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Analgesia for spinal anesthesia positioning in elderly patients with proximal femoral fractures

Dexmedetomidine-ketamine versus dexmedetomidine-fentanyl

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Abstract

Elderly patients with femoral fractures are anticipated to endure the most pain caused by positional changes required for spinal anesthesia. To improve pain relief, we compared the analgesic effects of intravenous dexmedetomidine-ketamine and dexmedetomidine-fentanyl combinations to facilitate patient positioning for spinal anesthesia in elderly patients with proximal femoral fractures. Forty-six patients were randomly assigned to two groups and received either 1 mg/kg of intravenous ketamine (group K) or 1 μg/kg of intravenous fentanyl (group F) concomitant with a loading dose of dexmedetomidine 1 μg/kg over 10 minutes, then dexmedetomidine infusion only was continued at 0.6 μg/kg/h for following 20 minutes, and titrated at a rate of 0.2 to 0.6 μg/kg/h until the end of surgery. After completion of the infusion of either ketamine or fentanyl, the patients were placed in the lateral position with the fracture site up. The pain score (0 = calm, 1 = facial grimacing, 2 = moaning, 3 = screaming, and 4 = unable to proceed because of restlessness or agitation) was used to describe the pain intensity in each step during the procedure (lateral positioning, hip flexion, and lumbar puncture), and quality score (0 = poor hip flexion, 1 = satisfactory hip flexion, 2 = good hip flexion, and 3 = optimal hip flexion) was used to describe the quality of posture. Group K showed a median pain score of 0 (0-1), 0 (0–0) and 0 (0–0) in lateral positioning, hip flexion and lumbar puncture, respectively, while group *F* showed a score of 3 (2.75–3), 3 (2–3) and 0 (0–1), respectively. The pain score in lateral positioning ($P < .0001$) and hip flexion ($P < .0001$) was significantly lower in group *K* than group *F*. Group *K* showed the significantly higher quality scores of spinal anesthesia positioning ($P = .0044$) than group *F*. Hemodynamic adverse effects, such as bradycardia, hypotension, and desaturation, were not significantly different between the groups. The administration of dexmedetomidine-ketamine showed a greater advantage in reducing pain intensity and increasing the quality with patient positioning during spinal anesthesia in elderly patients with proximal femoral fractures, without any serious adverse effects.

Abbreviations: BIS = bispectral index, HR = heart rate, MBP = mean blood pressure, NRS = numerical rating scale, POD = postoperative delirium, SD = standard deviation, SPO2 = peripheral pulse oximetry.

Keywords: analgesia, dexmedetomidine, fentanyl, ketamine, spinal anesthesia

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

Proximal femoral fractures are a critical cause of morbidity and mortality in elderly patients.[1,2] Surgery has become the standard treatment for femoral fractures.[3] Many studies have investigated the relationship between anesthesia type and postoperative outcomes. The excellent effect of spinal anesthesia in cases of femoral fracture compared to that of general anesthesia has long been controversial,[4] but spinal anesthesia was the preferred anesthetic technique with advantages in terms of one-month mortality and deep vein thrombosis, and spinal anesthesia was mainly applied in elderly patients.[5]

For proximal femoral fractures, passive movement causes severe pain when the affected patient is in the lateral position with lumbar flexion.[6,7] It is a definite cause of discomfort and anxiety in conscious elderly patients, who are therefore more likely to become agitated with screaming and uncontrolled movements. Sufficient pain relief and adequate sedation in older patients can lead to proper posture and successful spinal anesthesia in unfamiliar operating rooms. When trying to change the position of the patient on the operating table, much effort has been made to minimize pain. However, to date, few studies have compared analgesic methods for relieving pain.

Elderly patients with femoral fractures can benefit from spinal anesthesia. However, postural changes that are essential for

spinal anesthesia are expected to cause severe pain. Dexmedetomidine infusion is effective for alleviating anxiety and providing sedation,[8] but dexmedetomidine alone is limited in controlling pain associated with postural changes. Ketamine and fentanyl may be used in addition to dexmedetomidine for postural change-evoked pain. The combination of dexmedetomidine-ketamine or dexmedetomidine-fentanyl has become progressively utilized for painful procedures in children and adults,[9,10] but there have been few studies on dexmedetomidine-ketamine or dexmedetomidine-fentanyl use during spinal anesthesia in elderly patients.

This study was performed to compare the analgesic effects of dexmedetomidine-ketamine and dexmedetomidine-fentanyl infusion on postural change-evoked pain for spinal anesthesia in elderly patients with proximal femoral fractures.

2. Methods

2.1. Study design and patient population

Forty-six patients were enrolled in this randomized, double-blind study and underwent proximal femoral fracture surgery at our hospital from May 2014 to October 2016. This study was approved by the Institutional Review Board of our institution (129792–2014–027), and written informed consent was obtained from all patients.

2.2. Criteria for inclusion and exclusion

Patients who were classified as American Society of Anesthesiologists physical status I-III, had proximal femoral fractures, and were aged over 70 years were included. Patients were excluded if they had hemorrhagic diathesis, bradycardia, atrioventricular block, mental disorders, and any history of allergic reactions to the drugs used (dexmedetomidine, ketamine, fentanyl, and ropivacaine).

2.3. Preoperative preparations and anesthesia protocol

The patients were randomly divided into 2 groups using a computer-generated allocation sequence; those in group K received intravenous infusions of dexmedetomidine and ketamine, while those in group F received intravenous infusions of dexmedetomidine and fentanyl (Fig. 1). An anesthesiologist evaluated the patient's numerical rating scale (NRS) score the day before surgery. No premedication was given to the patients. One anesthesiologist prepared either ketamine (1 mg/kg) or fentanyl citrate (1 μg/kg) mixed with normal saline to form a total of 10 ml, and dexmedetomidine (200 μg) mixed with normal saline to form a total of 50 ml Upon arriving in the operating room, all patients were monitored with electrocardiography, invasive arterial blood pressure, peripheral pulse oximetry (SpO2), and bispectral index (BIS) monitoring.

Patients in groups K and F received intravenous ketamine (1 mg/kg) and fentanyl (1 μg/kg) via the syringe pump, respectively, for 10 minutes and then discontinued. All patients were given concomitantly dexmedetomidine with either ketamine or fentanyl, and for the first 10 minutes a loading dose of dexmedetomidine (1 μg/kg) was administered via another syringe pump, and then the continuous infusion of dexmedetomidine only (0.6 μg/kg/h) was maintained for following 20 minutes, and the infusion of dexmedetomidine was titrated at a rate of 0.2 to 0.6 μg/kg/h according to mean blood pressure (MBP), heart rate (HR) and BIS until the end of surgery (Fig. 2).

The patients were placed in the lateral position, the fracture side up, followed by flexion of the hip and lumbar spine, after completion of the infusion of either ketamine or fentanyl. Lumbar puncture was performed at the L3–4, L4–5 or L5-S1 interspace by another anesthesiologist who was not aware of which group to which the patient belonged, and ropivacaine (10 to 15 mg) was injected intrathecally after confirmation of the free flow of cerebrospinal fluid.

Hemodynamic parameters were recorded at a 5-minute interval during anesthesia, and the data were collected during the first 30 minutes from the start of either dexmedetomidine-ketamine or dexmedetomidine-fentanyl administration. A small intravenous bolus of ephedrine 5 mg was administered in case of hypotension (MBP < 60 mm Hg). Atropine 0.5 mg was intravenously administered when HR was less than 50 beats per minute. If desaturation (SpO2 < 90%) was noted, supplemental oxygen was provided at 6 L/min via facial mask. If the patient groaned during the surgery, fentanyl 50 μg was intravenously administered. A supplemental bolus of propofol 10 mg was repeatedly given as needed for the patients showing agitation that could otherwise interrupt surgery.

2.4. Measurements

The length of time taken for spinal anesthesia (i.e., the time from lateral positioning until completion of the intrathecal ropivacaine injection) was recorded by a nurse who was blinded to the patients' allocated treatment groups. Pain intensity was assessed by an assessor, and quality scores representing the quality of spinal anesthesia were determined by the anesthesiologist who conducted spinal anesthesia, both of whom were also blinded to the treatment allocation. The pain score (0 = calm, 1 = facial grimacing, 2 = moaning, 3 = screaming, and 4 = unable to proceed because of restlessness or agitation) was used to describe the pain intensity in each step during the procedure (lateral positioning, hip flexion, and lumbar puncture), and quality score (0 = poor hip flexion < 30 degrees, 1 = satisfactory hip flexion ≥30 and < 60 degrees, 2 = good hip flexion ≥ 60 and < 90 degrees, 3 = optimal hip flexion ≥90 degrees) was used to describe the quality of posture.

2.5. Statistical analysis

The primary goal of this study was to compare the pain intensity in the lateral positioning for spinal anesthesia between the 2 groups. In a pilot study of 10 patients per group, the sample size was estimated by comparing the proportion of patients with severe pain scores (≥3) at the time of lateral positioning. It was estimated that at least 19 patients per group would be required, allowing a 5% α error and a 10% β error, and a 50% difference in the proportion of patients with severe pain. Assuming a drop-out rate of 15%, the final sample size was a set of 23 patients per group. The secondary goals were to compare the quality scores, adverse events, and hemodynamic changes. Data were analyzed using MedCalc 19.2.0 (MedCalc Software, Ostend, Belgium). Parametric variables are described as the mean ± standard deviation (SD). Qualitative variables are described as a number (percentage) and median (interquartile range). Independent samples *t*-test, paired samples *t*-test, chi-squared test, Mann-Whitney test, and repeated measures analysis of variance were

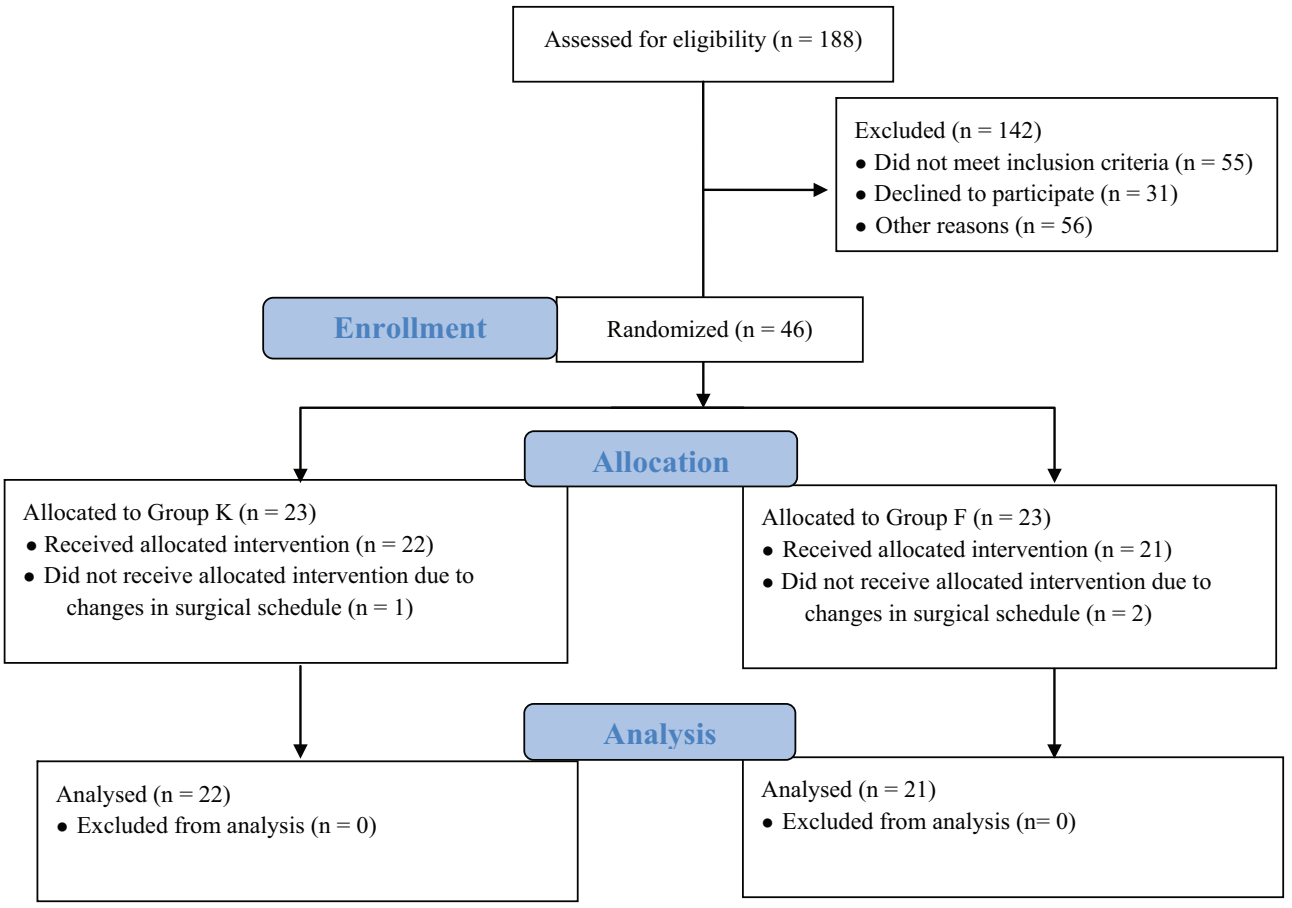

Figure 1. CONSORT flow diagram.

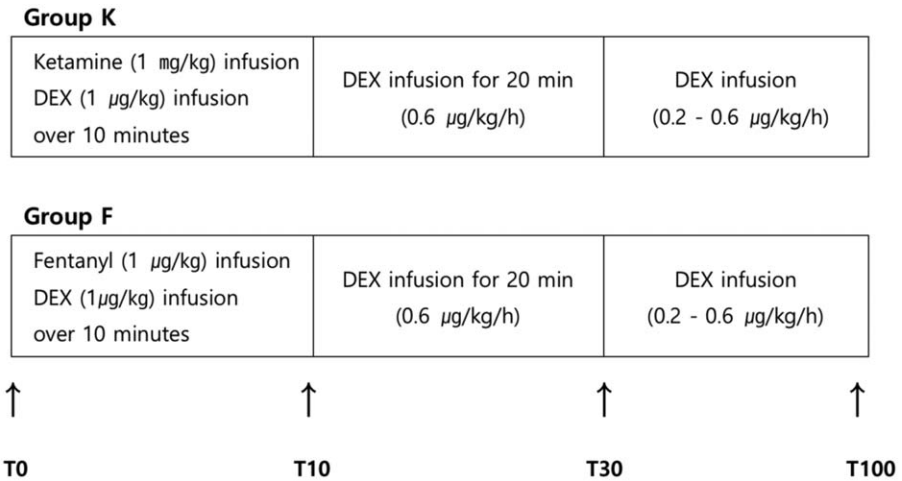

Figure 2. Infusion plan. Intravenous ketamine (1 mg/kg) or fentanyl (1 μg/kg) was infused, concomitant with a loading dose of dexmedetomidine 1 μg/kg over 10 minutes. Then ketamine or fentanyl infusion was discontinued, and the infusion of dexmedetomidine was continued at 0.6 μg/kg/h for the next 20 min, and then titrated at a rate of 0.2–0.6 μg/kg/h until the end of surgery. Group K = patients who received dexmedetomidine-ketamine, Group F = patients who received dexmedetomidine-fentanyl. T0: at the beginning of infusion, T10: 10 min later, T30: 30 minlater, T100: at the end of surgery.

used as appropriate to compare the two groups. A P value $< .05$ was considered to indicate statistical significance.

3. Results

A total of 46 patients were enrolled in this study, but 1 patient from group K and 2 from group F were excluded from the data analysis due to changes in surgical schedules, respectively (Fig. 1). The patients' demographics and anesthetic characteristics are described in Table 1. The time to surgery after trauma was 1 (1 to 2) day in group K and 2 (1 to 3.25) days in group F. The anesthesia time, the surgical procedure time, and dexmedetomidine infusion time were 117 ± 37, 64 ± 30 and 96 ± 23 minutes (min), respectively, in group K, and 109 ± 27, 58 ± 25 and 88 ± 27 min, respectively, in group F. There were no statistically significant differences in the anesthesia time, the surgical procedure and dexmedetomidine infusion time between the groups.

The preoperative resting NRS score was not different between the groups (3.9 ± 1.4 in group K, 3.3 ± 0.8 in group F). The median pain score in lateral positioning, hip flexion, and lumbar puncture was 0 (0–1), 0 (0–0) and 0 (0–0), respectively, in group K and 3.0 (2.75–3), 3 (2–3), and 0 (0–1) in group F (Table 2). The pain score in lateral positioning ($P < .0001$) and hip flexion ($P < .0001$) was significantly lower in group K. The median quality scores in spinal anesthesia positioning were 2 (1–3) in group K and 1 (0.75–1) in group F (Table 3). Group K showed the higher quality score in spinal anesthesia positioning ($P < .0044$). The median number of lumbar puncture attempts was 1 (1–2) in group K, and 1 (1–1.25) and group F. The length of time needed for spinal anesthesia was 5.8 ± 2.4 and 5.5 ± 2.0 minutes in groups K and F, respectively (Table 3). There were no statistically significant differences in the number of lumbar puncture attempts and the length of time needed for spinal anesthesia between the groups.

Intraoperative hemodynamic adverse effects, including bradycardia, hypotension, and desaturation are shown in Table 4. They were not significantly different between the groups. Desaturation in this study was common, with a rate of 81.8% in group K and 66.7% in group F. Hemodynamic changes in terms of the MBP, HR, SPO2, and BIS were recorded at a 5-minute interval during the first 30 minutes from the beginning of dexmedetomidine administration with either ketamine or fentanyl, as shown in Figures 3–5, respectively. No difference was found in the MBP, HR or SPO2 between the groups. The MBP after 20 minutes (T20), 25 minutes (T25), and 30 minutes (T30)

Table 1

Patient demographics and spinal anesthetic characteristics.

	Group K (n = 22)	Group F (n = 21)	*P* value
Age (years)	78.3 ± 6.5	79.6 ± 7.1	0.5352
Male/female (n)	2/20	7/14	0.0535
Height (cm)	156.5 ± 6.2	160.3 ± 7.1	0.0650
Weight (kg)	52.2 ± 8.7	55.8 ± 8.2	0.1723
ASA classification (1/2/3) (n)	0/15/7	0/9/12	0.1065
Time from trauma to surgery (days)	1 (1 to 2)	2 (1 to 3)	0.1012
Preoperative resting pain (NRS)	3.9 ± 1.4	3.3 ± 0.8	0.0936
Type of fracture			0.6289
Femur neck fracture [n, (%)]	10 (45.5)	8 (38.1)	
Intertrochanteric fracture [n, (%)]	12 (54.5)	13 (61.9)	
Surgical techniques			0.4562
Hemiarthroplasty [n, (%)]	10 (45.5)	7 (33.3)	
ORIF [n, (%)]	12 (54.5)	14 (66.7)	
Anesthesia time (min)	117 ± 37	109 ± 27	0.4272
Surgical procedure time (min)	64 ± 30	58 ± 25	0.4484
Dexmedetomidine infusion time (min)	96 ± 23	88 ± 27	0.3429

Mean ± standard deviation, median (interquartile range), ASA classification = American Society of Anesthesiologists classification, Group F = patients who received dexmedetomidine-fentanyl, Group K = patients who received dexmedetomidine-ketamine, NRS = numerical rating scale, ORIF = open reduction and internal fixation.

Table 2

Pain scores related to positional changes during spinal anesthesia procedures.

	Group K (n = 22)	Group F (n = 21)	*P* value
Lateral position [n, (%)]			
0	15 (68.2)	0 (0)	
1	5 (22.7)	0 (0)	
2	2 (9.1)	5 (23.8)	
3	0 (0)	16 (76.2)	
4	0 (0)	0 (0)	
Median (interquartile range)	0 (0–1)	3 (2.75–3)	< .0001
Hip flexion [n, (%)]			
0	17 (77.3)	1 (4.8)	
1	3 (13.6)	0 (0)	
2	1 (4.5)	6 (28.6)	
3	1 (4.5)	14 (66.7)	
4	0 (0)	0 (0)	
Median (interquartile range)	0 (0–0)	3 (2–3)	< .0001
Lumbar puncture [n, (%)]			
0	17 (77.3)	11 (52.4)	
1	2 (9.1)	8 (38.1)	
2	3 (13.6)	2 (9.5)	
3	0 (0)	0 (0)	
4	0 (0)	0 (0)	
Median (interquartile range)	0 (0–0)	0 (0–1)	.1708

Pain scores (0 = calm, 1 = facial grimacing, 2 = moaning, 3 = screaming, 4 = unable to proceed because of restlessness or agitation) were assessed in 3 sequential steps during positioning for spinal anesthesia. Group F = patients who received dexmedetomidine-fentanyl, Group K = patients who received dexmedetomidine-ketamine.

Table 3

Assessment of posture quality and difficulty performing a lumbar puncture.

	Group K (n = 22)	Group F (n = 21)	*P* value
Quality scores of posture [n, (%)]			
0	3 (13.6)	5 (23.8)	
1	6 (27.3)	13 (61.9)	
2	5 (22.7)	3 (14.3)	
3	8 (36.4)	0 (0)	
Median (interquartile range)	2 (1–3)	1 (0.75–1)	.0044
The number of lumbar puncture attempts [n, (%)]			
1	16 (72.7)	16 (76.2)	
2	3 (13.6)	2 (9.5)	
3	3 (13.6)	2 (9.5)	
4	0 (0)	1 (4.8)	
Median (interquartile range)	1 (1–2)	1 (1–1.25)	.8738
Time taken for spinal anesthesia (min)	5.8 ± 2.4	5.5 ± 2.0	.4562

Mean ± standard deviation. Quality scores of spinal anesthesia positioning (0 = poor hip flexion < 30 degrees, 1 = satisfactory hip flexion ≥ 30 and < 60 degrees, 2 = good hip flexion ≥60 and < 90 degrees, 3 = optimal hip flexion ≥ 90 degrees) were assessed estimating the degree of hip flexion. Group F patients who received dexmedetomidine-fentanyl, Group K patients who received dexmedetomidine-ketamine.

Table 4

Intraoperative hemodynamic adverse effects and perioperative complications.

	Group K (n = 22)	Group F (n = 21)	*P* value
Bradycardia	18 (81.8)	14 (66.7)	.2606
Hypotension	21 (95.5)	20 (95.2)	.9734
Desaturation	18 (81.8)	14 (66.7)	.2606
PONV	4 (18.2)	2 (9.5)	.6640
Agitation	1 (4.5)	1 (4.7)	.9734
Incomplete anesthesia	1 (4.5)	0 (0)	.3286
Postoperative delirium	6 (27.3)	5 (23.8)	.7971

Data are presented as n (%). Bradycardia = Heart rate < 60 beats/min, Group F = patients who received dexmedetomidine-fentanyl, Group K = patients who received dexmedetomidine-ketamine, Hypotension = mean blood pressure < 60 mm Hg or decrease in systolic blood pressure > 20%), PONV = postoperative nausea and vomiting.

was statistically lower than that at the beginning (T0) in both groups. The HR at T15 began to become significantly lower than that at T0 in group K, while a significant reduction in the HR began at 20 minutes (T20) in group F. The BIS at T15 was 82 ± 9 and 75 ± 14 in groups K and F, respectively, which were significantly different ($P = .0489$). The MAP, HR, and BIS tended to significantly decrease over time ($P < .001$) in both groups.

Perioperative complications of dexmedetomidine with either ketamine or fentanyl are shown in Table 4. There were four patients (18.2%) and 2 patients (9.5%) in groups K and F, respectively, who complained of postoperative nausea and vomiting (PONV, $P = .6640$). Both groups had one patient who received intravenous propofol for the management of agitation ($P = .9734$), and only 1 patient in group K was given additional fentanyl ($P = .3286$). The incidence of postoperative delirium (POD)was noted in 5 patients in group F, 6 patients in group K (23.8% and 27.3%, $P = .7971$), and eleven patients (25.6%) in total.

4. Discussion

Dexmedetomidine is widely used for proximal femoral fracture surgery under spinal anesthesia in our institution because the dexmedetomidine infusion provides sedation as well as analgesia in elderly patients. Dexmedetomidine can also be used in patients waiting for spinal anesthesia to reduce pain and anxiety. Movement-evoked pain in cases of femoral fracture for positioning, however, is difficult to manage with dexmedetomidine using a sole agent. Dexmedetomidine can be used in combination with ketamine or fentanyl. When considering the technique used to aid patient positioning for spinal anesthesia, the intravenous agents used were ketamine and fentanyl.[7] Our results demonstrate that dexmedetomidine-ketamine had greater benefits than dexmedetomidine-fentanyl in reducing the pain intensity and improving the quality of patient posture during positional changes for spinal anesthesia in elderly patients with proximal femoral fractures.

Ketamine, rather than fentanyl, resulted in reduced pain intensity and greater quality in lateral positioning and hip flexion in this study, which suggests that ketamine (1 mg/kg over 10 minutes) could produce better pain relief when compared to

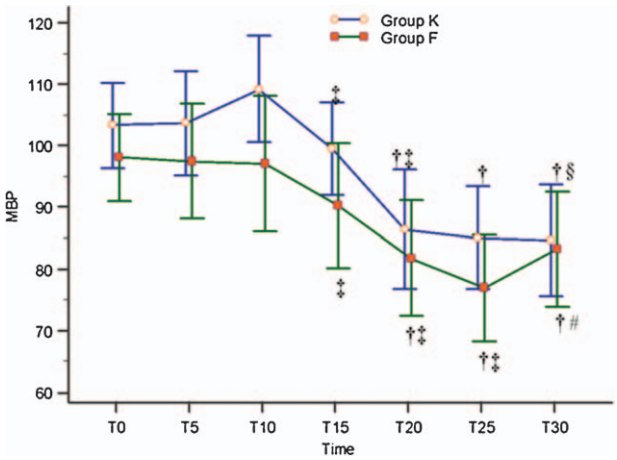

Figure 3. Mean blood pressure (MBP) at a 5-minute interval during the first 30 min from the beginning of dexmedetomidine administration with either ketamine or fentanyl. Intravenous ketamine (1 mg/kg) or fentanyl (1 μg/kg) was infused, concomitant with a loading dose of dexmedetomidine 1 μg/kg over 10 min. Then ketamine or fentanyl infusion was discontinued, and the infusion of dexmedetomidine was continued at 0.6 μg/kg/h for the next 20 minutes. There was no statistically significant difference in the MBP between groups K and F. The MBP at T20, T25 and T30 were significantly lower than that at T0 in both groups. There were significant differences in the MBP between T10 and T15, and between T15 and T20 in group K, while significant differences were shown in the MBP between T10 and T15, between T15 and T20, and between T20 and T25 in group F. There was a significant decrease over time in each group (§: $P < .001$ in group K, #: $P < .001$ in group F). Data are presented as the mean ± SD. Group K = patients who received dexmedetomidine-ketamine, Group F = patients who received dexmedetomidine-fentanyl. †: $P < .05$ compared with baseline value, ‡: $P < .05$ compared with previous value.

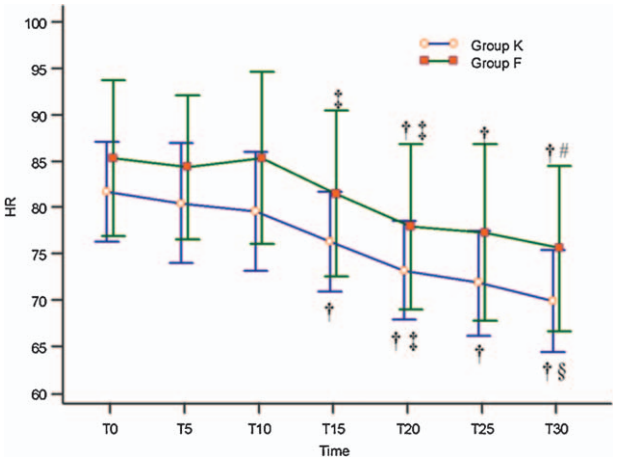

Figure 4. Heart rate (HR) at a 5-minute interval during the first 30 min from the beginning of dexmedetomidine administration with either ketamine or fentanyl. Intravenous ketamine (1 mg/kg) or fentanyl (1 μg/kg) was infused, concomitant with a loading dose of dexmedetomidine 1 μg/kg over 10 minutes. Then ketamine or fentanyl infusion was discontinued, and the infusion of dexmedetomidine was continued at 0.6 μg/kg/h for the next 20 minutes. There was no statistically significant difference in the HR between groups K and F. The HR at T20, T25, and T30 were significantly lower than that at T0 in group K, while the HR at T15, T20, T25, and T30 were significantly lower than that at T0 in group F. There was a significant difference in the HR between T15 and T20 in group K, while there were significant differences between T10 and T15, and between T15 and T20 in group F. There was a significant decrease over time in each group (§: $P < .001$ in group K, #: $P < .001$ in group F). Data are presented as the mean ± SD. Group K = patients who received dexmedetomidine-ketamine, Group F = patients who received dexmedetomidine-fentanyl. †: $P < .05$ compared with baseline value, ‡: $P < .05$ compared with previous value.

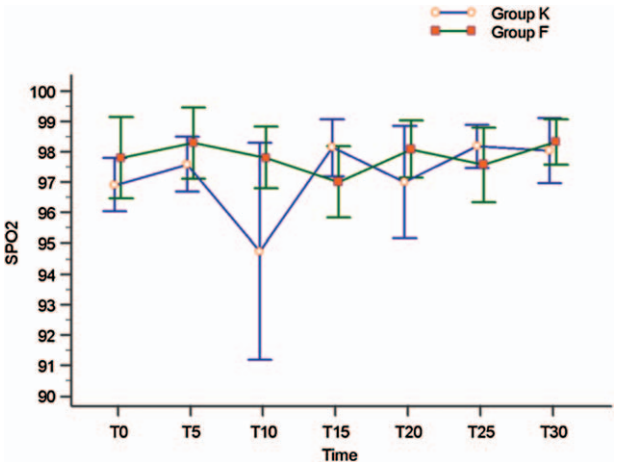

Figure 5. Pulse oximetry saturation (SpO2) at a 5-min interval during the first 30 min from the beginning of dexmedetomidine administration with either ketamine or fentanyl. Intravenous ketamine (1 mg/kg) or fentanyl (1 μg/kg) was infused, concomitant with a loading dose of dexmedetomidine 1 μg/kg over 10 minutes. Then ketamine or fentanyl infusion was discontinued, and the infusion of dexmedetomidine was continued at 0.6 μg/kg/h for the next 20 minutes. There was no statistically significant difference in the SPO2 between groups K and F. Data are presented as the mean ± SD. Group K = patients who received dexmedetomidine-ketamine, Group F = patients who received dexmedetomidine-fentanyl.

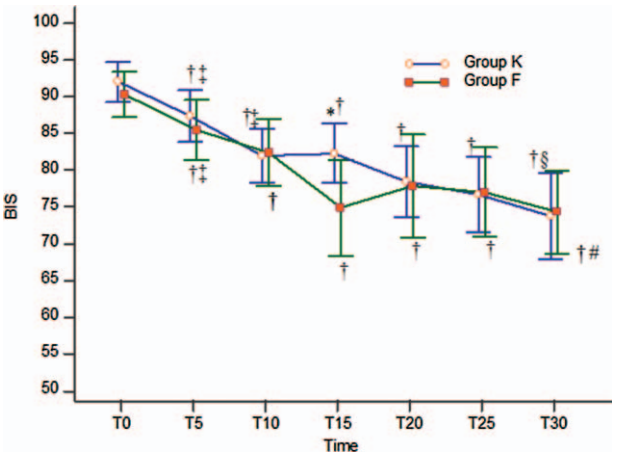

Figure 6. Bispectral index (BIS) at a 5-min interval during the first 30 min from the beginning of dexmedetomidine administration with either ketamine or fentanyl. Intravenous ketamine (1 mg/kg) or fentanyl (1 μg/kg) was infused, concomitant with a loading dose of dexmedetomidine 1 μg/kg over 10 min. Then ketamine or fentanyl infusion was discontinued, and the infusion of dexmedetomidine was continued at 0.6 μg/kg/h for the next 20 minutes. The BIS at T15 was 82 ± 9 and 75 ± 14 in groups K and F, respectively, and there was a statistically significant difference between groups K and F ($P = .0489$). The BIS at T5, T10, T15, T20, T25, and T30 were significantly lower than those at T0 in both groups. There was a significant difference in the BIS between T0 and T5, and between T5 and T10 in group K, while there was a significant difference between T0 and T5 in group F. The BIS tended to decrease over time, and there was a significant decrease over time in both groups (§: $P < .001$ in group K, #: $P < .001$ in group F). Data are presented as the mean ± SD Group K = patients who received dexmedetomidine-ketamine, Group F = patients who received dexmedetomidine-fentanyl. *: $P < .05$ compared with group F, †: $P < .05$ compared with baseline value, ‡: $P < .05$ compared with previous value.

fentanyl (1 μg/kg over 10 minutes). Intravenous ketamine provides longer postoperative analgesia, reduces postoperative analgesic consumption and may be useful in acute pain management.[11,12] Due to the advantages of dexmedetomidine, which attenuates the cardiostimulatory effects and adverse effects of ketamine on the central nervous system, the dexmedetomidine-ketamine combination also showed better analgesia and hemodynamic parameter stability, with better recovery profiles.[13,14] The dexmedetomidine-midazolam-fentanyl combination showed a similar analgesic effect and a better sedative effect than the dexmedetomidine-ketamine combination.[15] The dexmedetomidine-fentanyl combination seemed to provide better sedation, stable hemodynamics, and postoperative pain relief than the midazolam-fentanyl combination during tooth extraction.[16] Therefore, the appropriate combination of dexmedetomidine and adjuvant drugs with the careful adjustment of their doses is required to achieve adequate analgesia and sedation.

The analgesic effect of ketamine compared to fentanyl in elderly patients have been unreported in the literature. The previous studies failed to show differences of analgesic effect between intravenous ketamine (0.5 mg/kg) and fentanyl (1 μg/kg) in children following adenotonsillectomy, and between intranasal ketamine (1.5 mg/kg) and fentanyl (2 μg/kg) in children presenting with acute extremity.[17,18] This result may be interpreted as a difference in morphine equivalent dose between ketamine and fentanyl. Considering that ketamine 0.3 mg/kg has analgesic effects similar to morphine 0.1 mg/kg, which is equivalent to fentanyl 1 μg/kg, the morphine equivalent dose of ketamine (1 mg/kg) in this study may be superior to that of fentanyl (1 μg/kg). However, the opioid requirement decreases with age in the elderly patients, and the dose of fentanyl (1 μg/kg) was administered rather than higher doses, in order to help reduce pain and improve the anesthesia posture, with fewer side effects.

This study was designed to compare the effect of ketamine infusion (1 kg/μg over 10 minutes) and fentanyl infusion (1 μg/kg over 10 minutes) instead of a single bolus. Fentanyl is most commonly used for perioperative pain control, and analgesic action can occur as soon as 1 to 2 minutes after the intravenous administration of fentanyl.[19] Many studies have reported that the analgesic and side effects of fentanyl and ketamine are correlated with plasma concentration.[20] The infusion of a drug slowly reaches the target plasma concentration compared to a single bolus injection, with a slower onset and fewer side effects.[21] Opioids should be administered in the most favorable doses for patients over 70 years old, that is, starting from approximately 25% to 50% of the approved starting dose in adults, and then slowly titrated to minimize negative consequences.[22] In this study, the average age of the patients was 78.3 ± 6.5 and 79.6 ± 7.1 in groups K and F, respectively, and we infused the study drugs over 10 minutes to minimize adverse effects, such as respiratory depression, hypotension, and bradycardia. However, desaturation frequently occurred, when dexmedetomidine was administered concomitant with fentanyl or ketamine in elderly patients (Table 4). Planning anesthesia and analgesia techniques for senior patients with multiple comorbidities would be a great burden on anesthesiologists, taking into account the risk of respiratory depression and hemodynamic adverse effects, caused by dexmedetomidine-ketamine or dexmedetomidine-fentanyl. This result suggests that precaution should be taken when administering dexmedetomidine concomi-

tant with other drugs, and further studies on the combination of sedative and analgesic agents are needed.

The positioning of femoral fracture patients for spinal anesthesia is regularly problematic because even minimal overriding of the fracture ends is extremely painful.[23] There are several strategies to reduce postural pain during spinal anesthesia in these patients. The administration of opioids, the femoral nerve block (FNB), and the fascia iliaca compartment block can be used for analgesia.[6] However, the degree of pain relief differs according to the concentration of opioids and local anesthetics.[7,23] There are several studies on FNB for suppressing pain during postural changes in patients with femoral fractures, and the comparative effects of FNB and fentanyl were not consistent in these studies. The FNB was more advantageous than the intravenous administration of fentanyl to facilitate a sitting position,[24] while it was not superior to intravenous fentanyl for lateral positioning.[7] However, these 2 studies had some differences in the final patient position (sitting vs lateral position) and in the fracture site (femoral shaft vs proximal femur), which could have led to different results. All patients included in this study had proximal femoral fractures. FNB was thought to be less effective than intravenous analgesics, considering that the proximal femur is innervated by the lateral femoral nerve, the femoral nerve, the obturator nerve, the genitofemoral nerve, and sciatic nerve. In addition, it may be more difficult to perform FNB without an expert, and its onset would be slower than 15 minutes. The time to induce anesthesia with FNB is significantly longer than that with the intravenous administration of opioids.[6] We assumed that the intravenous administration of analgesics would be easier and less invasive than the FNB. Therefore, we provided either intravenous dexmedetomidine-ketamine or dexmedetomidine-fentanyl administration to produce analgesic and sedative effects.

This is the first clinical study to compare the feasibility and analgesic effect of ketamine and fentanyl concomitant with a loading dose of dexmedetomidine for sedation. Recently, prophylactic low-dose dexmedetomidine appreciably decreased the incidence of delirium after noncardiac surgery and hip arthroplasty.[24,25] Patients with a proximal femoral fracture are usually elderly, and a significant proportion of these patients have comorbidities and are at an increased risk for POD. The rate of POD in this study was 25.6%, which is similar to the incidence of POD reported in other studies.[26] Although ketamine stimulates the central nervous system and raises the intracranial pressure, which can cause delirium-like symptoms, no difference was found in the incidence of POD between the groups (27.3% in group K, 23.8% in group F). One groaning patient in group K was diagnosed with inadequate anesthesia during surgery and given an additional 50 μg of intravenous fentanyl. There was one agitated patient in each group who once received 10 mg of intravenous propofol. Pain, discomfort, and anxiety in elderly patients can generate agitated screaming and uncontrolled movement. Adequate sedation with dexmedetomidine-ketamine can provide sufficient pain relief during positional changes and lead to successful spinal anesthesia.

In this study, bradycardia, hypotension, and desaturation were common complications during the entire anesthesia, which may be relevant to spinal anesthesia itself under continuous dexmedetomidine infusion, but their incidences with the administration of dexmedetomidine-ketamine were not significantly different from those with the administration of dexmedetomidine-fentanyl. There was no difference in the MBP, HR, or SPO2 between groups K and F. This study also shows that there was a significant decrease over time in the MBP and HR in both groups, and the BP and HR began to decline after 15 minutes compared to the baseline or previous values (Figs. 3 and 4). The intravenous infusion of dexmedetomidine was initiated with a loading dose (1 μg/kg) over 10 minutes, followed by a maintenance infusion (0.6 μg/kg) in this study. Our results are consistent with that dexmedetomidine resulted in a decrease in the BP and HR due to presynaptic α2 receptors reducing norepinephrine release, inhibiting central sympathetic outflow.[8]

There was a significant decrease over time in the BIS in both groups. In addition, there was a statistically significant difference in the BIS at T15 between groups K and F, and the values were 82 ± 9 and 75 ± 14 ($P = .0489$), respectively. This should be cautiously interpreted, considering ketamine significantly increased the BIS, despite cortical depression by dexmedetomidine,[15,16,27] and deepening sedation.[28] As ketamine is known to increase the activity of the electroencephalography towards higher frequencies and desynchronization, an elevated BIS value may reflect greater cortical activity rather than consciousness.[29]

There are some limitations to this study. First, the patients' subjective expression of pain and satisfaction were not taken into account. The analgesic effect was assessed by the evaluator based on objective expressions, such as the facial expressions or voice of the patient. This study failed to show the difference in difficulty of spinal anesthesia which was demonstrated by the number of lumbar puncture attempts and the length of time needed for spinal anesthesia, despite the differences in both pain score and quality of positioning. This might indicate the degree of hip flexion was inadequate to assess the overall quality of positioning. Further investigation is needed for the clinical relevance between postural change evoked pain and difficulty of spinal anesthesia. Second, BIS was measured, instead of a clinical sedation level, such as the modified observer's assessment alertness/sedation scale, to minimize painful or verbal stimulation of the elderly patients. BIS value paradoxically increases as deeper planes of anesthesia are achieved by infusion of ketamine which stimulates the activity of encephalogram. BIS can also greatly change with time, which leads to misinterpretation of the sedation status. Third, the infusion of sedatives before spinal anesthesia prevented the anesthesiologist from accurately measuring the patient's level of motor and sensory blockade. Fourth, the dose of analgesics previously administered before surgery was not taken into account, although the preoperative resting NRS score was not different between the groups (3.9 ± 1.4 in group K vs 3.3 ± 0.8 in group F). Fifth, the dose and infusion duration of fentanyl and ketamine were arbitrary for researchers and determined based on the convenience of study within the scope of clinical use. The results of this study may be interpreted as the pharmacodynamic and pharmacokinetic differences between ketamine and fentanyl in elderly patients. Further studies are needed to clarify the doses of fentanyl and ketamine. The conclusion that dexmedetomidine-ketamine is superior to dexmedetomidine-fentanyl is difficult to generalize through this study. However, it is of value in this study that dexmedetomidine-ketamine helps to suppress postural pain and improve postural maintenance in elderly patients with hip fractures. Providing longer time for drug action after the infusion of ketamine and fentanyl may also affect the results.

In conclusion, the concomitant administration of dexmedetomidine and ketamine can be an effective and excellent method for suppressing the pain of postural changes for spinal anesthesia in elderly patients with proximal femoral fractures and for

maintaining stable sedation during the operation. The dexmedetomidine-ketamine combination may be useful for analgesia without serious adverse reactions; therefore, further studies are required to clarify the dose and infusion duration.

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