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ORIGINAL ARTICLE

Comparative study between the effects of postoperative analgesia using intravenous dexamethasone versus intravenous pethidine in patients undergoing surgical repair of fractured neck femur

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ABSTRACT

Keywords: Intravenous dexamethasone, Intravenous pethidine, Fractured neck femur

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Background: Pain is the most dreaded fear associated with bone fractures. Intravenous opioids have been commonly used to manage the pain but their side effects like respiratory depression, cognitive impairment, vomiting, urinary retention. Dexamethasone is a synthetic adrenocortical steroid used widely as an antiemetic in surgical patients. Dexamethasone can induce long-acting postoperative analgesia for 24 hours and more. **Objective:** Comparative study between patients who received preoperative intravenous dexamethasone and those who received preoperative intravenous pethidine in postoperative analgesia using a visual analog scale. **Patients and methods:** This prospective randomized study was performed in Aswan University Hospital on 60 adult patients aged from 20 up to 70-years-old of both genders, with ASA physical status I and II. **Results:** We found that there was a significant difference between the studied groups in VAS that was higher in the **opioid** group when compared with the **dexamethasone** group at 4hrs, 6hr, 8hrs, 12hrs, and 24hrs postoperative. Regarding rescue analgesia; we found that no significant difference between the two study groups regarding the request of additional analgesia, the first request, or the total pethidine consumption. As regards complications, there was no significant difference between the two study groups regarding postoperative nausea and vomiting, and no other complications were found. **Conclusion:** Intravenous dexamethasone is a promising analgesia for postoperative pain following femoral neck fracture with minimal side effects and no complications.

INTRODUCTION

More than 250,000 hip fractures occur annually in the United States and are evenly divided between the femoral neck and intertrochanteric fractures [(1)]. This number is projected to double by the year 2050 [(2)]. Seventy-five percent of hip fractures occur in women [(3)]. The incidence in younger patients is very low and is associated mainly with high-energy trauma. The majority occur in the elderly (average age of 72 years) as a result of low-energy falls [(4)].

Pain is one of the most disturbing consequences associated with bone fractures, not just psychologically but also clinically. A neck femur fracture is one of the extremely painful fractures, ineffective pain management

can result in delayed healing, lack of patient compliance, and prolonged hospital stay.

Guidelines for the management of postoperative pain recommend opioids for postoperative analgesia[5]. Postoperative pain is often continuous initially and often requires analgesia during the first 24 hours. Long-acting oral opioids are generally not recommended or labeled for use in the immediate postoperative period because of the need to titrate doses and the lack of evidence showing superiority over short-acting oral opioids, with the possible exception of patients who receive long-acting opioids before surgery [6].

Opioids are commonly used, but their side effects profile including respiratory depression, cognitive impairment, vomiting, urinary retention, abuse or dependence, and others limits their clinical utility during injuries of the head, chest, or abdomen [7].

The need for more safe analgesics and less in their side effects has arisen. Multiple studies were found the effectiveness of dexamethasone in reducing postoperative pain scores and the frequent need for opioids to match adequate pain scores.

Dexamethasone is a synthetic adrenocortical steroid, used widely in anesthesia as an antiemetic in surgical patients. Dexamethasone inhibits cortisol secretion by inhibiting the hypothalamic-pituitary-adrenal axis [8]. Cortisol exists in free (unbounded) and protein-bound forms in serum but only in a free form in saliva. The free form is the biologically active one [9].

Preoperative dexamethasone reduces postoperative nausea, prolonged suppressive effect on the inflammatory response, and decreases dynamic pain 24 h after orthopedic surgery [10]. Administration of intravenous dexamethasone before intrathecal meperidine injection enhances postoperative analgesia and reduces postoperative nausea and vomiting [11].

AIM OF THE STUDY

The aim of the present study was a comparative study between patients who received preoperative intravenous dexamethasone and those who received preoperative intravenous pethidine in postoperative analgesia using a visual analog scale, the first requirement of postoperative analgesia, opioid consumption, and complications.

The scope of this study was to be performed in Aswan University Hospital on patients who had fractured neck femur for surgical repair that had attended between February 2019 and February 2020.

PATIENTS AND METHODS

This prospective randomized trial was conducted at Aswan University Hospitals during the period from February 2019 to February 2020 after approval from the ethics and research committee of Aswan University Hospitals (IRB 335/2/19). Informed written consent was obtained from each patient. We studied patients with ASA physical status I or II, aged between 20 and 70-years-old of both genders, scheduled for surgical repair of fractured neck femur under spinal anesthesia block.

We excluded patients if they refused to participate or were outside age range, if they have cognitive disorders, allergy to any medication used, Cushing syndrome, endocrine disorders other than controlled diabetes_, respiratory disorders, bleeding tendency, corticosteroid treatment in the last 4 months, head injury or any associated injuries, hepatic or renal patients, failed spinal anesthesia and coagulation defects or any contraindication to spinal anesthesia.

Sample randomization using a randomization table created by a computer software program was used to allocate patients into 2 equal parallel groups :

Dexamethasone group: group (D) received heavy Bupivacaine (0.5%) 0.3mg/kg intrathecal with 0.2 mg/kg intravenous dexamethasone. (Dexamethasone by AMRIYA, Egypt, 8 mg/ 2 ml).

Opioid group: group (O) received heavy Bupivacaine (0.5%) 0. 3mg/kg intrathecal with 0.5mg/kg intravenous pethidine. (PETHIDINE by -EXIR , EGYPT 50MG/1ML AMP).

Sampling and sample size:

A total of 60 patients were determined to be included in this study. The minimum sample size required for the present study was calculated by using PASS software (PASS 11 citation: Hintze J (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA). To our knowledge, no previous studies assessed intravenous dexamethasone versus intravenous pethidine in patients undergoing surgical repair of fractured neck femur. Based on the previous report by **Szucs *et al*. [(12)],** pain scores at rest 6 h after the surgery (the principal outcome) were lesser in the dexamethasone group compared with the placebo group (0.8(1.3) vs. 3.9(2.9), mean(SD) p=0.0004). Setting alpha error at 5% and power at 90%, the minimum required sample size for the study is determined to be 26 participants per group, with accounting for a dropout rate of 10%, the minimum sample size was determined to be 30 patients per group.

All patients are subjected to:

Preoperative evaluation and preparation; by proper history taking and clinical examination, to exclude cardiovascular, respiratory, neurological, and metabolic diseases, routine laboratory investigations, and echocardiography for patients aged more than 60 years old or associated co-morbidities or atherosclerosis.

On arrival in the operating room, each patient was attached to a multi-channel monitor and basal hemodynamic values were recorded before the start of anaesthesia. A 20-gauge cannula was inserted, premedication with midazolam was done and lactated Ringer's solution 500 mL was infused. All patients in group (D) received a single dose of intravenous dexamethasone (0.2 mg/kg) and those in the group (O) received a dose of intravenous pethidine (0.5 mg/kg) just before administration of spinal anesthesia. Then, using an aseptic technique, a 25-gauge needle was inserted intrathecally via a midline approach into the L3–4 or L4–5 interspace with the patient in the sitting position. After the free flow of cerebrospinal fluid, both groups received 0.3 mg/kg of heavy bupivacaine 0.5%, then the patient was turned to supine position. Bradycardia (<50 bpm) was treated with Atropine (0.1 mg/kg)i.v, and hypotension (systolic arterial blood pressure <90 mm Hg) was treated with vasoactive drugs; ephedrine (5 mg bolus i.v). Any further complications occurring intraoperatively were recorded.

Intraoperative and postoperative fluid regimes were assessed according to the hemodynamics of the patient. All patients received paracetamol 1 g i.v. during surgery and rescue analgesia consisted of (0.5-1 mg/kg) of pethidine i.v. if their visual analog scale (VAS) > 4

After finishing the operation, the patient was transferred to the post-anesthesia care unit for monitoring of hemodynamics and the severity of postoperative pain was measured and recorded using a 10-cm visual analog scale (VAS), where 0 = no pain and 10 = the worst possible pain. Evaluation of pain score was done immediately, after 1, 2, 4, 6, 8, 12, and 24 hours.

Outcomes of the study:

Primary outcome; pain scores at 1h, 2h, 4h, 6h, 8h, 12h, and 24h after the surgery using a visual analog scale.

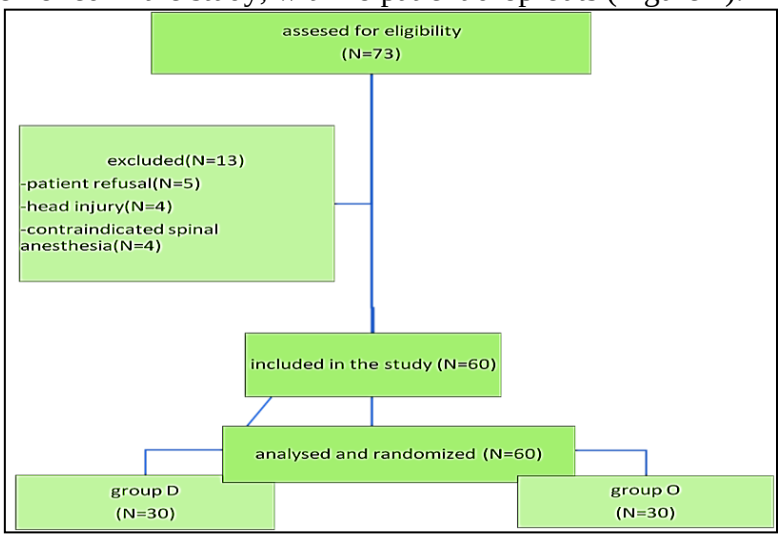
Secondary outcomes; to compare the need for rescue analgesia between the two groups, hemodynamic changes, and the incidence of postoperative nausea or vomiting.

STATISTICAL ANALYSIS:

The data were analyzed using the IBM SPSS Statistics 24.0 program. Setting α=0.05 and confidence interval 95%. Screening for extreme values in quantitative variables was done using an independent student t-test. Discrete and categorical variables were screened using frequency distribution. Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi 2$) to calculate the difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P-value < 0.05 was considered significant.

RESULTS

Seventy-three patients were screened for eligibility to participate in this study and 60 patients Subsequently were enrolled in the study, with no patient drop-outs (Figure 1).



There was no statistically significant difference between the two study groups regarding demographic data. Table (1)

Table (1): Demographic data of the two study groups.[mean ± SD]

Demographic variable		Group D (n=30)	Group O (n=30)	P-value
Age	**Mean±SD**	51.83±14.9	46.43±14.3	0.158
Gender	**Male no(%)**	16(53.3%)	21(70%)	0.288
	Female no(%)	14(46.7%)	9(30%)	
BMI	**Mean±SD**	24.4±4.0	23.1±3.4	0.191
ASA	**I**	22(73.3%)	25(83.3%)	0.532
	II	8(26.7%)	5(16.7%)	

Analysis of quantitative data by independent t-test, Analysis of qualitative data by chi-squared test, P-value is considered significant at <0.05.

Hemodynamic data:

Mean arterial pressure (MAP):

Between the two study groups: there was no statistically significant difference regarding MAP between both study groups all over the 24hrs postoperatively. Table (2)

Table (2): Comparison between the two studied groups according to MAP. [mean ± SD]

MAP	Group D	Group O	t	P-value

	(n=30)	(n=30)		
Baseline	78.5±9.8	74.6±10.1	1.505	0.138
1Hr	78.1±9.4	75.5±9.7	1.034	0.305
2Hr	79.7±9.9	76.0±9.9#	1.451	0.152
4HR	80.3±9.8#	77.1±10.0#	1.476	0.145
6HR	80.2±9.2#	77.7±10.4#	0.972	0.335
8HR	80.2±8.2	76.8±9.7	1.450	0.152
12HR	78.9±8.5	75.3±9.8	1.533	0.131
24HR	77.5±8.4	73.6±10.3	1.611	0.113
F	7.712	11.095		

t: Independent student t-test. F: repeated measures ANOVA test in each study group. #: Significant difference from 1hr postoperative value among each group individually Bonferroni post-hoc test. P-value is considered significant at <0.05.

Heart rate (HR):

Between the two study groups: there was no statistically significant difference regarding HR between both study groups all over the 24hrs postoperatively. Table (3)

Table (3): Comparison between the two studied groups according to HR. [mean ± SD]

HR	Group D (n=30)	Group O (n=30)	t	P-value
Baseline	74.2±9.5	72.3±9.7	0.780	0.439
1Hr	74.1±9.4	72.2±8.8	0.823	0.414
2Hr	75.8±9.6	74.9±9.3#	0.384	0.702
4HR	78.5±9.9#	75.9±9.9#	0.990	0.326
6HR	76.8±9.0#	77.5±8.9#	-0.302	0.763
8HR	75.7±8.3	76.3±8.4#	-0.310	0.758
12HR	75.2±8.6	74.9±9.1	0.131	0.896
24HR	73.6±7.4	72.7±8.8	0.414	0.680
F	9.188	10.877		

t: Independent student t-test. F: repeated measures ANOVA test in each study group. #: Significant difference from 1hr postoperative value among each group individually Bonferroni post-hoc test. P-value is considered significant at <0.05.

Postoperative pain assessment using the visual analog scale (VAS):

There were lower VAS records in group **D** in comparison with group **O** at 4hrs, 6hrs, 8hrs, 12hrs, and 24hrs postoperatively. Table (4)

Table (4): Comparison between the two studied groups according to VAS. [mean ± SD]

VAS	Group D (n=30)	Group O (n=30)	U	P-value
1Hr	1.97±0.765	1.9±0.759	428.5	0.792
2Hr	2.1±0.819	2.5±0.860#	357.0	0.138
4HR	2.3±0.994	3.5±0.820#	159.0	0.000*
6HR	2.2±0.774	3.6±0.935#	123.5	0.000*
8HR	1.8±1.2	3.1±1.1#	186.5	0.000*
12HR	1.2±0.504#	2.4±0.971	113.0	0.000*
24HR	0.9±0.548#	2.0±0.643	108.0	0.000*
F	14.845	15.402		
P-value	0.000*	0.000*		

U: Mann-Whitney test. F: repeated measures ANOVA test in each study group. #: Significant difference from 1hr postoperative value among each group individually Bonferroni post-hoc test

P-value is considered significant at <0.05.

Rescue analgesia and complications:

5 patients (16.7%) in group D & 14 patients (30%) in group O requested additional analgesia in the form of pethidine 0.5 mg/kg at 4hrs, 6hrs, and 8hrs with no statistically significant difference between the two study groups regarding the request of additional analgesia, the first request or the total pethidine consumption.

PONV was found in 1 patient in group D and 3 patients in group O with no statistically significant difference between the two study groups regarding complications & no other complications were found. Table (5)

Table (5): Comparison between the two studied groups according to rescue analgesia and complications. [numbers & incidence of patients]

Rescue analgesia		Group D (n=30)	Group O (n=30)	P-value
Analgesia request	**Yes**	5(16.7%)	14(46.7%)	0.025*
	No	25(83.3%)	16(53.3%)	
First request	**4HR**	1(3.3%)	5(16.7%)	0.045*
	6HR	1(3.3%)	6(20%)	
	8HR	3(10%)	3(10%)	
Total pethidinedose in mg	**Mean±SD**	60.0±22.4	100.0±34.0	0.027*
Complications	**PONV**	1(3.3%)	3(10%)	0.612

Analysis of quantitative data by independent t-test. Analysis of qualitative data by chi-squared test. P-value is considered significant at <0.05.

DISCUSSION

Concerning the primary outcome of the present study, we found that VAS was significantly higher in group O when compared with group D at 4hrs, 6hr, 8hrs, 12hrs, and 24hrs postoperative.

In agreement with our findings, **Szucs *et al.* [(12)],** conducted a randomized, double-blinded controlled study to define the postoperative analgesic efficacy of a single dose of dexamethasone administered preoperatively in patients undergoing operative fixation of fractured neck of femur. The VAS decreased significantly in the dexamethasone group.

To our knowledge, there are no other published studies that assessed the efficacy of dexamethasone in femoral neck fracture. However, other reports investigated the role of dexamethasone in orthopedic and other types of surgeries.

For example, **Waldron *et al.*[(13)]**performed a meta-analysis of 45 randomized controlled trials that involved a total of 5,796 patients. Patients in the studies that were included were randomized into either a group receiving a perioperative dose of dexamethasone 1.25 to 20 mg or a group receiving a placebo. Five studies that received multiple doses of dexamethasone were included. Of those studies. Results of this meta-analysis demonstrated a statistically significant reduction in the VAS pain scores following dexamethasone[(13)]**.**

Kardash *et al.*[(10)]performed an RCT of 50 patients undergoing elective, unilateral, primary total hip arthroplasty, randomly assigning them to a control group or a treatment group. The treatment group received a single 40-mg dose of dexamethasone before surgery, and after they received an intrathecal dose of 15 mg of plain 0.5% bupivacaine, IV sedation with propofol followed. The results of this study did not indicate any improvement with pain at rest between the treatment group and the control group at any time. However, pain with movement was significantly lower starting at the 12-hour mark in the group receiving dexamethasone and persisting through the end of the measurement, which occurred at the 48-hour mark.

An RCT performed by **Kim *et al.*** [14] examined the effects of dexamethasone on the inflammatory response and pain of women undergoing uterine artery embolization (UAE) for the treatment of symptomatic fibroids. The 64 patients were randomly assigned to a treatment group receiving dexamethasone, 10 mg, or a placebo group receiving just saline. Results of the study demonstrated a significantly lower pain score on the NRS at 12 hours and 24 hours postoperatively in the group that received dexamethasone.

In contrast with our study, **Saryazdi *et al.*** [15] conducted a double-blind randomized study on 48 male patients undergoing knee arthroscopic meniscectomy receiving intra-articular fentanyl 50 mic pethidine 20 mg or dexamethasone 8 mg at the end of arthroscopy during general anesthesia. Postoperative pain scores using the visual analog scale were measured and also analgesic requirements and the time of ability to walk were recorded. The analgesic requirements during the first 24 h after intra-articular was similar between the studied groups.

Femoral neck fractures are rare among young people – they are only 2% in patients under 50 years of age. The incidence increases with age, and after 50 years is doubled for each subsequent decade and is 2-3 times higher in women than in men [16].

In the present study, the mean age of the included patients was 51.83±14.9 and 53% of them were males accounted.

In line with our findings, **Daniachi *et al.*** [17] conducted an epidemiological study on fractures of the proximal third of the femur in elderly patients who were treated at a teaching hospital in the central region of São Paulo. The mean age of patients was around 50 years old; however, the vast majority were females,

Likewise, **Zhou *et al.*** [18] investigate the clinical features of femoral neck fractures and analyze related causes A total of 219 patients (106 male and 113 female) was analyzed. All patients aged more than 50 years old.

The exact cause of such difference in gender distribution may be attributed to different epidemiological characteristics and different sample sizes.

In terms of rescue analgesics, we found that 5 patients (16.7%) in group D & 9 patients (30%) in group O requested additional analgesia in the form of pethidine 0.5-1mg/kg with no statistically significant difference between the two study groups regarding the request of additional analgesia, the first request or the total pethidine consumption.

The strengths of the present study are that it is one of the few reports which assessed the efficacy and safety of intravenous dexamethasone for postoperative analgesia following femoral neck fracture and that it is done on a wide age range group.

We acknowledge that the present study has some limitations. The study was a single-center experience and therefore the results cannot be generalized to the general population. The sample size of the present study was relatively small, which might have hindered the effect size from reaching the margin of statistical significance. The use of subjective methods for pain assessment is another limitation.

CONCLUSION

In conclusion, Intravenous dexamethasone is a promising analgesia for postoperative pain following femoral neck fracture with minimal side effects & no complications.

RECOMMENDATIONS

We can use intravenous dexamethasone safely as an analgesic for postoperative pain following femoral neck fractures. However, its role in functional recovery and chronic pain development is still controversial. Thus, further studies with rigorous design, a large sample size, and multiregional cooperation are required.

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