Analgesia for positioning of spinal anesthesia in elderly patients with proximal femoral fracture under dexmedetomidine infusioin: Ketamine versus fentanyl

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Abstract

Background Changes in posture due to spinal anesthesia in instances of femur fracture can cause severe pain and stress in elderly patients. Dexmedetomidine (DEX) infusion is effective in preventing stress and inducing sleep, but DEX alone has limitations in controlling the pain caused by postural changes. To improve pain relief, we compared the analgesic effects of intravenous DEX–ketamine and DEX–fentanyl combinations to facilitate lateral positioning for spinal anesthesia in proximal femoral fractured patients. Methods Forty-six patients were randomly assigned to the group K or group F. Group K was intravenously given ketamine (1 mg/kg) for 10 minutes, while group F received intravenous fentanyl (1 mcg/kg) for 10 minutes. All patients in both groups received concomitantly a bolus of DEX 1 μg/kg over 10 minutes. Ten minutes after the administration of ketamine with DEX or fentanyl with DEX, patients were placed in the lateral position with the fracture site positioned up. Pain score and quality scores during spinal anesthesia (i.e., lateral positioning, hip flexion, and spinal block) were recorded. Results Pain scores during lateral positioning and hip flexion were significantly lower in group K than in group F ($P < 0.0001$). The quality scores of patients during all periods of spinal anesthesia were significantly lower in Group K than in Group F ($P < 0.05$). Hemodynamic parameters were not significantly different between the two groups. Conclusions Intravenous DEX–ketamine is a more effective combination of the lateral position for spinal anesthesia in patients undergoing surgery for proximal femoral fracture in comparison with intravenous DEX–fentanyl.

Background

Proximal femur fractures are a significant cause of morbidity and mortality for elderly patients [1] and surgery has become the standard treatment in most of these individuals [2]. Separately, the perioperative management of these patients is becoming more complex and increasingly important in the health care system overall [3]. Many studies have investigated the relationship between anesthesia type and postoperative results. Although the effects of spinal anesthesia (SA) for surgery constitute a longstanding subject of debate, it has been reported that regional anesthesia (RA) protocols like SA reduce the risks of pulmonary complications, deep vein thrombosis, and mortality [4, 5]. Spinal anesthesia is primarily applied in elderly patients versus general anesthesia (GA) [6] in our institution.

Movement in the instance of proximal femur fracture causes severe pain when an affected elderly patient is established in a lateral position with lumbar flexion [7, 8]. It is a definite cause of discomfort and anxiety in conscious elderly patients, who are therefore more likely to become delirious with screaming and uncontrolled movements. The sufficient relief of pain and adequate sleep in elderly patients in an unfamiliar operating room can facilitate proper posture and lead to successful SA. Much effort have been made to minimize the pain of changing the posture. However, there are few studies to date that have compared analgesic methods that alleviate the pain that occurs when changing postures for SA.

Dexmedetomidine (DEX), a highly selective α-2 adrenoreceptor agonist, has sedative, sympatholytic, analgesic, and anxiolytic properties without significant associated respiratory depression [9]. Although

DEX infusion provides adequate analgesia and reduces the level of discomfort for procedures, a sole DEX infusion agent was not uniformly successful and supplemental analgesics were required [10]. Therefore, we hypothesized that ketamine or fentanyl could be appropriate analgesics to control movement-evoked pain in elderly patients with proximal femur fracture who were undergoing DEX continuous infusion. This study was performed to compare the analgesic effects of intravenous (IV) ketamine infusion with IV fentanyl infusion prior to positioning patients who were receiving DEX infusion for SA.

Methods

Study design and patient population

This randomized, prospective, and double-blind study enrolled 46 patients from May 2014 to October 2016. This study was approved by the institutional review board of Inje University Haeundae Paik Hospital (129792-2014-027) and written informed consent was obtained from patients. This study was registered before patient enrollment began at ClinicalTrials.gov (NCT02150759; date of registration: December 23, 2013).

Criteria for inclusion and exclusion

Adult patients who were classified as having American Society of Anesthesiologists (ASA) physical status I-□ and proximal femoral fracture were included. Exclusion criteria were hemorrhagic diathesis, bradycardia, atrioventricular block, mental disorders, and an allergy to the study drugs being used (i.e., DEX, ketamine, fentanyl, and bupivacaine).

Preoperative preparations and anesthesia protocol

The study participants were randomly divided into two groups using an allocation sequence; those in group K reeived a ketamine and DEX infusion, while those in group F received a fentanyl and DEX infusion. No premedication was administered in these patients. Spinal anesthesia was initiated with infusing 6 mL/kg of crystalloid solution. Ketamine hydrochloride (Ketamine® 1 mg/kg; Huons, Sungnam, Republic of Korea) or fentanyl citrate (Fentanyl® 1 μg/kg; Hana Pharma Co., Seoul, Republic of Korea) was mixed with normal saline to form a total of 10 mL, with the preparations done by an anesthesiologist who was blinded to the details of this study. While in the operating room, all patients were monitored by electrocardiography, blood pressure, and pulse oximetry.

All patients received a bolus of DEX 1 μg/kg over 10 minutes and continuous infusion was set at 0.6 μg/kg/hr before SA. The patients in group K received IV ketamine (1 mg/kg) and those in group F received IV fentanyl (1 mcg/kg) for 10 minutes concomitantly with DEX (Precedex®; Hospira, Inc., Lake Forest, IL, USA). Ten minutes after the administration of ketamine with DEX or fentanyl with DEX, patients were placed in the lateral position with their fracture site up. Ropivacaine hydrochloride (Rocaine® 10–15 mg; Reyon Pharmaceutical Co., Seoul, Republic of Korea) was injected intrathecally after confirming free flow of cerebrospinal fluid at the L3-4, L4-5, or L5-S1 interspace by an anesthesiologist.

IV ephedrine or phenylephrine was administered when systolic blood pressure was decreased by more than 20% of its initial level. IV atropine was administered when bradycardia (heart rate < 50 bpm) occurred. When desaturation (SpO2 < 90%) was noted, patients underwent manual mask ventilation or supplemental 100% O2 6 L/min administration via facial mask. If the patient groaned during surgery, 50 μg of IV fentanyl was given. If the patient showed a degree of agitation that would interrupt surgery, then 10 mg of IV propofol was administered.

Measurements

Time to perform SA (i.e., the length of time from the beginning of patient lateral positioning to the completion of the intrathecal bupivacaine injection) was recorded. Pain score (0 = calm, 1 = facial grimacing, 2 = moaning, 3 = screaming, and 4 = unable to proceed because of restlessness or agitation) and quality score (0 = not satisfactory, 1 = satisfactory, 2 = good, and 3 = optimal) of patient positioning maintained for SA (i.e., lateral position, hip flexion, and spinal block) were also recorded.

Statistical analysis

The sample size was estimated from a pilot study involving 10 patients per group for the pain scores (≥ 3) during lateral positioning. Allowing for an α error of 5% and a β error of 20%, it was estimated that a minimum of 19 patients per group would be required to show a 50% difference in pain scores. Assuming a dropout rate of 20%, the final necessary sample size was set at 23 patients per group. Data were analyzed using Medcalc 14.12.0 (MedCalc Software bvba, Ostend, Belgium). Parametric variables are described as the mean ± standard deviation (SD). Qualitative variables were described as the number and median (interquartile ranges). Student's t-test, Fisher's exact test, or Mann–Whitney U test was used as appropriate to compare the two groups. $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 46 patients were enrolled in this study, but one patient in group K (due to a change in the surgical schedule) and two patients in group F (due to conversion to GA) were excluded from the final data analysis (Fig. 1).

Patients' demographics and anesthetic characteristics are described in Table 1. There was no statistically significant difference between group K and group F regarding ASA classification and type of proximal femur fracture. The times from trauma to surgery for group K and group F were one (1–2) day and two (1–3.25) days, respectively, while the SA procedure times for group K and group F were 5.83 ± 2.43 minutes and 5.49 ± 1.96 minutes, respectively. Thus, there were no significant differences between the two groups regarding the time from trauma to surgery and SA procedure time.

Table 1. Patients demographics and spinal anesthetic characteristics

	Group K (n = 22)	Group F (n = 21)	P-value
Age (years)	78.28 ± 6.47	79.57 ± 7.13	0.5352
Male/female (n)	2/20	7/14	0.0535
Height (cm)	156.46 ± 6.18	160.30 ± 7.09	0.0650
Weight (kg)	52.22 ± 8.67	55.79 ± 8.15	0.1723
ASA classification (1/2/3)	0/15/7	0/9/12	0.1065
Type of fracture (femur neck/intertrochanteric)	11/11	9/12	0.6427
Time from trauma to surgery (days)	1 (1 to 2)	2 (1 to 3.25)	0.1012
Time to perform spinal block (min)	5.83 ± 2.43	5.49 ± 1.96	0.6228

Data are presented as the mean (SD), median (interquartile range), or number of patients. ASA: American Society of Anesthesiologists.

Pain scores and quality scores of patients during SA are described in Tables 2 and 3, respectively. Pain scores for lateral position ($P < 0.0001$) and hip flexion ($P < 0.0001$) during position change were significantly lower in group K than in group F. Separately, quality scores for lateral position ($P < 0.0003$), hip flexion ($P < 0.009$), and spinal block ($P < 0.0124$) were significantly lower in group K than in group F.

Table 2. Pain scores related positional change during spinal anesthetic procedures

	Group K (n = 22)	Group F (n = 21)	P-value
Lateral position (0/1/2/3/4)	15/5/2/0/0	0/0/5/16/0	< 0.0001
Hip flexion (0/1/2/3/4)	17/3/1/1/0	1/0/6/14/0	< 0.0001
Spinal block (0/1/2/3/4)	17/2/3/0/0	11/8/2/0/0	0.0795

Data are presented as the number of patients. Pain score (0 = calm, 1 = facial grimacing, 2 = moaning, 3 = screaming, 4 = unable to proceed because of restlessness or agitation) of patient position maintained for spinal block was recorded.

Table 3. Quality scores of positional change and spinal anesthetic procedures

	Group K (n = 22)	Group F (n = 21)	P-value
Lateral position (0/1/2/3)	2/3/9/8	3/15/3/0	0.0003
Hip flexion (0/1/2/3)	3/6/5/8	5/13/3/0	0.0090
Spinal block (0/1/2/3)	1/7/6/8	3/13/5/0	0.0124

Data are presented as the number of patients. Quality score (0 = not satisfactory, 1 = satisfactory, 2 = good, and 3 = optimal) of patient position maintained for spinal block was recorded.

Both group K and group F had one patient each given an IV propofol injection for the management of agitation, while only group K included one patient given additional fentanyl. One patient in each group complained of intraoperative nausea and vomiting (P = 0.9734). The incidence of postoperative delirium was noted in five (23.8%) patients in group F and six (27.3%) patients in group K (P = 0.7971) for 11 (25.6%) patients total.

Hemodynamic values for bradycardia, hypotension, hypoxia, tachycardia, and hypertension are shown in Table 4. These parameters were not statistically different between the two groups.

Table 4. Hemodynamic adverse events of analgesia under with DEX infusion

	Group K (n = 22)	Group F (n = 21)	P-value
Bradycardia (n, %)	18 (81.8%)	14 (66.7%)	0.2606
Hypotension (n,%)	21 (95.5%)	20 (95.2%)	0.9734
Desaturation (n,%)	18 (81.8%)	14 (66.7%)	0.2606
Tachycardia (n,%)	2 (9.1%)	2 (9.5%)	0.9615
Hypertension (n,%)	2 (9.1%)	0 (0%)	0.1620

Data are presented as the number and percentage of patients.

Discussion

This study demonstrated that an IV ketamine infusion is more effective than an IV fentanyl infusion to facilitate the lateral position in proximal femur fracture patients receiving a concomitant DEX infusion.

Provided that the patient has more than moderate or severe pain, IV analgesics can serve as a means for pain reduction and can improve the ease of positioning for SA.

In our institution, DEX with SA is widely used for proximal femur fracture patients because DEX can prolong the duration of SA and elicit analgesia and sedation effects in elderly patients. DEX can be used alone as a medication for sedation and analgesia in patients waiting for SA. However, movement-evoked pain of the fractured femur generally cannot be completely addressed by DEX alone. DEX can be used in combination with ketamine, fentanyl, or midazolam. When considering the technique used to aid in positioning patients comfortably for SA, the IV agents selected herein were ketamine and fentanyl [7].

Fentanyl, a potent synthetic μ receptor-stimulation opioid is most often used for perioperative pain control. Analgesia may occur as soon as one to two minutes after IV administration of fentanyl [11]. DEX–fentanyl appears to provide better sedation, stable hemodynamics, and postoperative analgesia versus midazolam–fentanyl during tooth extraction [12].

Ketamine can prevent the development of tolerance and hyperalgesia by way of the inhibition of the NMDA receptors. Administration of low-dose IV ketamine provide lower amount of analgesic consumption and longer analgesic effect at postoperative period. Intravenous low-dose ketamine provides longer postoperative analgesia and lower postoperative analgesic consumption [4]. DEX better attenuates ketamine-induced cardiostimulatory effects and central nervous system symptoms in comparison with midazolam–ketamine [14]. A DEX–ketamine combination showed better recovery profiles with hemodynamic stability and analgesia than did a DEX–midazolam combination [15].

The positioning of femur fracture patients for SA is often big problem because even a minimal overriding of the fracture ends can provoke serios pain to the patients [16]. It also represents a large burden on the anesthesiologist, who plans the anesthesia and analgesic techniques for use in such elderly patients who often have many comorbid conditions. There are several existing methods to reduce postural pain during SA in these individuals. The administration of opioids, femoral nerve block [7, 16], and fascia iliaca compartment block [8] can be used for analgesia. However, the degree of pain relief was different according to the concentrations of opioids and local anesthetics [7, 16]. Peripheral nerve blocks are difficult to do without an expert and anesthetic induction time was significantly longer than that with the use of intravenous opioids [8]. We thought that the use of IV analgesics is an easier and less invasive option than peripheral nerve block. Also, the time to perform spinal anesthesia was short in this study (i.e., around five minutes).

Intraoperative sedation during RA has the benefit of avoiding postural discomfort, preventing intraoperative recall, and reducing autonomic reflexes [17]. Recently, prophylactic low-dose DEX significantly decreases the occurrence of postoperative delirium after noncardiac surgery and hip arthroplasty [17, 18]. Patients presenting with proximal femur fracture are usually elderly and therefore a significant proportion have coexistent disease and a high risk factor of postoperative delirium (POD). The rate of POD in this study was 25.6%, which is similar to the incidence of POD reported in other research [19]. Although ketamine may cause delirium-like symptoms by stimulating the central nervous system

and elevating the intracranial pressure, the incidence of POD in group K (27.3%) was not statistically significantly higher than that in group F (23.8%).

We suggest that precautions be taken when mixing other drugs with DEX. Hypotension (90%) and bradycardia (80%) were frequently observed in this study. Desaturation is not common in sedation with sole DEX [10], but is a more common occurrence (66%–82%) when DEX is mixed with fentanyl (66.7%) or ketamine (81.8%), as was true in our study.

There are some limitations to the present study. First, we did not evaluate patients' analgesic effects and satisfaction levels. The effects of analgesia were evaluated by an evaluator based on expressions such as a patient's facial expressions or voice. In addition, the quality of SA was estimated by an anesthesiologist, not by the patient with SA. Second, the femoral fracture extent and severity classification did not take into account the pain of posture induction. Patients participating in this study were included if they had a proximal femur fracture. This study also did not consider the method of operation of the femoral fracture. Third, the doses of analgesic and narcotic drugs given before surgery were additionally not considered. Elderly patients like those in our study typically are suffering from severe fractures upon presentation and are usually transported to our institution from a local emergency room to undergo emergency surgery. This study was conducted without considering the initially administered analgesic dose. Fourth, the determination of the dose of fentanyl and ketamine is arbitrary for researchers. The determination of dose was based on convenience of study within the scope of clinical use.

Conclusions

Concomitant injection of DEX and ketamine is an effective and excellent method for suppressing the pain of postural changes necessary for the performance of SA in elderly patients with proximal femur fracture and for maintaining a stable level of sedation during the operation. A DEX-ketamine combination can be used widely for analgesia without serious adverse reactions.

Declarations

Ethics approval and consent to participate: This study was approved by the institutional review board of Inje University Haeundae Paik Hospital (129792-2014-027) and written informed consent was obtained from study participants.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: SJ Lee: manuscript preparation and data acquisition; KH Lee, S Lee: data analysis and manuscript writing and editing; S Lee: design, study development, and final editing; J Park, MJ Ko: data acquisition and clinical studies; SH Kim: literature search and clinical studies; S Lee: idea development. All authors read and approved the final version of this manuscript.

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Abbreviations

ASA, American Society of Anesthesiologists; DEX, dexmedetomidine; GA, general anesthesia; IV, intravenous; POD, postoperative delirium; RA, regional anesthesia; SA, spinal anesthesia; SD, standard deviation

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Figures

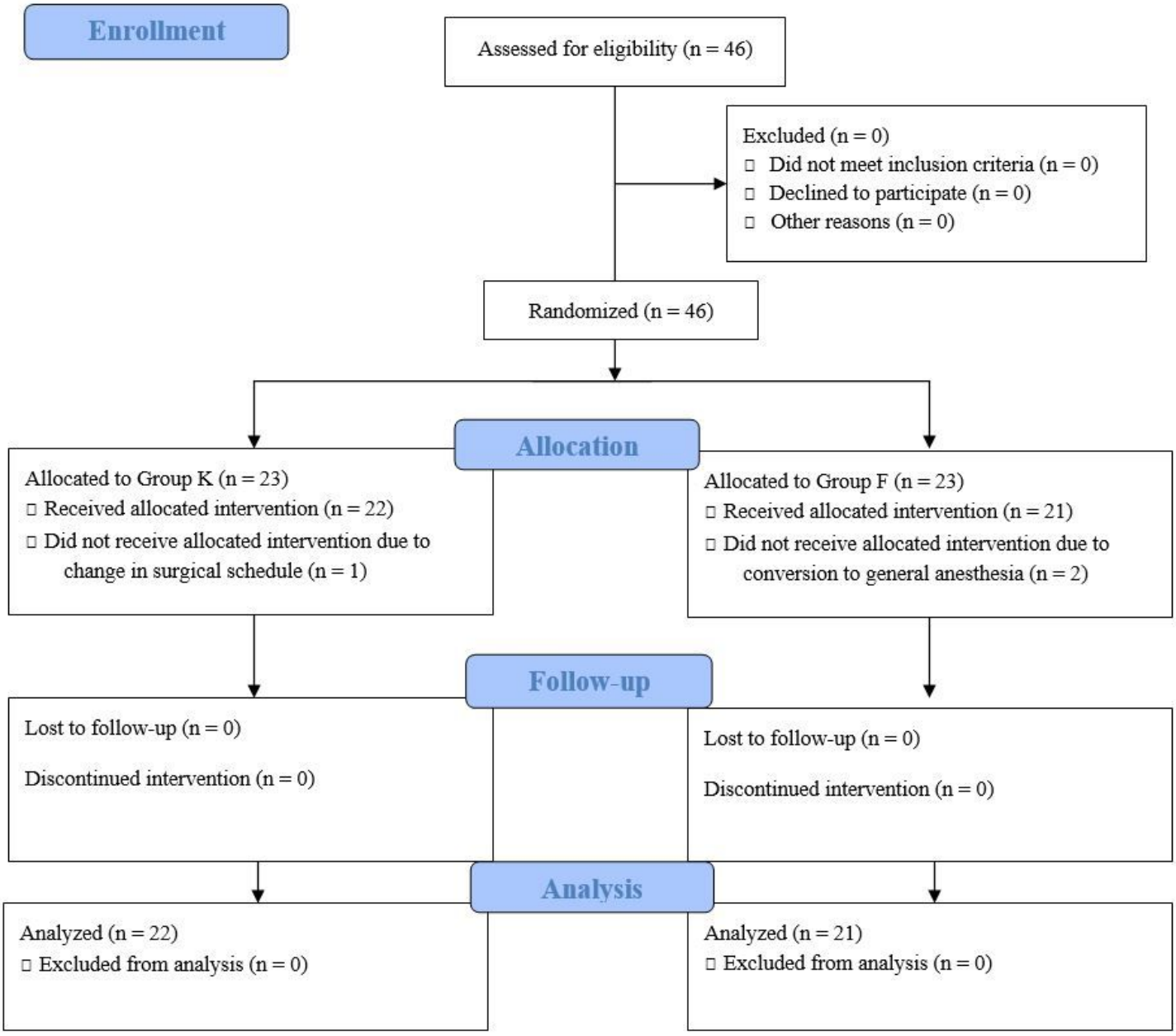

Figure 1

CONSORT flow diagram