www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i2.71

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Is Dexamethsone as Effective as Granisetron in Prevention of Post Operative Nausea and Vomiting in Gynecologic Laparoscopic Surgeries?

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Abstract
Objective: *The aim of this study is to compare the antiemetic effects of intravenous granisetron 40mcg/kg versus 8 mg dexamethasone for prevention of postoperative nausea and vomiting (PONV) in patients undergoing gynaecologic laparoscopic surgeries.*
Subject and Methods: *In this prospective comparative study, a total of 64 women recruited for the study who underwent elective abdominal gynaecologic laparoscopic procedures under general anesthesia with endotracheal intubation, 34 patients were assigned to granisetron group (A) and 30 patients were assigned to dexamethasone group (B). Preoperatively all patients were subjected to a thorough medical history, physical examination, laboratory investigations. Postoperatively patients were assessed according to nausea and vomiting score, hemodynamic changes, and the need for rescue antiemetics.*
Results: *After 6 hours and up to 24 hours postoperatively, 6 (20%) patients experienced nausea in group (B) compared to 2 (5.9%) patients in group (A) and 5 (16.7%) patients experienced vomiting in group (B) compared to only one (2.9%) patient in group (A) which was significant (P= 0.05, 0.046) respectively. Anti-emetics were used in 5(16.7%) patients in group (B) compared to only one (2.9%) patient in group (A) which was statistically significant (p= 0.045).*
Conclusion: *Dexamethasone is as effective as granisetron in controlling PONV during the first six hours postoperatively, however during rest of the first day granisetron showed more efficient control of PONV than dexamethasone. On the other hand, dexamethasone could be a good second alternative to granisetron particularly for economic basis in patients undergoing laparoscopic gynaecologic operations despite its expected side effects.*
Keywords: *dexamethasone, laparoscopic surgeries, granisetron, antiemetics.*

Introduction

Postoperative nausea and vomiting (PONV) is a frequent stressful complication that happens after all types of anesthesia.[1,2] PONV ranges from mild to severe or transient to persistent , it influences the postoperative outcome greatly and delay recovery and discharge thus increasing financial burden over the hospital especially after day care surgeries.[1] The incidence of nausea and vomiting after gynaecologic laparoscopic surgeries is high (40-77%) due to elevation of the intra-abdominal pressure, rapid peritoneal distension and stretch of peritoneum by insufflation and bowel distension because of carbon dioxide (CO2) diffusion inside it.[3,4] The risk factors involved in PONV include females, middle age (20-40 years), history of motion sickness, laparoscopic gynaecologic procedures, use of nitrous oxide, opioids and past history of PONV. [5]

Multiple areas in the brain and gastro-intestinal tract (GIT) are responsible for the process of PONV. These areas include the chemoreceptor trigger zone (CTZ) in the brain, the vestibular system, visceral afferents from the GIT, and the cerebral cortex.[6] These areas excite the vomiting center in the brain stem, that triggers the salivation center, respiratory center, and the pharyngeal, gastro-intestinal, and abdominal muscles that lead to vomiting.[7] The CTZ has many receptors including serotonin (5-Hydroxytryptamine) type 3 (5-HT_3), neurokinin-1 (NK_1) and dopamine (D_2). Abdominal vagal visceral fibers are flourished by 5-HT_3 receptors which are stimulated by infection, distension, and mucosal irritation. [8]

Persistent PONV may lead to tension on suture line, venous hypertension, subcutaneous bleeding, esophageal rupture and jeopardise the patient by increasing the risk of pulmonary aspiration if airway reflexes are not fully recovered due to anaesthetic residual.[9] Various methods to reduce postoperative nausea and vomiting have been tried along the years, which include physical manoeuvres like fasting regimens, pre-anesthetic emptying of stomach, avoiding distension of stomach during non invasive positive pressure ventilation, the use of various antiemetics like Phenothiazines, butyrophenones , antihistaminics , anticholinergics, benzamides, steroids, cannabinoids, and NK1 receptor antagonists. But these drugs have many side effects like sedation, extrapyramidal side effects, and drug interactions. [5,10]

Serotonin (5HT_3) receptor antagonists including ondansetron, granisetron, dolasetron and tropisetron showed significant improvement in patient's satisfaction, reduction of recovery time, discharge time and decrease in unexpected hospital admission. Granisetron is highly selective and with more potent and of longer duration of action than that of ondansetron. Granisetron has been used effectively in the treatment of cytotoxic induced vomiting (cisplatin). It has also recently been used effectively in PONV after gynaecologic surgeries and laparoscopies. [11]

Dexamethasone is a synthetic steroid that has powerful anti-inflammatory, anti-emetic properties which make it widely used to prevent PONV in surgical patients. It has been initially tried as an anti-emetic in patients on chemotherapy for more than three decades and was first studied in preventing PONV in the early nineties.[12] Although the exact mechanism of action is unclear yet, it has been suggested that the anti-emetic effect could be due to the inhibition of prostaglandin synthesis, prevention of serotonin 5HT_3 release in the gut, decrease in neural 5-hydroxytryptophan levels or release of endorphins.[13] The Society for Ambulatory Anaesthesia (SAMBA) guidelines for the management of PONV recommends a prophylactic dose of 4 mg to 5 mg for patients at high risk of PONV regardless of the surgical procedure.[14]

The aim of this study is to compare the antiemetic effects of intravenous granisetron 40mcg/kg versus 8 mg dexamethasone for prevention of PONV in patients undergoing gynaecologic laparoscopic surgeries.

Subjects and Methods

Study Design

This prospective comparative study was carried out at Ibn Sina College Hospital, Jeddah, Saudi Arabia from April 2016 till November 2017. A total of 64 women recruited for the study who underwent elective abdominal gynaecologic laparoscopic procedures under general anesthesia with endotracheal intubation, 34 patients were assigned to granisetron group (A) and 30 patients were assigned to dexamethasone group (B). This study was approved by the Hospital Research Ethics Committee and has been performed in accordance with the ethical standards as in Declaration of Helsinki (1964) and its latter amendments, and a written informed consent was obtained prior to the study.

Inclusion and Exclusion Criteria

The inclusion criteria of these female patients include class I–II according to American society of anaesthesiologists (ASA) physical status, with an age of 20 up to 40 years subjected to laparoscopic gynaecologic procedures. Exclusion criteria include; patients with ASA physical status class III –IV, pregnancy or lactation, severe hypertension , uncontrolled diabetes mellitus, cardiovascular disease, renal disease, any gastric illness, any anti-emetic drug intake during past 24hours, history of relevant drug allergy, any possibility of anticipated difficult intubation.

Participants in group (A) received 40 µg/kg granisetron intravenous (I.V) five minutes prior to induction of general anesthesia while participants in group (B) received 8 mg dexamethasone by the same route and at the same time.

Preoperative Anesthetic Assessment

All patients were subjected to a thorough medical history, physical examination, laboratory investigations (fasting blood sugar, kidney, liver function tests, serum electrolytes, coagulation profile, and electrocardiogram) preoperatively. They were also counselled about the anesthetic management and potential complications of both surgery and anesthesia. All these data were documented. A thorough airway assessment by Mallampati classification, mouth opening, neck movement, thyromental distance was done to find out any possibility of difficult intubation. If there was a chance of significant difficult intubation, the patient was excluded from the study. Adequate fasting of all the patients for at least 6 hours preoperatively should be confirmed. The patients were familiarized with a post-operative nausea and vomiting score, described as:

1= No nausea or vomiting.

2= Mild nausea (not requiring rescue antiemetic)

3= Severe nausea (requiring rescue antiemetic)

4= Mild vomiting (<2 vomiting episodes) , requiring rescue antiemetic

5= Severe vomiting (> 2 vomiting episodes), requiring rescue antiemetic.

Anesthetic Protocol

All patients premedicated with midazolam 0.02 mg/kg I.V one hour preoperatively. The studied drugs are given intravenously 5 minutes before induction of general anesthesia. General anesthesia started after pre-oxygenation for 3 minutes, it was induced with I.V thiopental 5 mg/kg, atracurium 0.5 mg /Kg then patients were intubated and then atracurium 0.2 mg/kg was given for maintenance of muscle relaxation based on using a peripheral nerve stimulator. Anesthesia was continued by mixture of O2 and N2O along with 2% sevoflurane. All patients received tramadol (1 mg/kg) for intra operative analgesia, and were mechanically ventilated to keep EtCO2 between 35-40 mm Hg. An oro-gastric tube was inserted to make the stomach empty of air and other contents. Peritoneal cavity was insufflated with carbon dioxide to keep intra-abdominal pressure <14 mmHg. At the end of procedure the muscle relaxant was antagonized by 40µg/kg neostigmine and 20µg/kg atropine I.V. The oro-gastric tube was suctioned and then removed prior to tracheal extubation, then awake extubation was

done and the patients were transferred to the recovery unit. Intramuscular diclofenac was given for postoperative analgesia.

- **Patients Assessment**

The patients were assessed in terms of:

1. All episodes of PONV (nausea, retching and vomiting) were recorded and classified according to nausea and vomiting score for 0-2 hours in post anaesthesia care unit and from 3-24 hours in postoperative ward. Patients with severe nausea and one or more episodes of vomiting were rescued with antiemetic metoclopramide 0.2 mg/kg I.V.
2. Percentage of emesis free patients and percentage of nausea free patients for 24 hours post-operatively
3. Percentage of patients requiring rescue antiemetics metoclopramide 0.2 mg/kg I.V.
4. Hemodynamic variables (heart rate, systolic, diastolic and mean arterial blood pressure) pre-anesthesia, 30 minutes post-induction, post-extubation, and thirty minutes postoperative and 2,6, and 12 hours postoperatively.

Statistical Analysis

The Data was collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 20) software. Arithmetic mean, standard deviation, t-test was used to compare the two groups. The level of significance was 0.05.

Sample size calculation: Sample size was calculated based on previous studies and by using Med Calc statistical software. Assuming area under ROC to be 0.80, an alpha of 0.05 and power of study 90.0%. A minimum sample size required was calculated to be 60 patients for this study.

Results

A total of 64 women recruited for this prospective comparative study who underwent elective laparoscopic gynaecologic procedures under general anaesthesia, 34 patients were assigned to granisetron group (A) and 30 patients were assigned to dexamethasone group (B). The demographic characteristics of the study participants are illustrated in table (1). There were no statistically significant differences between the two groups for maternal age, body mass index (BMI), parity, and smoking.

Operative variables particularly duration of surgery and anaesthesia were calculated. The mean duration of surgery was 62.5±9.25 minutes in group (A) compared to 65.7±8.25 minutes in group (B). On the other hand, the mean duration of anaesthesia was 73.3±5.98 minutes in group (A) compared to 78.4±6.58 minutes in group (B). These variables showed insignificant differences between two groups. (Table 1) Regarding gynecologic indications for laparoscopic surgeries, 27(42.2%) participants were admitted for ovarian cystectomy, 24(37.5%) participants for diagnostic laparoscopy, 8(12.5%) participants for ovarian drilling, and 5 (7.8%) participants for other indications. (Figure 1)

Concerning the incidence of postoperative nausea and vomiting during the first six hours, there were no statistically significant differences between both groups. (Table 2) On the other hand after 6 hours and up to 24 hours postoperatively, 6 (20%) patients experienced nausea in group (B) compared to 2 (5.9%) patients in group (A) and 5 (16.7%) patients experienced vomiting in group (B) compared to only one (2.9%) patient in group (A) Therefore, incidence of postoperative nausea and vomiting after the first six hours was significantly higher in group (B) compared to group (A) (P= 0.05, 0.046) respectively.(Table 3)

Furthermore, the necessity for rescue anti-emetics administration took place in 2 participants in group (B) compared to one participant in group (A) in first six hours postoperatively which is insignificant (p= 0.50), while after 6 hours and up to 24 hours postoperatively rescue anti-emetics were used in 5(16.7%) patients in group (B) compared to only one (2.9%) patient in group (A) which was statistically significant (p= 0.045). (Figure 2) Patients of both groups were

comparable regarding preoperative, operative, and postoperative hemodynamic status with no morbidity or mortality. (Table 4)

Table (1): The demographic data and clinical characteristics of patients in both groups

Variables	Group A "n=34"	Group B "n=30"	p
Age (years) mean±S.D	28.5±2.96	29.3±6.25	0.365
BMI (Kg/m^2) mean±S.D	23.21±2.64	24.19±3.15	0.298
Parity mean±S.D	0.8±0.69	1.2±0.71	0.365
Duration of Surgery (min) mean±S.D	62.5±9.25	65.7±8.25	0.521
Duration of Anesthesia (min.) mean±S.D	73.3±5.98	78.4±6.58	0.64
Smoking	8 (23.5%)	7(23.3%)	0.865

Data presented as mean± SD; *Significant ($p < 0.05$).

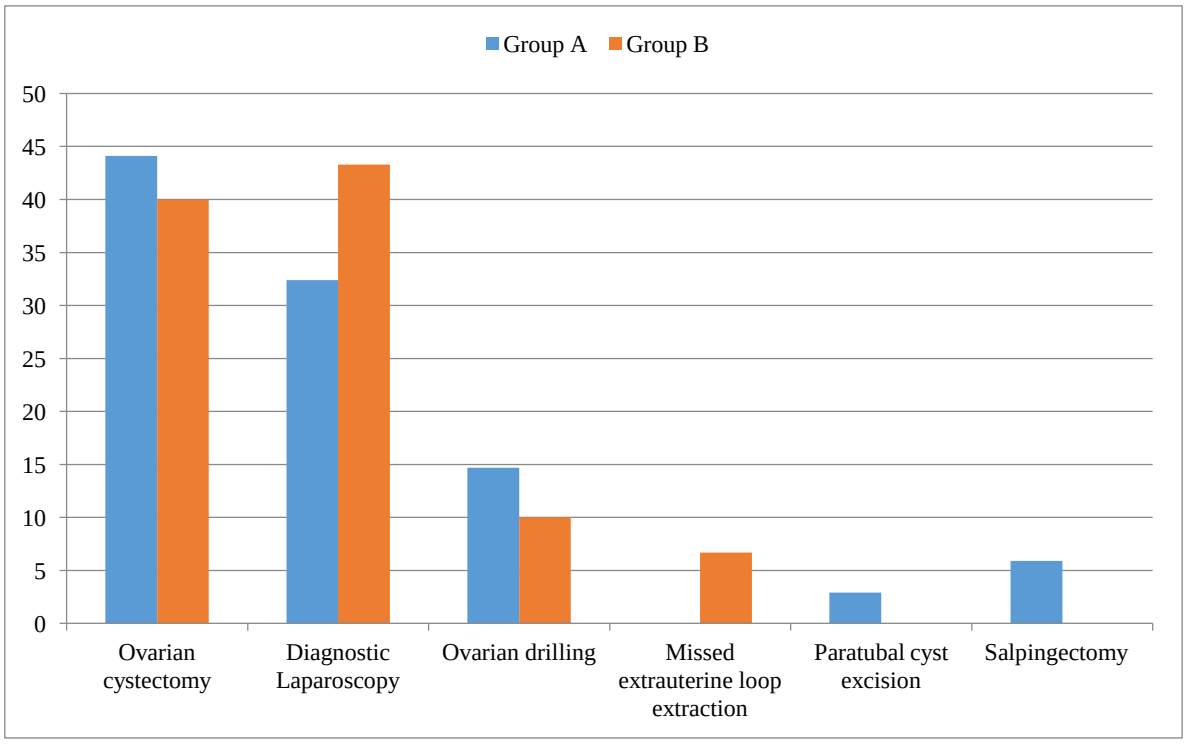

Figure (1): Types of laparoscopic surgeries in both groups

Table (2): Incidence of nausea and vomiting during first 6 hours postoperatively in both groups

Variables	Group A "n=34"		Group B "n=30"		p
	No.	%	No.	%	
Mild nausea	1	2.94	1	3.3	0.928
Severe nausea	0	0.00	1	3.3	-
Total number of nausea	1	2.94	2	6.7	0.500
Mild vomiting	1	2.94	1	3.3	0.928
Severe vomiting	0	0.00	0	0.0	-
Total number of vomiting	1	2.94	1	3.3	0.928
Total number of nausea and vomiting	2	5.9	3	10.0	0.521

Data presented as percentage of patients; *Significant ($p < 0.05$).

Table (3): Incidence of nausea and vomiting 6-24hours postoperatively in both groups

Variables	Group A "n=34"		Group B "n=30"		p
	No.	%	No.	%	
Mild nausea	1	2.9	3	10.0	0.144
Severe nausea	1	2.9	3	10.0	0.144
Total number of nausea	2	5.9	6	20.0	0.05*
Mild vomiting	1	2.9	3	10.0	0.144
Severe vomiting	0	0.0	2	6.7	0.126
Total number of vomiting	1	2.9	5	16.7	0.046*
Total number of nausea and vomiting	3	8.8	11	36.7	0.007*

Data presented as percentage of patients; *Significant ($p < 0.05$).

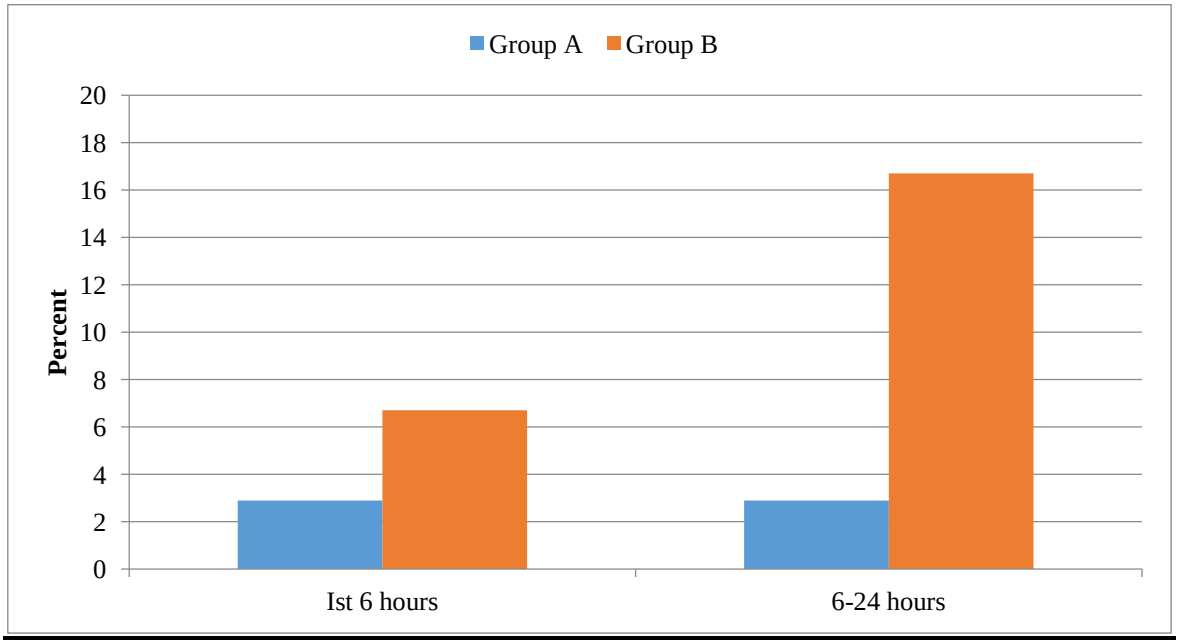

Figure (2): Frequency of rescue antiemetic received in two groups

Table (4): Hemodynamic status in patients in group (A), and group (B)

Variables	HR bpm			MAP (mmHg)		
	Group A "n=34"	Group B "n=30"	p	Group A "n=34"	Group B "n=30"	p
Pre- operative mean±S.D	82.3±7.48	84.2±7.02	0.332	75.3±6.28	80.2±6.68	0.311
30 minutes Pos- Induction mean±S.D	85.1±6.55	78.2±6.52	0.251	84.6±7.6	90.1±8.19	0.107
Post-Extubation mean±S.D	100.5±8.38	92.5±6.96	0.075	80.4±6.70	84.4±6.49	0.365
30 minutes after Recovery mean±S.D	100.4±9.13	102.3±8.53	0.652	88.2±7.35	89.4±7.45	0.711
2h post Recovery mean±S.D	85.2±7.75	89.7±7.48	0.228	87.4±6.72	88.4±7.37	0.725
6h post Recovery mean±S.D	80.4±6.70	83.7±6.98	0.365	88.1±8.01	89.2±6.86	0.825
12-h post Recovery mean±S.D	76.3±6.94	80.4±6.70	0.136	84.2±7.65	88.1±7.34	0.611

Data presented as mean± SD; *Significant ($p < 0.05$).

Discussion

PONV is a very distressing problem to the patient and is quite common in patients undergoing gynaecologic laparoscopic surgeries.[2] Many previous studies discussed the potent anti-emetic effects of granisetron postoperatively [15], Fujii et

al [16], recommended the use of granisetron in an I.V dose of 40 µg/kg which is more effective than lower dose (20 µg/Kg) and at the same time, it has the same effectiveness of 60 µg/ kg in controlling PONV. Wadaskar et al [17], also revealed that 40µg/kg granisetron intravenously was safer, more efficient, and cost effective than ondansetron for prevention of PONV in patients undergoing gynaecologic laparoscopic surgeries under general anesthesia. On the other hand dexamethasone has an established role for the prevention of PONV and it was proved to be as effective and safe as ondansetron in a meta analysis done by Wang et al [18] , over 608 patients undergoing laparoscopic surgeries, and marginally better than droperidol and cyclizine in addition to remarkable opioid sparing effects.[19]

In the present study, we compared the beneficial anti-emetic postoperative effects of I.V 40 µg/kg granisetron versus 8 mg dexamethasone after gynecologic laparoscopic surgeries, and we preferred to use PONV score due to its easiness to understand by the patients and feasibility of its application and evaluation. In our study the incidence of total PONV was (5.9%), (8.8%) in group (A) versus (10%), (36.7%) in group (B) at 0-6 hours and 6-24 hours respectively, which reveals that granisetron has more potent antiemetic effect than dexamethasone over the first 24 hours postoperatively.

Although the results of many previous studies as Fukami et al [20], Binachin et al [21], Feo et al [22], and Bisgard et al [23], proved that dexamethasone preoperatively in laparoscopic surgeries provided considerable reduction of PONV with doubtful effect on post operative pain which actually is in agreement with our results in the first 6 postoperative hours only, but it has not significant antiemetic effect in the next 18 hours postoperatively. From the opposed point of view, our results contradict other previous studies as Hessami M and Yari M [24], done on 104 patients and reported that 3 mg granisetron or 8 mg dexamethasone preoperatively had similar effects in prophylaxis of nausea and vomiting after laparoscopic cholecystectomy, and Erhan et al [25], they mentioned that injection of 8 mg dexamethasone is more effective than 3 mg granisetron in PONV prophylaxis but the differences were statistically insignificant. The similar anti-emetic effect of dexamethasone to granisetron could be explained by the inhibition of prostaglandin synthesis, prevention of serotonin $5HT_3$ release in the gut, decrease in neural $5HT_3$levels or release of endorphins.[26]

Conclusion

We concluded that dexamethasone is as effective as granisetron in controlling PONV during the first six hours postoperatively, however during rest of the first day granisetron showed more efficient control of PONV than dexamethasone. On the other hand, dexamethasone could be a good second alternative to granisetron particularly for economic basis in patients undergoing laparoscopic gynaecologic operations despite its expected side effects.

Declaration of Conflicting Interest

The authors declare that they have no competing interests.

Funding

Funding was not received from any other sources.

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