

## Effectiveness of Alizapride for Prophylaxis of Nausea and Vomiting after Spinal Anesthesia for Cesarean Section

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### ABSTRACT

**Background:** Nausea and vomiting are common side effects in parturients undergoing cesarean delivery performed under spinal anesthesia can be very unpleasant to the patients. The reported incidence of nausea and vomiting during cesarean performed under regional anesthesia varies from 50% to 80% when no prophylactic antiemetic is given. Therefore, use of prophylactic antiemetics in parturients undergoing cesarean delivery is recommended by some authors.

**Objective:** In this study, alizapride was evaluated, as a D2 receptor antagonist, on the prevention of nausea and vomiting following Spinal Anesthesia in parturients undergoing elective cesarean section.

**Patients and Methods:** The study was carried out in AL-Azhar University Hospitals, Obstetric and gynaecology department on 90 patients undergoing an elective, lower segment cesarean section (LSCS). All patients were identified by code number to maintain the privacy of the patients. Any unexpected risks appeared during the course of the research was cleared to the participants and the ethical committee on time. A written informed consent was obtained from all patients. Patients were divided into 3 groups, 30 patients for each group. Group I (Alizapride 50 group): Received intravenous (IV) Alizapride 50 mg diluted in 10 ml of normal saline over 1-5 minutes, immediately after clamping umbilical cord. Group II (Alizapride 100 group): Received intravenous (IV) Alizapride 100 mg diluted in 10 ml of normal saline over 1-5 minutes, immediately after clamping umbilical cord. Group III (Saline group): Received normal saline 10 ml, immediately after clamping umbilical cord.

**Results:** The incidence of nausea and vomiting was significantly decreased in group 2 (Alizapride 100 group) compared with group 1 (Alizapride 50 group) and both group was better than group 3 (control group). The use of ondansetron and chlorpheniramine was significantly decreased in group 1 and 2 when compared with group 3.

**Conclusion:** This study concluded that Alizapride 100 mg, given intravenously immediately after clamping umbilical cord would reduce PONV and pruritus in parturients undergoing an elective cesarean section under spinal anesthesia.

**Keywords:** Postoperative nausea and vomiting, cesarean section, alizapride

### INTRODUCTION

Postoperative nausea and vomiting (PONV) is a common complication for patients undergoing operation. The reported incidence of nausea and vomiting during cesarean performed under regional anesthesia varies from 50% to 80% when no prophylactic antiemetic is given. Therefore, the use of prophylactic antiemetics in parturients undergoing cesarean delivery is recommended by some authors <sup>(1)</sup>.

It causes both the physical and psychological distress to the patients as it involves uncontrolled vigorous contraction of muscle, which induces potential adverse effects such as aspiration, dehydration,

electrolyte disturbance and surgical site disruption <sup>(1)</sup>. The increase in risk of adverse effects can give rise to additional treatment, monitoring and nursing care, thus, the duration of hospital stay and medical expenses are increased <sup>(2)</sup>.

Pharmacological treatment by administration of antiemetic is the most common strategy to relieve PONV, but it usually leads to the side effects of antiemetic like fatigue, hypotension and dizziness <sup>(3)</sup>. Moreover, pharmacological treatment requires a significant cost and extra management and nursing care, and hence probable lengthening the hospitalization day. Non-pharmacological

treatment is suggested to be another way out for the patient with PONV<sup>(4)</sup>. A number of treatments have been introduced in order to reduce PONV, such as 5-HT<sub>3</sub> antagonists (ondansetron, granisetron and palonosetron), dopamine receptor antagonists, and antihistaminic drugs. However, each of these treatments is associated with critical limiting factors, namely cost with 5-HT<sub>3</sub> antagonists, extrapyramidal symptoms with dopamine receptor antagonists, excessive sedation and tachycardia with antihistamine drugs<sup>(5)</sup>.

Several classes of drug are used in the management of PONV, but no single class of drug is completely effective in controlling PONV. The D<sub>2</sub>-receptor antagonist alizapride is a methoxy-2-benzamide derivative, new drug structurally related to metoclopramide for treatment of nausea and vomiting.<sup>(7)</sup>

Alizapride is an established antiemetic that is widely used in oncology and perioperative medicine. Alizapride has a favorable safety profile with only infrequently occurring side effects, which include headache, dizziness, dry mouth and extrapyramidal syndromes. Alizapride 50 mg I.V. dose reduced the intensity of spinal morphine-induced pruritus<sup>(8, 10)</sup>. As it is very well tolerated in much higher doses, thus, it would be important to assess its antipruritic activity using a higher dose (100 mg I.V.)<sup>(9, 11)</sup>.

## AIM OF THE WORK

This study aimed to evaluate the efficacy and safety of Alizapride in preventing emetic symptoms during cesarean delivery under spinal anesthesia.

## Patients and Methods

**Design:** This prospective study has been designed to testify that spinal-induced nausea and vomiting could be minimized with the use of intravenous alizapride associated to preanesthesia administration of crystalloid (10-20 ml/kg), in parturients undergoing cesarean section. Patients were randomly enrolled to one of the three groups (Alizapride 50 group, Alizapride 100 group versus placebo control group). After clamping umbilical cord, patients in Alizapride 50 group received Alizapride 50 mg diluted to 10 ml of normal saline over 1-5 minutes. Patients in Alizapride 100 group received Alizapride 100 mg diluted

to 10 ml of normal saline over 1-5 minutes. Patients in placebo group received 10 ml of normal saline (control group) at the same time and rate.

**Setting:** The study was carried out in AL-Azhar University Hospitals.

**Inclusion criteria:** After obtaining the Research/Ethics committee approval and written informed consents, ninety adult obstetric patients who were ASA physical status I, II, between 18 and 40 years of age, with weight 60 kg to 80 kg and undergoing an elective cesarean section with spinal anesthesia constituted the population of this study. The decision to proceed with operative delivery was made by obstetric team independent of the investigators.

**Exclusion criteria:** Parturient who had smoker habit, Obstetric complications, Allergy to Alizapride, Evidence of fetal compromise, Patients who had motion sickness, gastrointestinal disease, Administration of antiemetic medication in the previous 24 hours, Any contraindication for spinal anesthesia will be excluded.

**Preoperative evaluation:** The patient was screened for suitability by: 1- History including assessment of the cardio-respiratory status. 2- Physical examination: chest and heart auscultation and airway assessment. 3- Investigations: complete blood picture, coagulation profile, liver function, kidney function, ECG.

**Patient monitoring** (standard monitoring): Pulse oximetry, ECG and Non-invasive blood pressure monitoring 5 min interval inside the operating room.

**Anesthetic technique:** In the pre-anesthesia room, a peripheral 18-gauge cannula was inserted. All patients received pre hydration with 15 ml/kg of Ringers lactate over a period of 20 minutes before spinal anesthesia and no additional fluid was given other than that required to keep IV peripheral cannula patent.

The spinal technique was performed with the patient in sitting position at L3-L4, L2-L3 interspace using a 25-gauge spinal needle under all aseptic precautions. When free flow of cerebrospinal fluid was obtained 12.5 mg of 0.5% bupivacaine and 25 µg fentanyl was injected slowly without barbotage. After withdrawal of spinal needle an antiseptic seal was applied at the site of lumbar puncture and the patients were then positioned

supine, with 15 degree left lateral tilt. Subsequently, the patients were placed in the position and bladder catheter was inserted.

Usually, data regarding age, height and weight, hemodynamic parameters, the presences of nausea, vomiting, discomfort or inadequate analgesia was collected in the anesthesiology records.

Motor block was assessed after the spinal anesthesia using the modified Bromage scale, and scored as:

- 0 = no motor block,
- 1 = being unable to move the hip,
- 2 = being unable to move the knee,
- and
- 3 = being unable to move the ankle.

The height of the sensory block was assessed using pin prick sensory method. Surgery was allowed to proceed after a block to T6 had been established and the block level at the end of surgery was documented. These studied drugs were administered I.V. immediately after clamping of the umbilical cord. Nausea and vomiting were recorded in the three groups every 4 hour in first 24 h. Side effects of spinal anesthesia was recorded.

Hypotension was defined as a decrease in the systolic arterial pressure (SAP) more than 20% from the baseline reading or a decrease of SAP to less than 90–100 mmHg or MBP < 70 mmHg as absolute value and was treated by boluses of ephedrine in doses of 5 mg.

Heart rate < 60 beats/min was treated with Atropine 0.5 mg.

At delivery all patients received 20 IU of oxytocin IV and no further oxytocin was given intra-operatively.

Nausea is defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit, and vomiting is the forceful expulsion of gastric contents from the mouth. Retching- defined as the labored, spasmodic, rhythmic contractions of the respiratory muscles without the expulsion of gastric contents- was not assessed as a separate entity and patients who experienced it were classified as nauseous.

The details of any other adverse effects are noted throughout the study following either general questioning of the patients by these anesthesiologists or spontaneously mentioned by the patients. The

intraoperative IV sedative medications, fluid administered, and estimated blood loss were also recorded. In the event of excessive blood loss (>900 ml), the patient was excluded from the study and treated appropriately.

The following indices were taken and statistically analyzed: Nausea and vomiting - baseline, at 4, 6, 12, 24 h after injection of studied drug. Pruritus - baseline, at 4, 6, 12, 24 h after injection of studied drug. Pain-before beginning surgery, 2, 6, 12, 24 hours after injection of studied drugs. The adverse effects of studied drug including, headache, dizziness, hypotension, sedation, extrapyramidal manifestation and hiccup were recorded.

#### **Statistical analysis:**

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean  $\pm$  standard deviation (SD). Qualitative data were expressed as frequency and percentage.

#### **The following tests were done:**

- A one-way analysis of variance (ANOVA) when comparing between more than two means.
- Post Hoc test: Least Significant Difference (LSD) was used for multiple comparisons between different variables.
- Chi-square ( $\chi^2$ ) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
- Probability (P-value)
  - P-value  $\leq 0.05$  was considered significant.
  - P-value  $\leq 0.001$  was considered as highly significant.
  - P-value  $> 0.05$  was considered insignificant.

#### **RESULTS**

Significant decreases in PONV were observed among groups (*P value* < 0.05). Differences were observed among groups from 2 h to 24 h. Those in Group B had a highly significance lower incidence (*P value* < 0.001), followed by group A and at least group C which had least effect (Table 1).

**Table (1):** Comparison between groups regarding to nausea and vomiting VAS

Nausea and Vomiting VAS	Group A Alizapride 50mg (n=30)	Group B Alizapride 100mg (n=30)	Group C Normal saline (n=30)	x <sup>2</sup>	p-value
<b>Baseline</b>					
No	19 (63.3%)	17 (56.7%)	17 (56.7%)	1.888	0.756
Mild 1-3	5 (16.7%)	8 (26.7%)	5 (16.7%)		
Moderate 4-7	6 (20.0%)	5 (16.7%)	8 (26.7%)		
Severe 8-10	0 (0.0%)	0 (0.0%)	0 (0.0%)		
<b>2 hrs</b>					
No	25 (83.3%)	27 (90.0%)	19 (63.3%)	7.926	0.094
Mild 1-3	3 (10.0%)	3 (10.0%)	7 (23.3%)		
Moderate 4-7	2 (6.7%)	0 (0.0%)	4 (13.3%)		
Severe 8-10	0 (0.0%)	0 (0.0%)	0 (0.0%)		
<b>6 hrs</b>					
No	28 (93.3%)	29 (96.7%)	20 (66.7%) <sup>ab</sup>	13.127	<0.001**
Mild 1-3	2 (6.7%)	1 (3.3%)	10 (33.3%)		
Moderate 4-7	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Severe 8-10	0 (0.0%)	0 (0.0%)	0 (0.0%)		
<b>12 hrs</b>					
No	29 (96.7%)	30 (100.0%)	20 (66.7%) <sup>ab</sup>	18.849	<0.001**
Mild 1-3	1 (3.3%)	0 (0.0%)	10 (33.3%)		
Moderate 4-7	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Severe 8-10	0 (0.0%)	0 (0.0%)	0 (0.0%)		
<b>24 hrs</b>					
No	29 (96.7%)	30 (100.0%)	21 (70.0%) <sup>ab</sup>	16.425	<0.001**
Mild 1-3	1 (3.3%)	0 (0.0%)	9 (30.0%)		
Moderate 4-7	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Severe 8-10	0 (0.0%)	0 (0.0%)	0 (0.0%)		

x<sup>2</sup>: Chi-square test; p-value >0.05 NS; \*\*p-value <0.001 HS

a: Significant difference group A.

b: Significant difference group B.

This table show statistically significant difference between groups regarding to nausea and vomiting VAS from 6hrs to 24hrs.

Significant decreases in the incidence and severity of pruritus were observed among groups (*P value* < 0.05). Differences were observed between groups from 2 h to 24 h. Those in Group B and A had a significantly lower incidence as *P value* < 0.05 (Table 2).

This table show statistically significant difference between groups according to pruritus from 2hrs to 24hrs.

Significant Decreases in use of Onansetron and Chlorpheniramine were observed in all groups (*P Value* < 0.05). Differences were observed between groups from 2 h to 24 h. Those in group A and B had significantly lower incidence of use of such drug As *P Value* < 0.05 (Table 3).

**Table (2):** Comparison between groups regarding to pruritus by 4 point scale.

Pruritus by 4 Point Scale	Group A Alizapride 50mg (n=30)	Group B Alizapride 100mg (n=30)	Group C Normal saline (n=30)	x <sup>2</sup>	p-value
<b>Baseline</b>					
No	21 (70.0%)	19 (63.3%)	21 (70.0%)	2.224	0.695
Mild	7 (23.3%)	7 (23.3%)	8 (26.7%)		
Moderate	2 (6.7%)	4 (13.3%)	1 (3.3%)		
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)		
<b>2 hrs</b>					
No	29 (96.7%)	29 (96.7%)	21 (70.0%)ab	13.870	0.008*
Mild	1 (3.3%)	1 (3.3%)	6 (20.0%)		
Moderate	0 (0.0%)	0 (0.0%)	3 (10.0%)		
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)		
<b>6 hrs</b>					
No	29 (96.7%)	30 (100.0%)	21 (70.0%)ab	16.575	0.002*
Mild	1 (3.3%)	0 (0.0%)	7 (23.3%)		
Moderate	0 (0.0%)	0 (0.0%)	2 (6.7%)		
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)		
<b>12 hrs</b>					
No	30 (100.0%)	30 (100.0%)	22 (73.3%)ab	17.561	0.002*
Mild	0 (0.0%)	0 (0.0%)	6 (20.0%)		
Moderate	0 (0.0%)	0 (0.0%)	2 (6.7%)		
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)		
<b>24 hrs</b>					
No	30 (100.0%)	30 (100.0%)	22 (73.3%)ab	17.561	0.002*
Mild	0 (0.0%)	0 (0.0%)	6 (20.0%)		
Moderate	0 (0.0%)	0 (0.0%)	2 (6.7%)		
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)		

$\chi^2$ : Chi-square test; p-value >0.05 NS; \*p-value <0.05 S;

a: Significant difference group A

b: Significant difference group B

**Table (3):** Comparison between groups regarding to need of Ondansetron, Chlorpheniramine, Ephedrine 5 mg and pethedine.

	Group A Alizapride 50mg (n=30)	Group B Alizapride 100mg (n=30)	Group C Normal saline (n=30)	x <sup>2</sup>	p-value
<b>Ondansetron 4 mg intake</b>	4 (13.3%)	1 (3.3%)	8 (26.7%)b	6.653	0.036*
<b>Chlorpheniramine intake</b>	0 (0.0%)	0 (0.0%)	10 (33.3%)ab	22.500	<0.001**
<b>Pethedine 50 mg intake</b>	3 (10.0%)	2 (6.7%)	5 (16.7%)	1.575	0.455
<b>Ephedrine 5 mg intake</b>	4 (13.3%)	6 (20.0%)	3 (10.0%)	1.259	0.533

$\chi^2$ : Chi-square test;

p-value >0.05 NS; \*p-value <0.05 S; \*\*p-value <0.001 HS

a: Significant difference group A

b: Significant difference group B

This table show statistically significant difference between groups regarding to ondansetron and chlorpheniramine.

## DISCUSSION

Spinal anesthesia is frequently used for cesarean section because it is a simple technique, which produces fast and highly effective anesthesia whilst avoiding the morbidity and mortality associated with general anesthesia. Moreover the quality of analgesia is better and blood loss is minimized (12, 13).

Postoperative nausea and vomiting (PONV) is a common complication for patients undergoing operation. It causes both the physical and psychological distress to the patients as it involves uncontrolled vigorous contraction of muscle, which induces potential adverse effects such as aspiration, dehydration, electrolyte disturbance and surgical site disruption (14).

In previous studies, the incidence of PONV in patients who did not receive antiemetic prophylaxis was as high as 70-80 % (15, 16). Among the many factors, female gender, past history of PONV and motion sickness, use of opioids, nitrous oxide and non-smoking history are the independent predictors for PONV (17).

A number of treatments have been introduced in order to reduce PONV, such as 5-HT<sub>3</sub> antagonists (ondansetron, granisetron and palonosetron), dopamine receptor antagonists, and antihistamine drugs. However, each of these treatments is associated with critical limiting factors, namely cost with 5-HT<sub>3</sub> antagonists, extrapyramidal symptoms with dopamine receptor antagonists, excessive sedation and tachycardia with antihistamine drugs (18).

Alizapride used in particular, because it has the same effect of metoclopramide with less side effect and for its anti-pruritic action. The selection of doses was based on previous studies reporting they were safe and effective (20, 21).

In this study, patients received the same type of anesthesia and underwent the same type of surgery.

Moreover, the variables age, gender, weight, height, physical status, non-smoker status, history of PONV, preoperative fasting time, duration of anesthesia, amount of fluid infused during surgery and time of PACU stay

(possible confounding biases) had homogeneous distribution between groups. This is important because the differences between groups could be attributed to the different antiemetic combinations administered.

In this randomized double-blind study, after obtaining approval from Al Azhar University Hospital ethics committee and written informed consent from each parturient undergoing elective cesarean delivery. Ninety parturients were enrolled randomly. Group (A), 30 female patients received Alizapride 50 mg immediately after clamping umbilical cord. Group (B), 30 female patients received Alizapride 100 mg immediately after clamping umbilical cord. Group (C), 30 female patients received 10 ml normal saline immediately after clamping umbilical cord. Alizapride 100 mg was shown to be more effective than other group.

In our study, the results showed no statistically significant difference in the demographic data in the studied groups as regards age, sex, height, weight and duration of surgery (as p value > 0.05).

This study revealed that incidence and severity of PONV and Pruritus were reduced with the use of IV Alizapride 100 mg given after clamping umbilical cord in parturient undergoing elective cesarean section. The use of ondansetron 4 mg and chlorpheniramate was also significantly reduced with Alizapride.

There was statistically significant difference between the three groups regarding the incidence and severity of postoperative nausea and vomiting (PONV) during the first 24 hours postoperatively. Group Alizapride 100 was better than group Alizapride 50 (p-value < 0.001) and both group was better than saline group. Group B (alizapride 100), show highly improvement from 56.7% at base to 90.0% after 2 h, 96.7% after 6 h, 100.0% after 12 h and the reset of 24 h. Group A (alizapride 50), show improvement from 63.3% at base to 83.3% after 2 h, 93.3% after 6 h, 96.7% after 12 h and the reset of 24 h.

Group C (Saline group), show slight improvement from 56.7% at base to 63.3% after 2 h, 66.7% after 6 h, 70.0% after 12 h and the reset of 24 h.

Regarding severity of PONV in the first 24 hours postoperatively there was statistically difference between the two groups. Group alizapride 100 was better than

alizapride 50 (p-value < 0.001) and both group was better than saline group.

The Ondansetron dose needed during the first 24 hours postoperatively was significantly lower in alizapride 100 group in relation to other group Alizapride 50, and saline (p-value < 0.05).

Regarding the effect on pruritus group alizapride 100 and 50 show better effect on lowering the incidence and severity of pruritus than saline group (p value < 0.002).

Regarding incidence of complications there were no statistically difference among the three groups with mild difference between groups showing that Alizapride 50 group was lower in incidence of complications (13.3%) in relation to Alizapride 100 (16.7%) and less in saline group (10%).

Regarding sedation and extrapyramidal manifestation there were no significant difference between three group.

In agreement with the results of this study regarding prevention of post-operative nausea and vomiting, **Stienstra *et al.*** <sup>(22)</sup> Evaluated the efficacy of Alizapride 100 mg in prevention of post-operative nausea and vomiting. The authors hypothesized that the use of IV alizapride 100 mg, droperidol 1 mg and ondansetron 8 mg intravenously was equally effective in the treatment of PONV after gynaecological procedures and that the newer drugs alizapride and ondansetron offer no advantage over droperidol.

**HUYS *et al.*** concluded that the use of high dose of alizapride was significantly better in preventing severe nausea and episodes of vomiting and of minor side effect as sedation and extrapyramidal manifestation compared with high dose of dompridone <sup>(23)</sup>.

**HORTA** and **VIANNA** stated that alizapride had significantly lower incidences of pruritus. As for the prevention of moderate and severe pruritus, alizapride had better effect compared with propofol and droperidol <sup>(24)</sup>.

In contrary to the present study results, **JOSS** and **GALEAZZI** concluded that alizapride did not prove much better effect in prevention of nausea and vomiting compared with high dose of metoclopramide and patients preferred the latter regimen <sup>(25)</sup>.

## CONCLUSION

This study concluded that Alizapride 100 mg, given intravenously immediately after clamping umbilical cord reduce PONV and

pruritus in parturients undergoing an elective cesarean section.

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