

Comparison of Fentanyl plus different doses of dexamethasone with Fentanyl alone on postoperative pain, nausea, and vomiting after lower extremity orthopedic surgery

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Abstract

Intravenous patient controlled analgesia (PCA) with opioids to provide perioperative analgesia is commonly used after orthopedic surgery, but have side-effects. Addition of adjuvant drugs results in reducing the side-effects and the dosage of opioids. The aim of current study was to evaluation the analgesic efficacy of combination of fentanyl and dexamethasone (8 and 16 mg) in compared with fentanyl alone in patients undergoing orthopedic surgery of the lower extremity. In a double-blind clinical trial, 102 patients were randomly allocated to receive PCA, which included: F+S group (fentanyl 1 mcg/ml + isotonic saline), F+8mD group (fentanyl 1 mcg/ml + dexamethasone 8 mg/ml), and F+16mD group (fentanyl 1 mcg/ml + dexamethasone 16 mg/ml). Anesthesia technique and rescue analgesia regimen were standardized. Postoperatively, pain was assessed based on visual analog scale (VAS). In addition, we evaluated the postoperative nausea and vomiting (PONV) in different groups. In over the post-operative period, the mean VAS-score was significantly lower in the F+16mD group than the F+S and the F+8mD groups ($p<0.001$ and $p<0.01$, respectively). In addition, the incidence of PONV significantly was lower in the F+16mD group than the F+S group ($p<0.05$). We conclude that the addition of preoperative intravenous high dose of dexamethasone (16 mg) to fentanyl was effective in reducing postoperative pain and PONV after orthopedic surgery of the lower extremity.

Key Words: Intravenous patient controlled analgesia; dexamethasone; fentanyl; orthopedic surgery.

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In orthopedic surgery, one of the main factors in limiting ambulation is pain, which can lead to thromboembolism as a result of immobility.^{1,2} Therefore, pain management in such situations with the use of appropriate analytical techniques can be very important. One of the most effective and commonly used methods for postoperative pain management is the intravenous patient-controlled analgesia (IV PCA) after an orthopedic surgery.³ Studies have shown that this method is healthy and effective in the treatment of moderate to severe pain.⁴ The use of this analgesic technique is often done in severe pain such as after orthopedic surgery pain, or chronic pain such as patients with advanced malignancies.^{4,5} Opioids are commonly used to control postoperative pain, especially in major surgery.⁶ On the other hand, although PCA is an effective method for controlling pain, it has been reported that it also has several side effects, such as postoperative nausea and vomiting (PONV),

hypotension, motor blockade, and urinary retention.¹ Even when using high doses of opioids with PCA, may occur side effects such as respiratory depression, confusion, constipation, pruritus, nausea, and vomiting.⁷ Therefore, it essential that the use of adjuvant drugs is necessary to decreasing the side effects of opioid in patients with orthopedic surgery. Previous studies have shown that adding corticosteroids to PCA opioid increases patient satisfaction and reduces pain score as well as decreases the dose of opioid and its side effects.^{8,9} In various studies, it has been shown that the dexamethasone as anti-inflammatory drug with long duration of action have some effects in surgery conditions such as: antiemetic, reduce shivering, and analgesic effect.^{10,11} The recommended analgesic dose of dexamethasone in reducing postoperative pain is variable. A number of studies have shown that a single dose of 8 mg dexamethasone is effective in reducing

Table 1. Baseline characteristics of the study population

Variables	Time of studies (hr)				
	Pre-operation	2	6	12	24
Pain, VAS (mean±SD)					
F+S	1±0.00	3.23±1.65	3.55±1.28	3.11±1.12	2.82±1.02
F+8mD	1±0.00	2.41±1.53	3.50±1.74	2.47±1.23	2.38±1.12
F+16mD	1±0.00	1.52±1.21	2.32±1.36	1.61±0.92	1.44±0.78
St. diff. between groups	-	0.000	0.001	0.000	0.000
Nausea (N)					
F+S	0	0	2	3	2
F+8mD	0	0	1	1	0
F+16mD	0	0	1	0	0
St. diff. between groups	-	-	-	-	-
Vomiting (N)					
F+S	0	0	2	2	2
F+8mD	0	0	1	1	0
F+16mD	0	0	0	0	0
St. diff. between groups	-	-	-	-	-
Need for Pethedine analgesia (N)					
F+S	0	4	9	13	9
F+8mD	0	1	5	7	7
F+16mD	0	1	3	1	0
St. diff. between groups	-	-	0.052	0.002	0.007
Sedation score(N)					
F+S	5	7	5	4	4
F+8mD	7	7	8	4	3
F+16mD	4	3	2	3	1
St. diff. between groups	-	-	-	-	-
Systolic pressure (mmHg)					
F+S	119.71±13.31	116.91±11.61	115.88±8.20	114.41±8.23	114.41±7.85
F+8mD	117.35±15.03	114.85±12.58	117.06±13.81	116.76±14.29	116.18±10.73
F+16mD	120.03±17.43	118.24±15.85	113.97±12.17	114.26±12.43	114.12±12.33
St. diff. between groups	-	-	-	-	-
Diastolic pressure (mmHg)					
F+S	74.26±10.01	71.91±11.51	71.91±9.04	67.35±6.65	68.97±6.48
F+8mD	72.50±12.56	71.91±11.41	72.35±10.16	69.70±9.68	71.17±9.53
F+16mD	74.55±10.47	71.11±15.95	71.32±8.64	70.73±8.53	70.58±8.50
St. diff. between groups	-	-	-	-	-
Heart rate					
F+S	76.58±12.21	76.85±8.53	77.55±8.04	76.29±8.09	76.64±7.82
F+8mD	71.85±13.93	75.20±7.45	72.58±14.88	75.35±9.30	75.32±8.17
F+16mD	71.73±8.23	73.41±8.61	74.41±8.61	72.64±8.03	73.26±9.28
St. diff. between groups	-	-	-	-	-

St. diff: statistical difference; F+S: fentanyl and isotonic saline group; F+8mD: fentanyl and 8mg dexamethasone group; F+16mD: fentanyl and 16mg dexamethasone group.

VAS: pain score of patient recorded by visual analog scale.

postoperative pain after dental surgery and thyroidectomy.^{6,12} On the other hand, it has been reported that in inguinal hernia repair surgery under spinal anesthesia, the used of single dose of dexamethasone (≤10 mg) there is no effect on postoperative pain reduction.¹³

Thus, in the current study, we investigated that the effect of combination of fentanyl and dexamethasone with different doses in improving the quality of pain control and decreasing the amount of fentanyl consumed in PCA and its possible complications in patients undergoing

orthopedic surgery of the lower extremity by spinal anesthesia.

Materials and Methods

Study Design

This study after approval by the university ethical committee and signing of the written consent with the patients (or family members) done at Ardabil Shaheed Fatemi Educational and Clinical Hospital, Ardabil, Iran. The inclusion criteria were American Society of Anesthesiologists physical status I and II patients, aged

Table 2. Spearman (or Phi and Cramer s V) correlation analysis of study parameters with study groups

	Study groups R	P value
VAS-score	-0.410	0.000
Nausea	0.125	0.042
Vomiting	0.132	0.028
Postoperation need for narcotic	-0.254	0.000

VAS-score: pain score of patient recorded by visual analog scale.

between 15 and 80 years old, scheduled for lower orthopedic spinal anesthesia surgeries. All surgical procedures were performed under lumbar spinal anesthesia with 10 mg (2cc) isobaric bupivacaine (0.5%) with anesthetized T₁₀ level. Patients with a history of hospitalization at ≤1 month before the study, infectious disease, chronic respiratory diseases, diabetes, chronic renal failure, hepatitis, cancer, and long-term use of non-steroidal anti-inflammatory analgesics or opioids were excluded from the study.

Using double-blind randomization technique, subjects were divided into 3 group receive Patient-Controlled Analgesia (PCA) post-operatively, 34 cases in each group. Group I: fentanyl 10 mcg/mL + 10cc isotonic

saline (F+S); group II: fentanyl 10 mcg/mL + dexamethasone 8 mg/10cc isotonic saline (F+8mD); and group 3: fentanyl 10 mcg/mL + dexamethasone 16 mg/10cc isotonic saline (F+16mD).

In the recovery unit to all patients under study, the auto fuser post-operative pain control pump with containing of fentanyl (Kaspian Company Company) 1 mg/100 mL isotonic saline (Bolus 10 mcg/cc, infusion 5 cc in hour, with an interval of 10 min, and duration 60 min) was connected. The recorded parameters at the time of 24 hour before surgery (T₀) or 2 (T₂), 6 (T₆), 12 (T₁₂), and 24 (T₂₄) after pump connection in recovery unit were including: systolic pressure, diastolic pressure, heart rate, VAS-score (pain score of patient recorded by visual

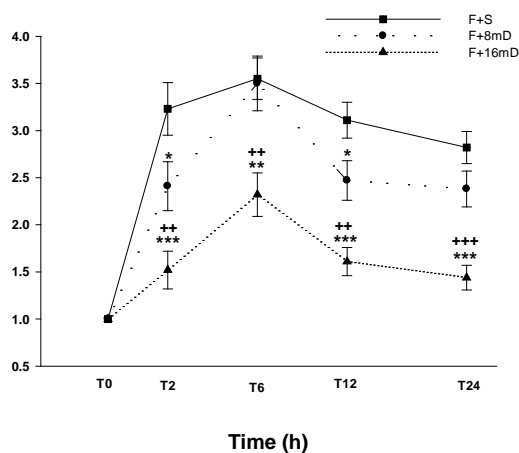


Fig 1. Comparison of the pain scores (VAS) in experimental groups in pre-operation (T₀ hr) and post operation times (2 (T₂), 6 (T₆), 12 (T₁₂), and 24 (T₂₄) hr of post-operation). Values are represented as mean±SEM. F+S: fentanyl and isotonic saline group, F+8mD: fentanyl and 8mg dexamethasone group, F+16mD: fentanyl and 16mg dexamethasone group. Differences between the results of F+S with those of other groups; *: p<0.05, **: p<0.01, ***: p<0.001. Differences between F+8mD group with F+16mD group; ++: p<0.01, +++: p<0.001. For each group, n=32.

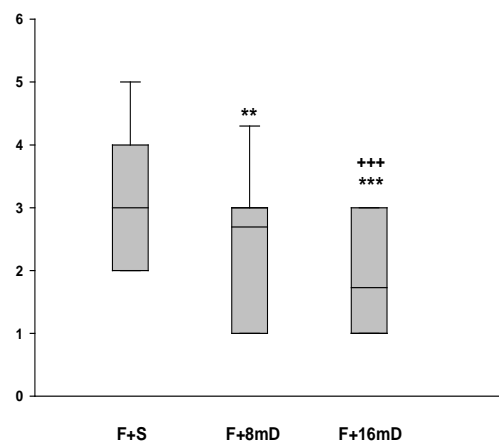


Fig 2. Mean postoperative VAS-scores±SD over the entire observation period of 24 hours. F+S: Fentanyl and isotonic saline group, F+8mD: Fentanyl and 8 mg/mL dexamethasone group, F+16mD: Fentanyl and 16 mg/mL dexamethasone group, VAS-score: pain score of patient recorded by visual analog scale. Differences between the results of F+S with those of other groups; **: p<0.01, ***: p<0.001. Differences between F+8mD group with F+16mD group; +++: p<0.001. For each group, n=32.

analog scale) (0: pain free; 1–3: mild pain, does not affect sleep; 4–6: moderate pain; 7–9: severe pain, cannot sleep or wake up from pain; and 10: sharp pain), sedation score (by Ramsey Sedation score) (1: anxious, restless, irritable; 2: cooperative, oriented, tranquil; 3: only responsive to instructions; 4: asleep, with a brisk response to stimulus; 5: asleep, with a sluggish response to stimulus; and 6: asleep, with no response), and incidence of nausea and vomiting [by N and V score (1-4)] (if the patient had no nausea or vomiting, a score of 0 was given; and if the patient had severe nausea and vomiting, a score of 4 was given). In cases with VAS ≥ 4 or sedation score zero, drug dose was increased 20% and 25 mg pethidine was injected for patients. In cases with VAS = 0 and (or) drug side-effects the dose decreased about 20%. In cases with nausea and vomiting metoclopramide (10 mg) was administered.

Statistical analysis

The results are given as the mean \pm standard error of the mean (SEM), or median and 25th–75th percentiles. Continuous variables were compared using the student's *t*-test. Data were compared between different groups using one-way analysis of variance (ANOVA) with Tukey-Kramer *post hoc* test, or by the Kruskal-Wallis test. Correlation coefficients were assessed using the Pearson's (or Spearman rank order) correlation test. A value of $p < 0.05$ was considered significant.

Results

The population study consisted of 102 patients (34 patients in each group): 27 women (26.5%) and 75 men (73.5%). Eighty-one (79.4%) patients were aged 15-50 and 21 (20.6%) were more than 50. All patients were enrolled from November 2016 to November 2017. Baseline parameters of the study population for the three groups based on study design are represented in Table 1. There was no statistically significant difference in age, heart rate, mean systolic and diastolic pressure, and sedation score among the three groups at each time point ($p > 0.05$) (Table 1).

The VAS-score course is shown in Figure 1. The value of VAS-score in all three groups increased over time T_6

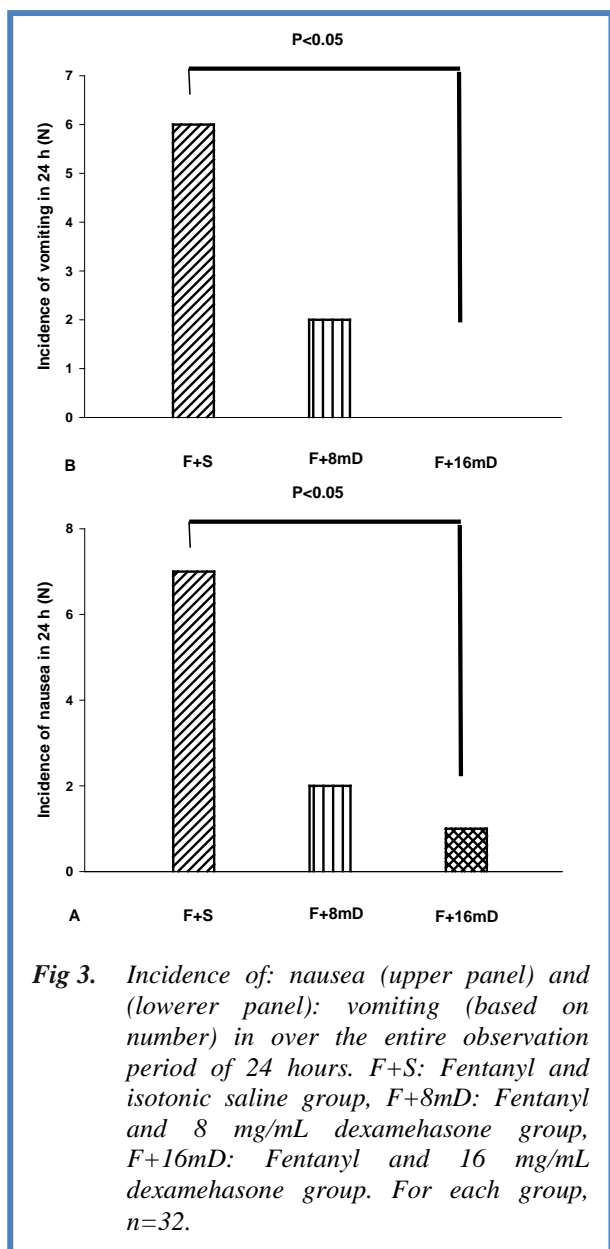


Fig 3. Incidence of: nausea (upper panel) and (lower panel): vomiting (based on number) in over the entire observation period of 24 hours. F+S: Fentanyl and isotonic saline group, F+8mD: Fentanyl and 8 mg/mL dexamethasone group, F+16mD: Fentanyl and 16 mg/mL dexamethasone group. For each group, n=32.

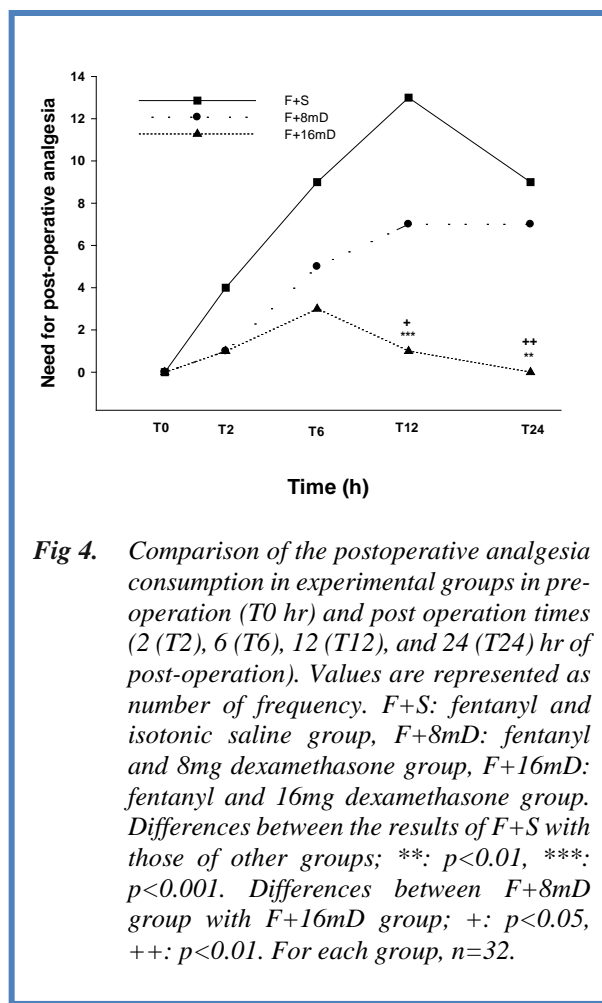


Fig 4. Comparison of the postoperative analgesia consumption in experimental groups in pre-operation (T0 hr) and post operation times (2 (T2), 6 (T6), 12 (T12), and 24 (T24) hr of post-operation). Values are represented as number of frequency. F+S: fentanyl and isotonic saline group, F+8mD: fentanyl and 8mg dexamethasone group, F+16mD: fentanyl and 16mg dexamethasone group. Differences between the results of F+S with those of other groups; **: $p < 0.01$, ***: $p < 0.001$. Differences between F+8mD group with F+16mD group; +: $p < 0.05$, ++: $p < 0.01$. For each group, n=32.

compared to T₀ and T₂. The results showed that VAS-score values in F+16mD group significantly decreased compared with F+S and F+8mD groups from T₂ to T₂₄ (p<0.01 to p<0.001) (Figure 1). On the other hand, at times T₂ and T₁₂, the value of VAS-score in F+8mD group decreased in compared with F+S group (p<0.05). In addition, in over the post-operative period (24 h), the mean VAS-score was significantly lower in the F+16mD group than the F+S and the F+8mD groups (p<0.001 and p<0.01, respectively) (Figure 2). Furthermore, in throughout the post-operative study period (24 h), the mean VAS-score was significantly higher in the F+S group than the F+8mD group (p<0.01).

Regarding the rate of nausea, the results showed that the incidence of nausea was not statistically significant in different groups. Interestingly, only at 6 hours after surgery, there was one case of nausea in F+16mD group. Indeed, intervention with dexamethasone in intervention groups (F+8mD and F+16mD groups) resulted in decreased nausea compared with F+S group, despite the lack of significant results. However, during 2-24 hours after surgery, the incidence of nausea significantly was lower in F+18mD group than F+S group (10% vs. 70%, p<0.05). There was no any significant differences between other groups in relation of nausea in 2-24 hours after surgery (Figure 3 upper panel).

The incidence rate of vomiting results indicated that the F+S group at 6, 12, and 24 hours after surgery had two vomiting cases at any time, which was higher than the other groups, however, there was no statistically significant difference. Interestingly, the F+16mD group did not have any vomiting symptoms during the study period after surgery in patients (table 1). Additionally, during 2-24 hours after surgery, the incidence of

vomiting significantly was higher in F+S group than the F+16mD group (75% vs. 0%, p<0.05) (Figure 3 lower panel), but there was no significant difference with F+8mD group (75% vs. 25%).

Regarding the need for narcotic after surgery, the results showed that at times T₃ and T₄, a narcotic need was higher statistically significant in both groups of F+S and F+8mD than F+16mD group (p<0.05 to p<0.001) (Figure 4). On the other hand, considering the need for narcotic in F+S group was more than F+8mD group at all times, but this difference was not statistically significant (Figure 4). However, at during 2-24 hours after surgery, the need for narcotic after surgery in the F+S group was statistically higher than the F+8mD and F+16mD groups (p<0.05 to p<0.001, respectively) (Figure 5). Additionally, the need for narcotic was higher in the F+8mD group than the F+16mD group (p<0.01) during 2-24 hours after surgery (Figure 5).

The correlation analysis showed that study groups were significantly associated with VAS-score (r = -0.410, P = 0.000), nausea (r = 0.125, P = 0.042), vomiting (r = 0.132, P = 0.028), and need for analgesia after surgery (r = -0.254, P = 0.000) (Table 2).

Discussion

We found that the combination of fentanyl with dexamethasone (dose-dependently) was significantly more effective in reducing the incidence of PONV, VAS, and postoperative pain, compared with fentanyl monotherapy.

The results showed that throughout the observation period (24 h) post-operation, patients in fentanyl dexamethasone combination groups (8 and 16 mg) had significantly both less pain score and analgesic requirement when compared to placebo group and they were more satisfied; with markedly pain reduced in F+16mD group, in agreement with that the previous studies in thyroidectomy,¹⁴ and laparoscopic cholecystectomy,¹⁵ after a single preoperative dose of dexamethasone 8 mg i.v.. In fact, the current study was consistent with our previous study that the addition of low-dose ketamine to morphine in PCA can lead to better control of pain after orthopedic surgery.⁹ It has been shown that using PCA pain pump after orthopedic surgery, it was shown that fentanyl and ketoralac combination was more effective in pain control than fentanyl alone.¹⁶

On the other hand, our detailed assessment of pain indicated that in F+8mD group, the reduced of pain did not was a prolonged analgesic effect in compared with F+16mD group. Therefore, it is conceivable that certain amounts of glucocorticoid (GC) is needed to reduce postoperative pain, especially in surgery with higher pain scores. A meta-analysis study by Diakos et al showed that the use of high-total dose dexamethasone (more than 10 mg in single) is more effective in reducing pain compared with low dose dexamethasone (≤8 mg).¹⁷ Also, in a meta-analysis study conducted by De Oliveira et al.,¹⁸ which

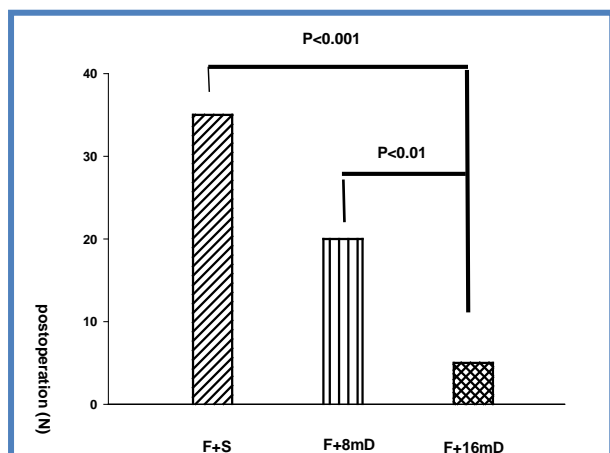


Fig 5. Total number of narcotic consumption in 24 h postoperation. Value are presented with cumulative number of frequency. F+S: fentanyl and isotonic saline group, F+8mD: fentanyl and 8mg dexamethasone group, F+16mD: fentanyl and 16mg dexamethasone group.

examined three different doses of dexamethasone in reducing postoperative pain, it was found that dexamethasone was effective in reducing pain at doses greater than 0.1 mg/kg⁻¹. Jokela et al showed that the use of high doses of dexamethasone (10 and 15 mg) reduced the oxycodone consumption after laparoscopic hysterectomy.¹⁹ Other studies were also unable to demonstrate the effectiveness of dexamethasone at low doses to reduce postoperative pain.^{19,20}

This can be due to the activation of various pathways for pain control, in addition to the direct effect of dexamethasone with its receptors. The major use of steroids is due to their anti-inflammatory effects. Indeed, corticosteroids inhibit the production of inflammatory cell factors and consequently reduce the release of lysosomal enzyme, decrease extravasation of leucocytes, and reduce vascular permeability in damaged areas.¹⁷ Altogether, these conditions reduce the oedema and the sensitivity of the nerve endings of the pain in the surgical site.^{21,22} In addition, corticosteroids, by inhibiting the phospholipase enzyme, block the lipoxygenase and cyclooxygenase pathways, leading to decrease prostaglandins and relieve pain.^{23,24} Furthermore, systemic GC administration have been shown to suppress the release of tissue bradykinin and neuropeptides and can be increase nociception in injury tissue.^{20,25} However, the low effectiveness of low-dose steroids, as compared to high-dose steroids, is not biologically clear.

The incidence rate of postoperative nausea and vomiting (PONV) results indicated that there was no significant difference between groups at any time of study. But, in throughout the observation period (24 h), the F+16mD group had significantly low incidence rate of PONV when compared with F+S group. There were several studies about the prophylactic role of GCs in reduce of PONV.²⁶⁻²⁸ Karanicolas et al., in a meta-analysis study on the prophylactic role of dexamethasone about PONV, showed that dexamethasone significantly reduce PONV in surgery conditions.²⁹ In addition, it was found that dexamethasone at high doses (≥ 8 mg) are more effective than low doses, that was in line with our study.²⁹

The exact dexamethasone antiemetic mechanism is not known. However, there are a number of related mechanisms, such as reduce the synthesis of eicosanoids (prostaglandins, prostacyclins, thromboxanes, leukotrienes, lipoxins, and hepxilins), inhibition of serotonin (5-HT)-receptors expression, antiemetic effect GCs related to hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis (with restores normal physiological function in people in a hypocortisol state), central antiemetic effect of GCs, and inhibiting the release of inflammatory mediators (e.g., prostaglandins and substance P).³⁰

It is noteworthy that the use preoperative of GCs may have side effects. A meta-analysis study about of side effects of GCs showed that preoperative methylprednisolone administration has no any adverse effects in various surgeries.²⁰ Different adverse effects

from using GCs, such as infection, glucose intolerance, or delayed wound healing, have not been seen in orthopedic, thoracic or abdominal surgery.^{20,31,32} Although various studies have shown that the use of single dose of dexamethasone does not have any special side effects, however, the use of different doses of dexamethasone requires more studies on its side effects. Our study has some limitations. We did not study dexamethasone administration side effects. Further studies with more sample size and longer follow-up are indicated to show side effects of dexamethasone. Also, there is a need for dose-ranging studies to obtain the minimum dose of dexamethasone in preventing PONV or pain. In addition, further studies must be accomplished in patients at higher risk for glucocorticoid-induced complications. It is known that postoperative fatigue can be present in patients from one week to several months depending on the type of surgery. Dexamethasone has been shown to be able to reduce fatigue in post-operative patients.¹⁵ We did not investigate the effect of different doses of dexamethasone on postoperative fatigue in orthopedic surgery.

We conclude that high dose (16 mg) of the preoperative iv dexamethasone when combined with fentanyl in PCA technique is effective in reducing postoperative pain and POVN complications after lower extremity orthopedic surgery. In addition, the rate of narcotic consumption was decreased in fentanyl-high dose dexamethasone combination condition.

List of acronyms

GC - glucocorticoid
HPA - hypothalamic-pituitary-adrenal
IV - intravenous
PCA - intravenous patient-controlled analgesia
POVN - postoperative nausea and vomiting
VAS - visual analog scale

Contributions of Authors

GAA, AME and FNA: conception and design of the study, acquisition, analysis and interpretation of data, wrote the manuscript, performed literature review, article drafting and revision, reviewed and edited the manuscript critically, all authors approved the final version.

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Conflict of Interest

The authors declare no conflict of interests.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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