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Research Article

Preoperative gabapentin alone or in combination with dexamethasone on postoperative pain relief after abdominal hysterectomies. A randomized controlled trial

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KEYWORDS

Gabapentin;
Dexamethasone;
Postoperative pain;
Hysterectomy

Abstract *Objectives:* To investigate the role of combining preoperative gabapentin with dexamethasone in the management of post-operative pain following abdominal hysterectomy.
Methods: This prospective randomized double blinded study included 60 females scheduled for abdominal hysterectomy under general anesthesia. They were randomized into three equal groups [20 patients each]; group C [Control]: received oral placebo and intravenous 2 cc normal saline 0.9%, group G [Gabapentin]: received 800 mg gabapentin orally and intravenous 2 cc normal saline 0.9% and group GD [Gabapentin/Dexamethasone]: received 800 mg gabapentin orally and intravenous 8 mg/2 cc dexamethasone. Intraoperative fentanyl requirement, postoperative pain, sedation and nausea and vomiting were assessed at 2, 6, 12 and 24 h postoperative. Time of the first request for analgesia and total postoperative meperidine dose over 24 h were calculated.
Results: Intraoperative fentanyl requirement, time of the first analgesic request, total 24 h meperidine consumption and VAS score at 2 and 6 h postoperatively showed highly statistically significant difference between group (GD) [added dexamethasone to gabapentin] and gabapentin (G) alone or control (C), meanwhile there was statistically significant difference between (G) and (C) groups. VAS score was statistically significant lower among the three studied groups when assessed at 12 h postoperatively. There were no statistically significant differences among the three groups as regards the postoperative sedation scale. PONV was highly statistically significant less observed in groups (GD) and (G) at 2 h and statistically significant less observed at 6 h postoperatively when compared to the control group (C).
Conclusion: Gabapentin alone reduced the intraoperative and postoperative opioid requirement as well as postoperative pain and PONV which was significant in comparison with the placebo effect in

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the control. Obviously these effects were more prominent and highly significant when dexamethasone was added to gabapentin.

1. Introduction

Postoperative pain affects the patient's recovery profile. Poorly controlled pain results in increased catabolism, heart rate and blood pressure in addition to immunosuppression [1]. Inadequate pain management has both physiological and psychological unwanted consequences and prolongs the recovery and discharge time leading to increased health care costs [2]. Postoperative pain is not only nociceptive in nature but also consists of inflammatory, neurogenic as well as visceral components [3]. Owing to the multiplicity of the mechanisms responsible for postoperative pain, an opioid and non-opioid analgesic combination is often used as a multimodal analgesic regimen to enhance analgesia and reduce opioid needs and side-effects [4].

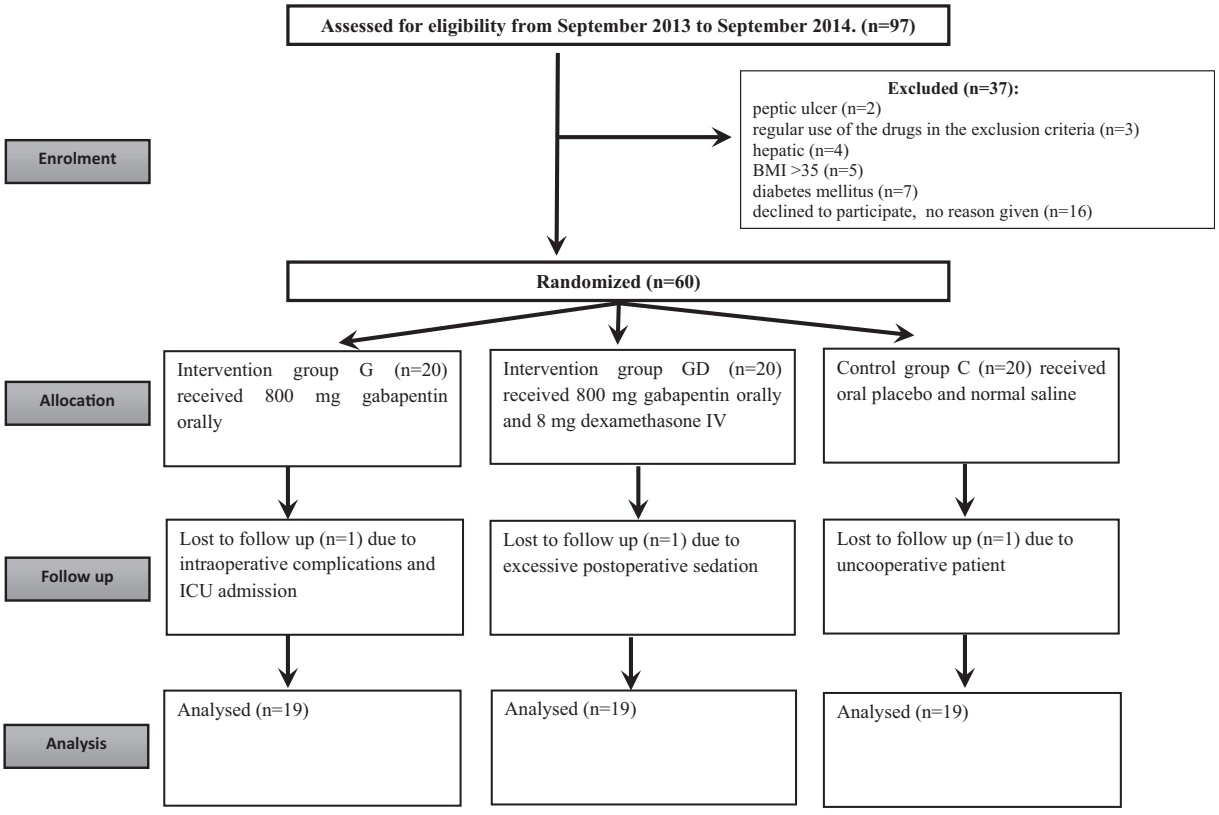
Gabapentin, a structural analog of gamma aminobutyric acid (GABA), was introduced in the United States as an anticonvulsant, used clinically to treat epilepsy. The drug causes amino acids release in the spinal cord dorsal horn and thus decreasing response to neural inputs and stabilizing the nervous activity. The mechanism of action of gabapentin on neuropathic pain is thought to bind to the alpha 2 delta subunit of the voltage-dependent calcium channel in the central nervous system, reducing calcium influx into the nerve terminals and decreases the release of neurotransmitters like glutamate [5]. Gabapentin, therefore, can be used for controlling chronic pain, as in diabetic neuropathy and other neuropathic disorders [6]. Some studies examined the effectiveness of gabapentin for postoperative pain relief [7,8]. A recent study concluded that gabapentin has a role in postoperative pain control, preoperative anxiolysis, attenuation of hemodynamic response to intubation, prevention of postoperative nausea and vomiting (PONV) and finally postoperative delirium [8].

Corticosteroids are used as anti-inflammatory as well as anti-immunological agents. They also posses antiemetic properties and in particular dexamethasone is used commonly for prevention of postoperative nausea and vomiting [9]. Earlier studies showed that glucocorticoids were effective in decreasing postoperative edema and pain in patients undergoing dental procedures [10,11]. A number of recent studies investigated the possible analgesic benefit of a single preoperative dose of dexamethasone [11–13]. Long-term glucocorticoid treatment is associated with several side-effects [14]. However, it is not clear yet if a single dose increases the risk of these side effects.

The aim of this clinical study was to evaluate the role of combining preoperative gabapentin with dexamethasone in the management of post-operative pain following abdominal hysterectomy.

2. Patients and methods

This is a prospective randomized controlled double blinded study, done at the gynecology and obstetric department in the *kasr Al Ainy* hospital during the period from September 2013 to September 2014.



After taking approval of the ethical committee and an informed consent from all patients, 60 females (40–70 years old), ASA I-II, scheduled for elective abdominal hysterectomies, were allocated randomly using a closed envelope technique into three groups:

- Group (G) [*gabapentin group (n = 20)*]: received oral gabapentin 800 mg once, one hour prior to the start of the procedure.
- Group (GD) [*gabapentin/dexamethasone group (n = 20)*]: received oral gabapentin 800 mg, one hour before surgery then dexamethasone 8 mg intravenously just before induction.
- Group (C) [*Control group (n = 20)*]: received similar looking placebo capsule, with the exact same packaging as the active capsules, one hour before surgery then 2 ml of normal saline intravenously just before induction.

Exclusion criteria included: ASA status > II, known allergy to any of the used drugs, regular use of certain drugs (corticosteroids, benzodiazepines, tricyclic antidepressants, NSAIDs, or other analgesics). The exclusion criteria also included patients using gabapentin or pregablin preoperatively. Also patients suffering from renal, neurological or psychiatric disorders, history of peptic ulcer, diabetes mellitus, or significant cardiac, pulmonary or hepatic disease and body mass index (BMI) > 35 were excluded.

All patients were instructed preoperatively for the pain visual analog scale (VAS) for measurement of pain.

One hour before the operation, patients in groups (G) and (GD) were given oral gabapentin 800 mg *(Gabapentine 400 mg, Neurontine, Pfizer®)* with 15 ml water, while patients in the control group (C) were given similar looking placebo capsule. The exact same packaging was used for the placebo capsules, as the active capsules.

All the patients were transferred to the operative theater; routine monitors (ECG, pulse oximetry and noninvasive BP) were applied and 18 gauge intravenous cannula was inserted followed by infusion of 500 ml Ringer's Acetate.

Just before induction of anesthesia, all the patients in the gabapentin/dexamethasone group (GD) were given 8 mg dexamethasone in 2 ml intravenously and all the patients in the gabapentin group (G) and the control group (C) were given the same volume of normal saline.

After 3–5 min of preoxygenation, induction of general anesthesia was carried out using fentanyl 1–2 μg/kg, and propofol 2 mg/kg. Endotracheal intubation was facilitated by atracurium 0.5 mg/kg. Anesthesia was maintained with sevoflurane 1 MAC, 100% oxygen and muscle relaxation was maintained with atracurium top-up doses of 0.1 mg/kg when needed. Lungs were mechanically ventilated to keep end-tidal CO_2 between 30 and 35 mmHg. Fentanyl increments of 50 μg were given to maintain blood pressure and heart rate within 20% of the preoperative values.

At the end of the procedure Sevoflurane was discontinued and the neuromuscular blockade was reversed using neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. After extubation, patients were transferred to the post-anesthesia care unit (PACU), and Paracetamol One gram was infused intravenously upon arrival. The patients were monitored for at least two hours, till full recovery and assessment of pain and sedation.

Postoperative analgesia was prescribed as; *Paracetamol* 1 gm IV infusion, 6 hourly. Meperidine was prescribed as 25–50 mg IV if the pain score was > 3 at the assessment time or as SOS between the assessments visits, provided that 4 h passed since the last dose.

The following parameters were evaluated:

- Demographic data of the patients (Age and BMI).
- Operative duration.
- Intraoperative fentanyl requirement.
- Time for the first request for analgesia postoperatively (as primary outcome) was recorded and the total dose of meperidine over the 24 h postoperative was calculated.
- Postoperative Pain Severity was assessed using visual analog score (VAS) where (0 = no pain and 10 = worst pain), at 2, 6, 12 and 24 h postoperative.
- Postoperative Sedation Level was assessed at the same intervals as VAS using a 4-point scale (1 = fully awake; 2 = somnolent, responds to verbal stimuli; 3 = somnolent, responds to tactile stimuli; and 4 = somnolent, responds to painful stimuli).
- Postoperative Nausea and Vomiting (PONV) was measured at the same intervals using a categorical scoring system (none = 0, mild = 1, moderate = 2, and severe = 3). Ondansetron 4 mg IV was prescribed for patients who complained of nausea or vomiting.

3. Sample size calculation

Power analysis was performed using one way Analysis of Variance (ANOVA) on time to first analgesic supplementation because it was the main outcome variable in the present study. A previous study (8) showed that the mean of the time to first analgesic supplementation was about 14.5 h with a standard deviation of 3.5 h in the gabapentin with dexamethasone group, the mean of the time to first analgesic supplementation

Table 1 Patients demographic data, operative time and intraoperative fentanyl requirement [data represented as mean ± SD].

Parameter	Group (C) (n = 19)	Group (G) (n = 19)	Group (GD) (n = 19)	P value
Age (Year)	55 ± 10	58 ± 9	54 ± 9	0.647
BMI (Kg/m^2)	27 ± 3.5	26 ± 3.7	27 ± 3.7	0.679
Operative time (min.)	114 ± 9	115 ± 8	118 ± 8	0.908
Intraoperative fentanyl requirement (μg)	187 ± 42	167 ± 24*	130 ± 25†	0.000

Group (C) = control, Group (G) = Gabapentin and Group (GD) = Gabapentin/Dexamethasone.
* Statistically significant compared to the Control group (C), ($p < 0.05$).
† Statistically highly significant compared to group (C) and (G), ($p < 0.001$).

Table 2 Time for first analgesic request and total meperidine dose during the first 24 h postoperatively [data represented as Mean ± SD].

Parameter	Group (C) (n = 19)	Group (G) (n = 19)	Group (GD) (n = 19)	P value
Time for 1st analgesic request (min)	44 ± 6	49 ± 6*	72 ± 5†	0.000
Postop. meperidine consumption (mg)	130 ± 29	115 ± 23*	75 ± 25†	0.000

Group (C) = control, Group (G) = Gabapentin and Group (GD) = Gabapentin/Dexamethasone.
* Statistically significant compared to the Control group (C), ($p < 0.05$).
† Statistically highly significant compared to group (C) and (G), ($p < 0.001$).

was 7.95 h with a standard deviation of 2.06 h in the gabapentin group and the mean of the time to first analgesic supplementation was 5.85 h with a standard deviation of 1.87 h in the placebo group. Taking power of 0. 95 and alpha error 0.05, a minimum sample size of 18 patients is calculated for each group. A total number of 20 patients in each group will be included to compensate for the possible dropouts.

4. Statistical analysis

Data management and analysis were performed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, IL). The data were statistically presented in terms of Median (range) & Mean ± standard deviation. Comparisons among numerical variables of three groups were done by one way ANOVA for parametric data or repeated measure ANOVA for non-parametric data. All P-values were considered significant when P-value is less than 0.05 and highly significant when P-value is less than 0.001.

5. Results

The results of the present study showed no statistically significant difference among the three studied groups as regards the demographic data of the patients and the operative duration. Meanwhile, the total intraoperative fentanyl requirement was statistically significant lower ($p < 0.05$) in gabapentin (G) group compared to the control group (C), and it was highly statistically significant lower ($p < 0.001$) in gabapentin/dexamethasone (GD) group compared to both group (C) and group (G), Table 1.

The time for the first request for postoperative analgesics was highly statistically significant ($p < 0.001$) prolonged in group (GD) when compared to either group (G) or group (C), with its values were (72 ± 5), (49 ± 6) and (44 ± 6) min, respectively. However this time showed statistically significant difference between the gabapentin (G) group and control group (C) ($p < 0.05$), we found that this difference was not clinically that significant, Table 2.

The total 24 h postoperative meperidine dose showed high statistically significant ($p < 0.001$) lower value in gabapentin/dexamethasone (GD) group compared to either gabapentin (G) or the control (C) groups, being (75 ± 25), (115 ± 23) and (130 ± 29) mg, respectively. The difference between group (G) and the control group (C) was statistically significant ($p < 0.05$), being lower in the former, Table 2.

The visual analog score (VAS) when compared among the three groups 2 h postoperatively showed high statistically significant ($p < 0.001$) lower value in gabapentin/dexamethasone (GD) group compared to the gabapentin (G) and the control (C) groups, being [3 (3–4), 4 (3–5)] and [5 (3–6)], respectively. Also, the 6 h postoperative values showed the same statistically significant pattern of differences among the three groups, Table 3.

Visual analog score values of the 12 h postoperative readings, showed that, the values of group (GD) were statistically significant ($p < 0.05$) lower compared to group (G) and to the control group (C), being [3 (3–4), 3 (3–4)] and [4 (3–4)], respectively. Meanwhile, there were no statistically significant differences among the three groups at 24 h postoperatively, Table 3.

The results of the present study showed no statistically significant differences among the three groups as regards the postoperative sedation scores when assessed at 2, 6, 12, and 24 h postoperatively, Table 4.

The Postoperative Nausea and Vomiting (PONV) at 2 h postoperatively, showed highly statistically significant ($p < 0.001$) lower values in groups (GD) and (G) when compared to the control groups (4/19), (3/19) and (13/19), respectively. Meanwhile, there was no statistically significant difference between group (GD) and (G), Table 5.

At 6 h postoperatively, PONV score showed statistically significant ($p < 0.05$) lower values in groups (GD) and (G)

Table 3 Post-operative VAS [data represented as median (range)].

Parameter	Group (C) (n = 19)	Group (G) (n = 19)	Group (GD) (n = 19)	P value
2 h post-operative	5 (3–6)	4 (3–5)*	3 (3–4)†	0.000
6 h post-operative	4.5 (3–5)	4 (3–5)*	3 (3–4)†	0.000
12 h post-operative	4 (3–4)	3 (3–4)*	3 (3–4)‡	0.024
24 h post-operative	2.5 (2–3)	2 (2–3)	2 (2–3)	0.117

Group (C) = control, Group (G) = Gabapentin and Group (GD) = Gabapentin/Dexamethasone.
* Statistically significant compared to the Control group (C), ($p < 0.05$).
† Statistically highly significant compared to group (C) and group (G), ($p < 0.001$).
‡ Statistically significant compared to the Control group (C), ($p < 0.05$).

Table 4 Post-operative sedation score [data represented as median (range)].

Parameter	Group (C) (n = 19)	Group (G) (n = 19)	Group (GD) (n = 19)	P value
2 h post-operative	3 (2–3)	2 (2–3)	3 (2–3)	0.154
6 h post-operative	3 (1–3)	3 (1–3)	3 (3–3)	0.908
12Hours post-operative	3 (2–3)	3 (2–3)	2.5 (1–3)	0.23
24Hours Post-operative	1 (1–2)	1.5 (1–2)	1 (1–2)	0.268

Group (C) = control, Group (G) = Gabapentin and Group (GD) = Gabapentin/Dexamethasone.
There were No Statistically significant differences among the three groups.

Table 5 Post-operative Nausea and Vomiting (PONV) [data represented as number of patients].

Parameter	Group (C) (n = 19)	Group (G) (n = 19)	Group (GD) (n = 19)	P value
2 h post-operative	13/20	3/20[†]	4/20[†]	0.000
6 h post-operative	9/20	3/20[*]	4/20[*]	0.017
12 h postoperative	3/20	3/20	3/20	0.995
24 h postoperative	1/20	0/20	1/20	0.601

Group (C) = control, Group (G) = Gabapentin and Group (GD) = Gabapentin/Dexamethasone.
[*] Statistically significant compared to the Control group (C), ($p < 0.05$).
[†] Statistically highly significant compared to group (C), ($p < 0.001$).

when compared to the control groups (4/19), (3/19) and (9/19), respectively. Meanwhile, there was no statistically significant difference between group (GD) and (G). There were no statistically significant differences among the three groups as regards PONV when assessed at 12, and 24 h postoperatively, Table 5.

6. Discussion

The present, prospective randomized double-blinded study was performed to compare the effect of preemptive administration of oral gabapentin alone or in combination with intravenous dexamethasone on intraoperative fentanyl requirements, postoperative pain relief and sedation, total 24 h postoperative meperidine requirements as well as incidence of postoperative nausea and vomiting after elective abdominal hysterectomies. Post-operative pain consists of nociceptive, inflammatory, neurogenic as well as visceral components. Multimodal analgesic techniques combining different drugs and thus obtaining synergistic and additive effects are recommended [3]. In the present study it was assumed that both gabapentin and dexamethasone have a different mechanism of action in acute pain management and therefore if they are used together they will have a synergistic effect with a possible reduction of the side effects.

The results of the present study showed a highly statistically significant difference between group GD and both G and C groups as regards the time for the ***first analgesic request*** as well as ***total meperidine consumption***. Also a highly statistically significant difference in the ***VAS score*** was found between group (GD) and both (G) and (C) groups at 2 and 6 h postoperatively and a statistically significant difference was found between both (G) and (C) groups at the same time intervals as well. These results proved that preoperative administration of gabapentin is valuable while combining gabapentin with dexamethasone is of a greater value.

The results of the present study best correlate with the results of the study done by *Dirks et al.*, who reported a decrease in pain scores after one dose of gabapentin in mastectomy patients [15]. Our results also resembled those of *Sen et al.*, which showed that gabapentin and ketamine have similar effect on early pain control and decreased opioid requirement following hysterectomies [16].

Similarly, *Durmus et al.*, studied the effects of 1200 mg gabapentin and a combination of gabapentin with acetaminophen in comparison with placebo in hysterectomy patients. Pain scores and morphine requirement decreased in either groups compared with placebo [7].

The results of the present study correlate with those of the study done by *Sabry Mohammad,* who studied the effect of oral gabapentin 10 mg/kg given 2 h before adenotonsillectomy, in children, alone and combined with dexamethasone 0.15 mg/kg after anesthesia induction. Gabapentin/dexamethasone combination significantly reduced the post-operative pain scores and opioid requirements without significant side-effects [8].

In contrast to the present study, the study done by *Dierking et al.*, showed no difference in postoperative pain after hysterectomy in patients treated with either 3000 mg gabapentin or placebo [17]. This contradiction may be attributed to their administration of PCA *(patient controlled analgesia)* of morphine of 2.5 mg with a lock-out time of 10 min for 24 h postoperatively, for all patients, whatever the reported pain score.

Again, the results of the present study were in disagreement with the results of the study done by *Bartholdy et al.*, who examined the effect of gabapentin on morphine consumption and pain after laparoscopic sterilization, where no significant difference was detected between gabapentin and placebo regarding pain or morphine consumption [18]. This might be explained by the relatively less painful laparoscopic tubal ligation compared to the open hysterectomy as well as the shorter time of oral intake of gabapentin (only 30 min) before surgery,

which may not be enough to achieve high blood level of the drug to imply a preemptive effect.

Still, results of the present study were in agreement with the results of *Thangaswamy et al*. which showed that, patients treated preoperatively with 8 mg dexamethasone had a significantly longer time to first analgesic dose and consumed significantly less opioid than both those pretreated with 4 mg dexamethasone and the control, during the first 24 h postoperatively following total laparoscopic hysterectomy [19].

Also the results of the present study were in accordance with those of *Kaan et al*. who studied the effect of preoperative dexamethasone on early postoperative pain after tonsillectomy and concluded that pre-operative dexamethasone use significantly reduced early post-operative pain [20].

The results of the present study showed no statistically significant difference among the three groups as regards the ***postoperative sedation score***. These findings may be assumed to known sedative effect of gabapentin in groups (GD) and (G) and to the early time for the first request for postoperative meperidine (44 ± 6 min), and the higher total meperidine requirement (130 ± 29 mg) in the control group, which affected the patients somnolence making the sedation score comparable with the gabapentin groups (G) and (GD).

These findings were in agreement with systematic review by *Ole Mathiesen et al*. who concluded that the well known sedative effect of gabapentin may be masked by the opioids used and also because patients were monitored in the early recovery phase after general anesthesia [21].

In contrast to our study, *Mikkelsen et al.,* reported different complications associated with gabapentin such as sedation, dizziness and gait disturbance, which occurred more significantly than placebo. However this study used 1800 mg/day of gabapentin for 5 days [22].

The results of the present study showed highly statistically significant ($P < 0.001$) lower ***PONV*** values in the (G) and (GD) groups compared to the control group (C) at 2 h postoperatively. Also, these values were statistically significant ($P < 0.05$) lower in the (G) and (GD) groups compared to the control group (C) at 6 h postoperatively. These findings may be assumed to the proved antiemetic effect of gabapentin and dexamethasone as well as the earlier and higher total meperidine requirement in the control group.

The findings of the present study were in agreement with the study done by *Koç et al.,* who concluded that combination of gabapentin and dexamethasone together an hour before varicocele surgery prevents postoperative nausea and vomiting better than if each drug is given alone [23].

Also, the present study was in agreement with that done by *Czarnetzki et al.,* regarding the risk of nausea and vomiting and postoperative bleeding after tonsillectomy in children, showing that, dexamethasone has a significant and dose-dependent antiemetic effect [24].

The results of the present study were not matching the results of the review by *Ole Mathiesen, et al.,* who noticed that, in spinal surgery patients, despite of the opioid sparing effect in gabapentin treated groups, nausea and vomiting were non-significant from the control groups [21].

The present study has some limitations such as; using a single concentration of gabapentin or dexamethasone, time of administration of studied drugs and using a particular pain scoring system, so, changing the drugs concentration, timing, the pain scoring, or studying a larger sample size might have an effect on the study results.

7. Conclusion

Gabapentin alone reduced the intraoperative and postoperative opioid requirement as well as postoperative pain and PONV which was significant in comparison with the placebo effect in the control. Obviously these effects were more prominent and highly significant when dexamethasone was added to gabapentin.

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