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ORIGINAL ARTICLE

Palonosetron, Dexamethasone and their combination for prevention of postoperative nausea and vomiting after laparoscopic gynecological surgeries

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ABSTRACT

Background: Palonosetron is a 5HT3 receptor antagonist which is used to prevent postoperative nausea and vomiting (PONV).**Design:**Prospective Randomized Double Blinded Controlled Clinical Trail.

Patients and methods:A total of 200 female patients of ASA physical status class I and II scheduled for gynecological laparoscopic surgery were randomly allocated into four groups: Control group (group C) received 5 ml saline; Palonosetron group (group P) received 0.075 mg palonosetron; Dexamethasone group (group D) received 8 mg dexamethasone and combined Palonosetron/ Dexamethasone (group P/D) group received a combination of 0.075 palonosetron and 8 mg dexamethasone. Studied drugs were given intravenously(iv) immediately before induction of anaesthesia. Anaesthesia was induced with propofol and fentanyl and maintained with isoflurane/oxygen/air. Diclofenac sodium was given intramuscularly for postoperative analgesia. Metoclopramide was used as rescue antiemetic. Overall incidence, severities of PONV, number of patients who needed rescue antiemetic and side effects of the used drugs were recorded during 1st 24 hours postoperatively.

Results: The overall incidences, severities of PONV and the number of patients who needed rescue antiemetic in group P, D and P/D were significantly lower than that in group C. Group P and P/D were comparable and significantly lower than that in group D. Side effects of the used drugs were minimal and comparable**.**

Conclusion: Palonosetron and combined palonosetron with dexamethasone were comparable and superior to dexamethasone in reducing the incidence and severity of PONV and need to rescue antiemetic in gynecological laparoscopic surgery.

Keywords:
Palonosetron, Dexamethasone, Postoperative nausea and vomiting, laparoscopic surgery.

INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of most frequent side effects after anaesthesia. It occurs in 30% of unselected patients and up to 70% of “high-risk” patients **(1).**

The risk factors are female gender, previous history of PONV and motion sickness, non-smoking status, volatile anaesthetic agents, N2O, excess opioids, intra-abdominal, gynecological, laparoscopic, middle ear and ophthalmic surgeries **(2).**

In general, combination therapy is superior to monotherapy for PONV prophylaxis **(3).**

Palonosetron is a 5-HT 3 antagonist approved for the prevention and treatment of PONV. It has been described as a "second generation" 5-HT 3 antagonist since it has greater receptor-binding properties, which results in a much longer half-life than the previously described 5HT3 antagonists **(4).**

Dexamethasone is a synthetic glucocorticoid used extensively in both adults and children **(5).** Its action in prevention of PONV is through inhibiting prostaglandin synthesis, decreasing 5HT levels in the nervous system **(6).**

The aim of this work was to compare between the efficacies of pre-induction IV administration of placebo, palonosetron, dexamethasone and combination of palonosetron with dexamethasone for prevention of PONV after laparoscopic gynecological surgeries to find out which one has the better outcome and least side effects.

Patient and methods:

After obtaining approval from Institutional Review Board (IRB) and written informed consent from each patient, this prospective double blinded randomized controlled clinical study was carried out at the Zagazig University Hospitals from August 2017 to August 2018.

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

A total of 200 female patients **with inclusion criteria:** of ASA physical status (PS) class I and II aged between 20-60 years with body mass index(BMI) not more than 35 kg $m^{2,,}$,Non-smokers, with or without history of previous PONV, undergoing laparoscopic gynecological surgeries were enrolled in this study.

Exclusion criteria were: history of hypersensitivity to any tested drug, contraindication to use corticosteroids, patients on (antidepressants, calcium channel blockers, opioids, steroids and antiemetics) before surgery.

The patients were randomly allocated into four groups by computer generated random number table which was sealed in opaque envelope.

- Control group (Group C) received 5 ml of normal saline as placebo.
- Palonosetron group (Group P): received 0.075 mg of palonosetron (1.5 ml) [Emegrand, Grand pharma] diluted to 5 ml with normal saline.
- Dexamethasone group (Group D) received 8 mg dexamethason (2 ml) [dexamethason, Medical Union Pharmaceuticals] diluted to 5 ml with normal saline.
- Combined palonosetron with Dexamethasone group (Group P/D) received both 0.075 mg palonosetron plus 8mg dexamethasone diluted to 5 ml with normal saline.

For blindness, one of the authors was responsible for giving the tested drug and other one unaware of the given drug was responsible for data collection. Also, patients were blind to group assignment.

All tested drugs were given iv immediately before induction of general anaesthesia.

General anaesthesia was induced by iv injection of 1.5 mg/kg propofol and 1ug/kg fentanyl. Tracheal intubation was facilitated by iv injection of 0.8 mg/kg rocuronium. Nasogastric tube was introduced after induction.

Anaesthesia was maintained with 1–1.5% isoflurane in oxygen/air (50%:50%). Ventilation was mechanically controlled throughout surgery. Patients were placed in the reverse Trendelenburg position and abdomen was insufflated with CO2 to a maximum of 17 mmHg.

At the end of surgery, the insufflated CO2 was removed and suction of gastric content was performed. The residual effect of rocuronium was reversed by iv administration of a mixture

of 0.05mg/kg neostigmine and 0.01mg/kg of atropine sulphate.

After extubation, all patients were shifted to post anaesthetic care unit and monitored for heart rate, blood pressure, SpO2 for first 24 hours postoperatively, diclofenac sodium (1.5 mg/kg) was given intramuscularly for analgesia.

Data collection:

Pre operative:

- The heart rate and mean arterial blood pressure values were recorded immediately before tested drug administration (Base line values).

Intra operative:

- Heart rate and the mean arterial blood pressure were recorded at 2 min, 5 min, 10 min, 20 min and 30 min after tested drug administration.
- Durations of general anaesthesia and surgery were recorded.

Post operative:

Through out the 1st 24 hours postoperatively, the following were recorded:

- The overall incidences and the various severities` levels of PONV (**Score 0**- no nausea , **Score 1**- nausea only, **Score 2**- nausea with retching , **Score 3**- vomiting).
- Number of patients (%) who received rescue antiemetic.
- The incidences of the various side effects as bradycardia, hypotension, dizziness, diarrhea and flushing of the face were recorded.

Sample size calculation:

According to the research work of Bala et al. (7). the incidence of no PONV with palonosterion/dexamethason was 74% and the incidence of no PONV with palonosterion alone was 50% and at 80% power and 95% Confidence Interval , the calculated sample size by using Epi Info version 6 program was 184 adult female patients. For compensation of the dropped cases 200 adult female patients with inclusion criteria was selected for this study and was randomly allocated into 4 equal groups by computer generated random table.

Statistical analysis:

Data were checked, entered, and analyzed using SPSS version 20. Qualitative values were represented as number and percentage and quantitative continues values were represented by mean ± SD. Chi square test (X2) was used for statistical analysis of Qualitative values. ANOVA or Kruskal Wallis test was used for statistical analysis of Quantitative values. P value <0.05 means significant differences and P value < 0.001 means highly significant difference.

RESULTS

Among the 200 patients who were eligible for the study, a total of 10 patients refused to participate and 6 patients were excluded due to ineligibility. A total of 184 patients were randomized to 4 groups **(Fig. 1).**

The demographic data (Age, BMI and ASA ps classes ratio), surgery and anaesthesia durations of the four tested groups were comparable **(Tab. 1).**

Statistically, the overall incidences of PONV in the patients of group P, group D and group P/D were highly significant, significantly and highly significant lower than that in group C respectively (p1=0.000 ,p6=0.037, p4=0.000) respectively . In group P, it was significantly lower than that in group D (p2= 0.012) and comparable with that in group P/D (p3=0.599). In group P/D, it was highly significant lower than that in group D (p5=0.001) (**Tab. 2).**

Statistically, the severity score of PONV in the patients of group P, group D and group P/D were highly significant, significantly and highly significant less than that in group C respectively (p1=0.000, p6=0.000,p4=0.001) respectively. In group P, PONV severity score was significantly less than that in patients of group D (p2=0.011) and comparable with that in patients of group P/D (p3=0.432) . In group P/D it was highly significant less than that in patients of group D (p5=0.012) **(Tab.3).**

Statistically, the number (%) of patients who were in need to rescue antiemetics throughout the first 24 h postoperatively in the patients of group P, group D and group P/D were highly significant lower than that in group C (p1=0.000 , p6=0.000 , p4=0.001) respectively.

In group P, it was significantly lower than that in group D(p2=0.01) and comparable with that in group P/D (p3=0.740). In group P/D, it was highly significant lower than that in groupD (p5=0.018) **(Tab.3).**

Statistically, heart rate and the mean arterial blood pressure values at various times of measurements in the four tested groups were comparable. Clinically, heart rate and MAP in group P/D was the highest followed by group D than group P and lastly group C **(Tab. 4 and 5).** The incidences of the various associated side-effects in the four groups were minimal and statistically comparable (**Tab. 6).**

Table (1): Demographic data (Age, BMI and ASA ps classes ratio), surgery and anaesthesia durations of the four tested groups.

	Group C (n= 46) Mean±SD	Group P (n=46) Mean±SD	Group D (n=46) Mean±SD	Group P/D (n=46) Mean±SD	F	P
Age (years).	26.5±4.8	28.6±5.88	26.5±4.5	28.8±6.7	**2.397**	**0.07**
BMI (kg/m2).	26.9±3.2	27.6±7.53	27.4±2.9	28.2±3.2	**0.695**	**0.556**
Surgery duration (min).	33.8±25.3	35.1±20.9	38.4±20.1	39.7±24.9	**4.3**	**0.231**
Anaesthesia duration (min).	38.8±25.3	40.3±20.8	43.5±20.1	44.7±24.9	**4.24**	**0.237**
	Ratio	**Ratio**	**Ratio**	**Ratio**	**X^2**	**P**
ASA ps class I/ II (Ratio).	10/36	8/38	5/41	6/40	**6.06**	**0.108**

Data are expressed as Mean ± Standard Deviation (SD) or numbers.
Group C = Control group. Group P= Palonosetron group.
Group D =Dexamethason group. Group PD=Palonosetron plus Dexamethasone group.
BMI = Body Mass Index.
ASA ps class=American Society of Anesthesiology physical status class.
F = one way ANOVA test.
K = Kruskall Wallis test (Non parametric data).

Table (2): The overall incidence of PONV in the four tested groups.

	Group C (n=46)	Group P (n=46)	Group D (n=46)	Group P/D (n=46)	x^2	P
	N (%)	**N (%)**	**N (%)**	**N (%)**		
PONV Incidence	29 (63%)	10 (21.7%)	19 (46%)	8 (17.4%)	**26.547**	**P<0.001** P1=0.000** P2=0.012* P3=0.599 P4=0.000** P5=0.001** P6=0.037***

Data are expressed as number and percentage.
n =Group number. N= number of patients who suffered from POVN in each group.
Group C = Control group. Group P =Palonosetron group
Group D=Dexamethason group Group P/D=Combined palonosetron and Dexamethasone group.
P= Comparison among the four tested groups.
P1= Group P vs Group C. P2= Group P vs Group D.
P3= Group P vs Group P/D. P4 = Group P/D vs Group C.
P5= Group P/D vs Group D. P6 =Group D vs Group C.
PONV= Postoperative Nausea and Vomiting.

Table (3): The severity Scores of PONV and numbers (%) of patients who were in need to rescue antiemetic throughout the first 24 h postoperatively in the four tested groups.

PONV severity score	Group C (n=46)	Group P (n=46)	Group D (n=46)	Group P/D (n=46)	X^2	P
	N (%)	**N (%)**	**N (%)**	**N (%)**		
Score:					**28.831**	**P= 0.001****
0	17 (37.0%)			38 (82.6%)		**P1=0.000****
1	10 (21.7%)	36 (78.3%)	27 (58.7%)	6 (13.0%)		**P2=0.011***
2	12 (26.0%)	7 (15.2%)	10 (21.7%)	1 (2.2%)		**P3=0.432**
3	7 (15.2%)	2 (4.3%)	5 (10.9%)	1 (2.2%)		**P4=0.001***
		1 (2.2%)	4 (8.7%)			**P5=0.012****
						P6=0.000**
Number (%) of patients who were in need to rescue anti emetics.	19 (41.3%)	3 (6.5%)	9 (19.5%)	2 (4.3%)	**26.993**	**P<0.001** P1=0.000** P2=0.01* P3=0.740 P4=0.001** P5=0.018** P6=0.000****

Data are expressed as number and percentage. n = number of patients in the each group.
Group C = Control group. Group P =Palonosetron group
Group D=Dexamethason group. Group P/D=Combined palonosetron and Dexamethasone group.
P= Comparison among the four tested groups.
P1= Group P vs Group C. P2= Group P vs group D.
P3= Group P vs group P/D. P4 = Group P/D vs group C.
P5= Group P/D vs Group D. P6 =Group D vs Group C.
PONV= Postoperative Nausea and Vomiting.

Table (4): The mean heart rate values (beats/min) at the various times of measurements of the four tested groups.

Heart rate values (min).		Group C (n=46) Mean ± SD	Group P (n=46) Mean ± SD	Group D (n=46) Mean ±SD	GroupP/D (n=46) Mean ±SD	F	P
- Immediately before tested drug administration (Basal level).		86.8±13.1	88.4±13.9	89.6±14.3	90.2±14.1	0.543	0.653
- At various times after tested drug administration: - 2 min.		82.5±10.4	84.6±9.5	85.2±10.6	88.3±12.2	2.362	0.076
- 5 min.		73.4±9.3	74.5±12.1	74.7±14.7	76.1±13.7	0.340	0.797
- 10 min.		70.6±10.7	72.7±15.1	74.5±10.3	73.4±14.2	1.864	0.137
- 20 min.		68.5±12.2	69.2±11.5	71.7±13.1	72±14.6	0.769	0.513
- 30 min.		69.1±10.1	70.7±11.9	70.9±11.4	71.5±13.4	0.252	0.860

HR for heart rate. F for one way ANOVA.
Data are expressed as Mean ± Standerd Deviation (SD)
n = number of patients in the each group.
Group C = Control group. Group P =Palonosetron group.
Group D=Dexamethason group Group P/D=Combined palonosetron and Dexamethasone group.
P= Comparison among the four tested groups.

Table (5): Mean arterial blood pressure values (mmHg) at the various times of measurements of the four tested groups.

MAP values (mmHg).	Group C (n=46) Mean ± SD	Group P (n=46) Mean ± SD	Group D (n=46) Mean ± SD	Group P/D (n=46) Mean ± SD	F	P
- Immediately before tested drug administration (Basal level).	94.6±12.1	88.6±10.9	91.8±93	89.6±12.4	2.518	0.060
- At various times after tested drug administration - 2 min.	84.4±10.7	85.4±12.8	87.4±13.8	89.2±9.8	1.447	0.231
- 5 min.	80.1±13.2	83.2±16.6	84.5±13.2	85.3±8.7	1.446	0.231
- 10 min.	79.7±12.8	82.2±8.7	82.1±13.1	82.2±12.8	0.492	0.688
- 20 min.	79.1±10.8	79.9±9.7	81.7±10.1	82.3±12.3	0.784	0.504
- 30 min.	77.2±9.9	77.6±10.1	79.1±9.5	79.3±7.8	0.425	0.735

Data are expressed as Mean ± Standerd Deviation (SD). MAP =Mean arterial pressure.
F for one way ANOVA.
n = number of patients in the each group.
Group C = Control group. Group P =Palonosetron group.
Group D=Dexamethason group. Group P/D=Combined Palonosetron and Dexamethasone group.
P= Comparison among the four tested groups.

Table (6): The incidences of the associated various side-effects.

	Group C (n=46)	Group P (n=46)	Group D (n=46)	Group P/D (n=46)	x^2	P
	N (%)	**N (%)**	**N (%)**	**N (%)**		
Bradycardia	5 (10.9%)	3 (6.5%)	2 (4.3%)	1 (2.2%)	3.384	0.336
Hypotension	3 (6.5%)	2 (4.3%)	1 (2.2%)	1 (2.2%)	0.68	0.876
Headache	0 (0.0%)	2 (4.3%)	0 (0.0%)	1 (2.2%)	3.7	0.292
Dizziness	0 (0.0%)	3 (6.5%)	0 (0.0%)	2 (4.3%)	5.5	0.136

Data are expressed as number and percentage.
n= number of patients in each group.
Group C = Control group. Group P =Palonosetron group.
Group D=Dexamethason group. Group P/D=Combined Palonosetron and Dexamethasone group.
P= Comparison among the four tested groups.
P> 0.05 = non significant.

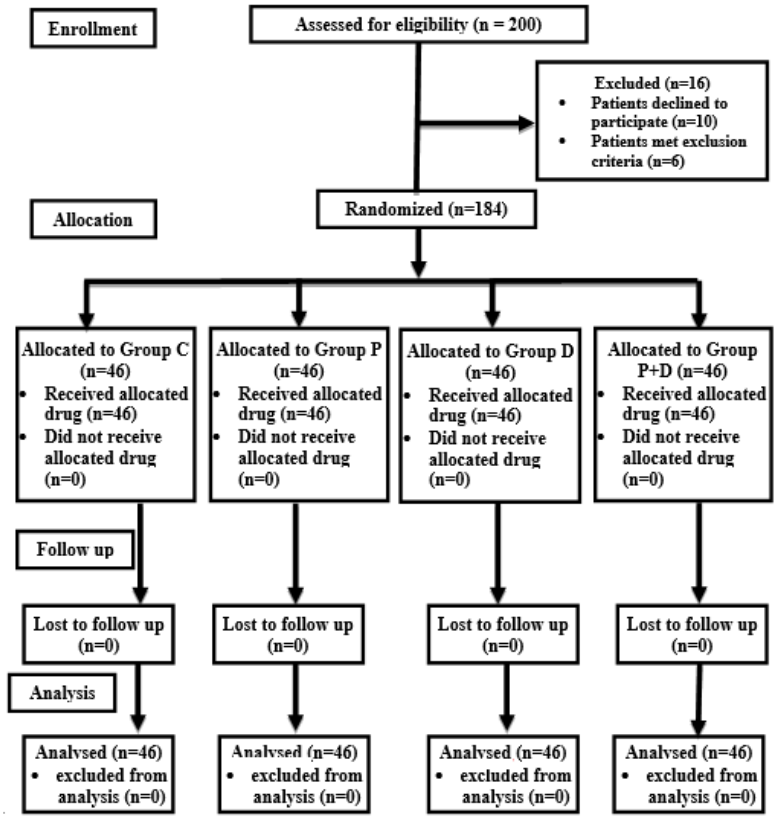

Fig. (1): Flow chart of the study

Group C = Control group.
Group P= Palonosetron group.
Group D =Dexamethason group.
Group PD=Palonosetron plus Dexamethasone group.
n =Group number.

DISCUSSION

The present study showed that, palonosetron, dexamethasone and combined palonosetron with dexamethason were effective in lowering the incidence of PONV when used in female patients undergoing laparoscopic surgery under general anaesthesia. Also, this present study showed that, the effect of palonosetron alone was comparable with that of combined palonosetron with dexamethasone and the effect of each of them was superior to dexamethasone in lowering the incidence of PONV.

These results were in agreement with some workers. Fujii and Itakura **(8)** reported that, the prophylactic therapy with 8 mg dexamethasone was effective in reducing PONV after laparoscopic cholecycstectomy.

Blitz, et al. **(9),** Park, et al. **(10),** Kim, et al. **(11)** and Srivastava, et al. **(12)** reported that, palonosetron alone and combined palonosetron with dexamethason were comparable in lowering the incidence of PONV when used in patients undergoing elective laparoscopic surgery under general anaesthesia.

In contrast, the results of the present study were in disagreement with other workers` results. Bhattarai, et al., **(13)** reported that, the combined ondanoserton with dexamethason was superior to ondanosetron alone in lowering the incidence of PONV when both were used in patients undergoing laparascopic surgeries. D`souza, et al. **(14)** reported that

dexamethasone was more effective in decreasing PONV than ondanosetron in females undergoing laparoscopic gynecological surgery**.** Bala, et al. **(7)** reported that, combined palonosetron with dexamethason was superior to palonosetron alone in lowering the incidence of PONV when both were used in laparoscopic choleycystectomy. Kim, et al.,**(11)** found that, palonosetron and dexamethasone were comparable in lowering the incidence and severity of PONV in patients undergoing thyroid surgery under general anaesthesia **.**

This controversy between the present study findings and the findings of the other workers was attributed to some factors as the use of premedications which have some antiemetic effects, the use of different anaesthetic drugs for maintenance of general anaesthesia and the use of different types of antiemetic and the administration of the antiemetics at different times. Bhattarai, et al **(13)** used midazolam and diazepam for premedication which have some antiemetic effects but no premedication was used in the present study also they used ondanosetron for prevention of PONV 5 min before induction of anaesthesia ,whereas in the present study, palonosetron was used for prevention of PONV immediately before induction of general anaesthesia. D`souza, et al., **(14)** used oxygen (40%), nitrous oxide (60%), sevoflurane (2%) for maintenance of general anaesthesia and ondanosetron and dexamethasone for prevention of PONV 5 min before induction of anaesthesia ,but in the present study, a mixture of isoflurane and oxygen/air (50%:50%) was used for maintenance of general anaesthesia and palonosetron, dexamethasone and their combination were used for prevention of PONV immediately before induction of general anaesthesia. Bala, et al., **(7)** used mixture of isoflurane and nitrous oxide for maintenance of general anaesthesia and palonosetron and combined palonosetron/ dexamethasone for prevention of PONV immediatley before induction of anaesthesia ,but in the present study, a mixture of isoflurane and oxygen/air was used for maintenance of general anaesthesia and palonosetron , dexamethasone and their combination was used for prevention of PONV immediately before induction of general anaesthesia.

The present study showed that, the effect of palonosetron alone was comparable with that of combined palonosetron with dexamethasone and the effect of each of them was superior to dexamethasone in lowering severity of PONV.

These present study findings were in agreement with some workers. Ghosh et al. (**15)** found that, palonosetron alone was comparable with combined palonosetron with dexamethason in lowering the severity of PONV when used in patients scheduled for laparoscopic choleycystectomy under general anesthesia .Song and lee **(16)** reported that, ramosetron (the 5HT3 antagonist) was superior to dexamethasone, in lowering the severity of PONV in females undergoing thyroid surgery .Bala et al. **(7)** reported that there was no significant difference in the severity of PONV between palonosetron and palonosetron/dexamethasone groups in patients undergoing laparoscopic cholecystectomy .

The detected superiority of palonosetron over dexamethasone in lowering the severity of PONV in the present study was attributed to the longer period of palonosetron efficacy than dexamethasone as it has a strong affinity for 5HT3 receptor allosteric site **(17).**

In contrast to these present study finding, Kim, et al. **(11)** reported that, palonosetron was comparable with dexamethasone in lowering the severity of PONV in patients undergoing thyroid surgery under general anaesthesia and receiving opioid based patient controlled analgesia (PCA) for post operative analgesia .

The controversy between the present study finding and Kim, et al., **(11)** finding was attributed to the different type of surgery and to the different analgesic type that was used for post operative analgesia. Kim, et al., performed their study on patients undergoing thyroid surgery and they used opioid based patient controlled analgesia (PCA) for post operative analgesia ,but the present study was performed on females undergoing laparoscopic

gynecological surgery and the usage of Diclofinac sodium as postoperative analgesia.

In the present study, it was found that, hemodynamics (heart rate and mean arterial pressure) values at various times of measurements in group C, group P, group D and group P/D were comparable. These results were in agreement with Ghosh, et al. **(15)** who reported that, there was no significant difference in hemodynamic parameters, oxygen saturation and ECG changes between palonosetron/dexamethasone group and palonosetron group in patients undergoing laparoscopic cholecystectomy .In contrast Paul, et al., **(18)** found that, there was significant difference noted in mean heart rate between palonsetron group and dexamethasone group in patients undergoing ear and nose surgeries under general anaesthesia .

The controversy between the present study finding and, Paul,et al. **(18)** finding was attributed to the premedication, the different antiemetic administration time, the different drugs which were used for anaesthesia and different type of surgery. Paul, et al. used midazolam for premedication, administered anti emetic 5 minutes before induction, used thiopental for induction and vecronium in muscle relaxation and they performed their study on patients who were scheduled for ear and nose surgery. In the present study, no premedication was given, anti emetic was given immediately before induction, proprofol was used for induction and rocronium for muscle relaxation and this present study was performed on female patients who were scheduled for laparoscopic gynecological surgeries.

In this study, the incidences of the various associated side-effects in the patients of group P, group D and group P/D were minimal and comparable. These detected findings were in agreement with some workers. Kim, et al. **(11)** reported that, the overall incidence of side effects was low and didn't significantly differ among palonosetron group and palonosetron /dexamethasone group in highly susceptible thyroidectomy patients .Ghosh, et al. **(15)** found that, none of the patient had any clinically serious side effects in patients undergoing laparoscopic cholecystectomy. Tiwari et al. **(19)** reported that, the incidence of adverse effect in palonosteron group and palonosetron /dexamethasone group was nill in patients undergoing laparoscopic surgery under general anaesthesia .

The limitations of the present study:

The anti emetics effects of the studied drugs were not evaluated during the second 24 h postoperatively. The population of the present study was limited to ASA physical status class I and ASA II adult females patients undergoing laparoscopic surgery only. Only one dose of the various tested drugs is evaluated.

CONCLUSION

Palonosetron (0.075 mg) alone is similar to combined palonosetron (0.075mg) with dexamethasone (8mg) in reducing the incidence and severity of PONV. Both palonosetron alone and combined palonosetron/dexamethason are superior to dexamethasone (8mg) and in reduction of the incidence, severity of PONV with minimally associated side effects**.**

RECOMMENDATION

Palonosetron (0.075 mg) alone is recommended for prevention of PONV in laparoscopic surgeries.

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