes before the administration of spinal anaesthesia. There were no significant differences between the three groups regarding patient characteristics (age, body weight, height and previous history of motion sickness and PONV), type of surgery, type of anaesthesia, and duration of pre-operative starvation, duration of surgery and administration of post-operative analgesics. Patient data were analysed by chi-square test and standard error or difference between proportions. P value of 0.05 or less was considered significant. CONCLUSION: By our placebo controlled clinical trial it has been proved that the incidence of PONV is nearly 60% in caesarean deliveries performed under
spinal anaesthesia. On the basis of the present study it can be concluded that injection Granisetron in a dose of 1 mg. I.V. is much more effective in minimizing severe nausea and vomiting than ondansetron in a dose of 4 mg. I.V. and is free from the side effect headache which is a drawback of ondansetron. The use of granisetron as prophylactic antiemetic for high risk group may be recommended. Granisetron seems to be useful alternative and relatively safe drug for effective anti-emetic prophylaxis.

**KEYWORDS:** Granisetron, Ondansetron. Post-Operative Nausea and Vomiting Elective LSCS.

**INTRODUCTION:** The most common and distressing symptoms that follow anaesthesia and surgery are pain and vomiting, Pain causes greater amount of suffering, but in some instances nausea and vomiting may be more distressing, particularly after minor surgery.

Spinal anaesthesia has been shown to be easy, rapid and safe technique for caesarean section. Nevertheless, it has some minor side effects, including nausea and vomiting in more than 66% of the cases. (Ref (Chestnut D) H 1987).

In spite of various advances, nausea and vomiting still occur with unacceptable frequency in association with surgery and anaesthesia. Incidence of postoperative nausea and vomiting (PONV) after spinal anaesthesia for caesarean section as high as 75-80%.¹

The abrupt diaphragmatic contractions, and protrusion of the abdominal viscera causes surgery more difficult, and aspiration is a hazard.

Hence we intended to compare the preventive and therapeutic effects of Granisetron and Ondansetron on the incidence of postoperative nausea and vomiting (PONV) in patients undergoing elective Lower segment caesarean section under spinal anaesthesia.

**AIMS OF THE STUDY:** Post -operative nausea and vomiting (PONV) are commonly reported adverse events after surgery and can contribute to the development of aspiration, wound dehiscence, and increased bleeding. Prophylaxis with anti-emetics has been shown to reduce the incidence of PONV as well as improve patient satisfaction.

The main aim of this study is to compare the efficacy and safety of Granisetron with that of Ondansetron and placebo in the prevention of post-operative nausea and vomiting in patients undergoing lower segment caesarean section under spinal anaesthesia.

This study is also intended to know the incidence of postoperative nausea and vomiting in this group of patients. Incidence of adverse effects of ondansetron and granisetron is also noted in this study.

**MATERIALS AND METHODS:** The main aim of the study is to compare the efficacy and safety of Granisetron with that of Ondansetron and Placebo in the prevention of post-operative nausea and vomiting after caesarean sections done under spinal anaesthesia. None of the currently available antiemetic regimens are entirely effective. Droperidol minimized the incidence of peripartum nausea and vomiting in caesarean Delivery performed under spinal anaesthesia. Use of droperidol may cause prolonged sedation and respiratory depression. Ondansetron one of 5-HT3 receptor antagonists, has been shown to be effective in the prevention of chemotherapy induced emesis. Granisetron one of the new class 5-HT3 receptor antagonists, is a recent drug in
the prevention of nausea and vomiting due to chemotherapy and post-operative nausea and vomiting. We undertook a double blind randomized study to assess the efficacy and safety of Granisetron in comparison to ondansetron administered intravenously before induction of spinal anaesthesia for prophylaxis of nausea and vomiting after caesarean delivery.

Since the incidence of PONV is highly variable and dependent on a number of factors, the trails will be placebo controlled and of an adequate size of population, to properly detect the role of Granisetron and Ondansetron as as antiemetic agents.

With prior approval from the Institutional ethical committee and written informed consent 75 of ASA grade I, aged between 20–30 years, weight ranging from 45kg to 65 kg were. All the patients were subjected for elective caesarean sections.

Patients who were classed ASA grade III and IV who had experienced vomiting or who had taken antiemetic treatment during previous 24 hours were excluded. Those patients with confounding co-existing medical conditions and those receiving concomitant medications that could interfere with the evaluation of the study drug in particular phenothiazines and gastro prokinetic drugs were excluded from the study. Patients who required methylergometrine and prostadin during surgery were also eliminated from the study group.

Patients were allocated randomly in equal number (25 in each group) into three different groups. Patients belonging to group ‘P’ received injection normal saline 10ml I.V. Group ‘O’ received injection ondansetron 4 mg I.V diluted with 10 ml of normal saline and Group ‘G’ received injection Granisetron 1 mg diluted with 10 ml of normal saline. In all the cases the drugs were administered slowly 10 minutes prior to administration of spinal anaesthesia.

The elimination half-life for Granisetron is 3–4 hours, since the duration of surgery in our study was less than 1.30 hours in most cases it is justifiable to give the drug before giving spinal anaesthesia.

In the pre-operative assessment patients were enquired for history of motion sickness, history of previous exposure to anaesthesia and history of PONV, history of APD, history of drug allergy. Vital signs like pulse rate and SPO$_2$ and blood pressure were recorded on every patient. Investigations noted are urine: albumin, sugar. Blood: Hemoglobin, sugar, urea, creatinine and blood grouping and typing.

Just after I.V cannulation the study drugs were injected slowly through the intravenous route.

Each patient received 20 ml/kg of lactated ringers’ solution (As recommended by Chestnut et al) before administration of spinal anaesthesia to prevent hypotension. All patients received oxygen via face mask at a flow of 5lits/min since the induction of spinal anaesthesia. Women were positioned in the left lateral decubitus and a 25 gauze Quinke spinal needle was introduced through the mid line approach at the L3 L4 interspace. Patients received 10mg of 0.5% of Bupivacine (Hyperbaric) subarachoid injection. Aortocaval compression was avoided by placing a single folded blanket beneath the right buttock for left uterine displacement. The level of analgesia was assessed by pinprick and all patients had analgesia up to T4 level. Blood pressure measurements were recorded every 5 minutes by automatic non-invasive machine until delivery of baby. Then every 10 minutes till the patient was transferred to the recovery room. The eyes of the patients were covered with cotton pads to minimize anxiety evoked by the atmosphere of the
operation theatre. Injection oxytocin 10 units were given after the delivery of baby to facilitate uterine contractions.

Hypotension was defined as a decrease in systolic blood pressure of 20% from the base line or a systolic blood pressure below 100mm Hg. Duration of operation was noted. Post-operative analgesia was achieved by injection diclofenac sodium 75 mg IM.

Retching and/or vomiting were taken as positive responses for vomiting. Each patient remained in the recovery room for 6 hours and was observed for the post-operative occurrence of nausea and vomiting.

FOLLOWING PARAMETERS WERE RECORDED:

Pre-operatively: Pulse rate, SPO₂, Blood pressure, previous history of PONV, previous history of motion sickness, history of APD, history of drug allergy.

Intra Operatively: Pulse rate, Blood pressure and SPO₂.

Post Operatively: Pulse rate SPO₂, Blood pressure, nausea and vomiting.

Presence of headache, drowsiness, flushing or any allergic reactions and extra pyramidal symptoms are also noted.

Assessment of emetic Episodes: A single vomit or retch or combination of vomits and/or retches occurring within one minute of each other was considered as a ‘single emetic episode’.

INTERPRETATION OF SYMPTOMS: (KNAPP AND BEECHER, 1956)

Nausea: The feeling is best described by the patients as the desire to vomit without indulging in expulsive movements.

Retching: When no stomach contents are expelled, the expulsive efforts are classified as retching.

Vomiting: It is the production of even the smaller amount of stomach contents due to expulsive efforts.

Interpretation of Nausea Score:
Grade 0 = No nausea.
Grade 1 = Nausea.
Grade 2 = Nausea + retching.
Grade 3 = single episode of vomiting.
Grade 4 = More than one episode of vomiting.

OBSERVATIONS AND RESULTS: We have studied 75 patients of ASA grade I they were divided into three groups. 25 patients (group–p) received inj. Normal saline I.V 25 patients (group–o) received inj. Ondansetron 4mg I.V same quantity of 10 ml & 25 patients (group-G) ing. Granisetron 1mg I.V diluted in 10ml normal saline control experimental drugs were administered 10 minutes before the induction of anaesthesia.
There were no significant differences between the three groups regarding patient characteristics (age, body weight, height and previous history of motion sickness and PONV), type of surgery, type of anaesthesia, and duration of pre-operative starvation, duration of surgery and administration of post-operative analgesics.

Patient data were analysed by chi-square test and standard error or difference between proportions. P value of 0.05 or less was considered significant.

|                          | Group–p | Group-0 Ondansetron | Group–g Granisetron |
|--------------------------|---------|---------------------|---------------------|
| Age (years)mean          | 21      | 20                  | 22                  |
| Weight (kg)mean          | 54      | 54                  | 55                  |
| Duration of anaesthesia  | 60      | 63                  | 58                  |
| H/o motion sickness      | 3       | 4                   | 1                   |
| H/o ponnv                | 0       | 0                   | 0                   |

**Table 1: Showing demographic characteristics**

The efficacy grades of the surgeons, anaesthetists, and post-operative nursing care were same for all the patients.

So to conclude there was absolutely no significant difference between the three groups as far as anaesthesia and operating conditions are concerned. So the comparative study can be said to be valid. Ondansetron and granisetron had no significant effect on pulse rate, Blood pressure and SPO₂.

SPO₂ has no considerable variation between the three groups, preoperatively, intraoperatively and post operatively. We supplement O₂ with mask ventilation for all the patients in three groups throughout the surgery and in recovery room.

|                          | Group–p Placebo | Group-0 Ondansetron | Group–g Granisetron |
|--------------------------|-----------------|---------------------|---------------------|
| Before Spinal            | 81.2            | 88.2                | 92.2                |
| After Spinal             | 84.3            | 80.6                | 90.1                |
| Immediate Post Operative | 86.4            | 89.2                | 90.9                |
| 2 Hours Post-Operative   | 85.1            | 90.0                | 89.9                |
| 4 Hours Post Operative   | 80.3            | 86.0                | 93.2                |
| 6 Hours Post Operative   | 82.0            | 83.2                | 94.2                |

**Table 2: Pulse Rate (Mean and Range)**
**Table 3: mean arterial pressure mm of hg (Mean and range)**

|                          | Group – p Placebo | Group-0 Ondansetron | Group–g Granisetron |
|--------------------------|-------------------|---------------------|---------------------|
| Before spinal            | 83.8(70-100)      | 93.3(85-106)        | 91.8(80-104)        |
| After spinal             | 88.3(70-106)      | 91.6(81-100)        | 90.2(76-102)        |
| Immediate post Operative | 85.1(76-103)      | 91.4(81-105)        | 88.2(77-104)        |
| 2 hours post Operative   | 86.8(70-120)      | 89.2(77-103)        | 86.8(76-103)        |
| 4 hours post Operative   | 84.8(70-100)      | 88.4(75-101)        | 90.7(80-108)        |
| 6 hours post Operative   | 83.2(72-99)       | 90.2(76-102)        | 88.2(78-104)        |

**Table 4: Showing incidence emesis**

| No. of active Episodes | Group–p Placebo | Group-0 Ondansetron | Group–g Granisetron |
|-----------------------|-----------------|---------------------|---------------------|
| None                  | 12              | 20                  | 23                  |
| Single                | 10              | 4                   | 2                   |
| Multiple              | 4               | 1                   | -                   |
| Over all Emesis       | 14              | 5                   | 2                   |

**Adverse Effects:** Three patients in group – P, 2 patients in group – O one patient in group – G developed head ache.

Two patients in group – P, one patient in group - O and none in group – G had drowsiness.

No patients had developed flushing of any allergic reactions in all the three groups.

No patients in three groups had extra pyramidal symptoms.

| Adverse Effects          | Group-p Plaubo | Group-o Ondansetr | Group-g Granisetron |
|--------------------------|----------------|-------------------|---------------------|
| Head ache                | 3              | 2                 | 1                   |
| Drowsiness               | 2              | 1                 | 0                   |
| Extra Pyramidal Symptoms | -              | -                 | -                   |

**Table 5: Showing no. of patients developed adverse effects**
DISCUSSION: Postoperative nausea and vomiting (PONV) is described as “The Big Little Problem” and from the patients perspective PONV is among the most distressing complication of anesthesia and surgery. Pregnant women in general are more prone to develop nausea and vomiting at various stages of their pregnancy and labour. The incidence of post-operative emetic symptoms after caesarian delivery is more under spinal anaesthesia. Although there has been general trend towards decrease in the incidence and intensity of the problem, it still occurs with an unacceptably high frequency. It is distressing to the patient and potentially detrimental to post-operative recovery. Serious complications include Mallory – Weiss syndrome, rupture of oesophagus, dehydration, alkalosis, electrolyte imbalance and aspiration of vomitus.

Recent awareness in improved patient care has led to a continuous search for an effective and safe anti-emetic drug. The antiemetic drugs which are currently used, such as prochlorperazine, droperidol, antihistaminics and Metoclopramide are associated with adverse side effects.

Ondansetron and Granisetron are selective 5-HT3 receptor. The use of these 5-HT3 receptor antagonists have been shown to improve patients’ satisfaction, decrease recovery time, early discharge and reduce an unanticipated hospital admission.

The role of a new 5-HT3 antagonist Granisetron has been proved to be effective in preventing chemotherapy and radiotherapy induced nausea and vomiting.

Granisetron has been shown to prevent PONV in out-patient surgery and in women undergoing ambulatory gynaecological surgery.

The aetiology of PONV is multi factorial and includes factors both related to anaesthesia and unrelated to anaesthesia. The later includes factors such as age, gender and weight. Anaesthesia and operative factors include type and duration of operation, anaesthetics used for induction and maintenance. Female gender has been associated with higher incidence of PONV compared to male patients. On an average, female patients suffer three times more often from PONV than men.

The incidence of emetic symptoms is high during pregnancy because of increased concentration of progesterone in the body. Progesterone decreases gastro-intestinal motility and reduces lower esophageal pressure. These physiological and anatomical changes may predispose the pregnant patients to develop emetic sequelae. Furthermore, the incidence of nausea and vomiting during regional anaesthesia for caesarean delivery is relatively high. Factors attributed are younger age, surgical skill, peritoneal traction, exteriorization of the uterus, fundal pressure during difficult delivery, anaesthetic management and prevention of hypotension in women undergoing caesarian delivery with spinal anaesthesia. However, in our study, most of these factors were well controlled, so that any difference in emesis – free episodes during spinal anaesthesia for caesarean delivery can be attributed to the study drugs.

In the present study, the efficacy of Granisetron to prevent PONV in caesarean sections done under spinal anaesthesia was tried and was compared with ondansetron.

We choose 1mg. of Granisetron as our study dose because several studies have demonstrated that Granisetron is more effective in treating or preventing post-operative emetic symptoms. According to Raphael, optimal dose of Ondansetron for preventing post-operative nausea vomiting is 4 mg and half-life is 3 hours. While optimal dose of Granisetron is 2 mg and half-life is 8-9 hours.
Datta et al\textsuperscript{9} and Kang et al\textsuperscript{10} observed that the incidence of emetic complications during caesarean section correlated with the presence of arterial Hypotension we have taken all precautions to prevent hypotension in our study like preloading 20 ml/ kg of lactated Ringer’s solution preventing aortocaval compression by placing a folded towel under the right buttock.

We choose 4 mg. IV ondansetron as an active dose, because it happens to be the best documented dose for prevention of PONV.

There is no significant alteration seen in pulse rate, SP02, and blood pressure in the patients of all groups of our study immediately after induction of anaesthesia, during surgery and upto 6 hours post operatively.

Incidence of nausea was 60\% in placebo group, 20\% in on dansetron group, 12\% in grani setron group, our findings are similar to that A Rudra et al\textsuperscript{11}. Thus ondansetron and granisetron are effective in preventing severe nausea, but Granisetron is more effective than ondansetron. It has been stated that after spinal anaesthesia the incidence of PONV ranges to 60\% (Chest nut DH 1987) which corroborates with the present findings (Vomiting incidence 60\% in group-p placebo).

Injection Granisetron in a dose of 1mg reduce the incidence of vomiting from 60\% in the placebo (P) group to 12\% only in group (G) P <0.05.

The incidence of Vomiting in Group-O ondansetron was 24\% as compared to 60\% placebo group. (P<0.05). So both ondansetron and Granisetron are effective in preventing post-operative vomiting, but Granisetron is much more effective than ondan setron. (P<0.05).

As physicians and surgeons by necessity have to become more cost conscious articles have appeared questioning the effectiveness of the new antiemetic Granisetron. As the incidence of PONV is in the range of 30-70\% it seems logical that routine prophylactic use may not be practical.

However in patients with higher risk of PONV than the general population (Patients undergoing abdominal, middle ear, strabismus or laparoscopic surgeries, those with higher risk of PONV, women undergoing surgery in 1-7 days of their menstrual cycle) prophylactic therapy even with this costly drug may be entirely appropriate.

**SUMMARY & CONCLUSION:** By our placebo controlled clinical trial it has been proved that the incidence of PONV is nearly 60\% in caesarian deliveries performed under spinal anaesthesia.

On the basis of the present study it can be concluded that injection Granisetron in a dose of 1 mg. I.V. is much more effective in minimizing severe nausea and vomiting than ondansetron in a dose of 4 mg. I.V. and is free from the side effect headache which is a drawback of ondansetron.

The use of granisetron as prophylactic antiemetic for high risk group may be recommended.

Granisetron seems to be useful alternative and relatively safe drug for effective antiemetic prophylaxis.
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