ORIGINAL RESEARCH

Comparative Analysis of Ketamine and Fentanyl Combined with Dexmedetomidine for Lumbar Anesthesia in Proximal Femur Fractures Among the Elderly

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ABSTRACT

Objective • This study aimed to compare the effects of ketamine and fentanyl combined with dexmedetomidine in lumbar anesthesia for proximal femur fractures among elderly patients.

Design • This study employed a prospective, randomized controlled trial (RCT) design.

Settings • The study was conducted at Beijing Jishuitan Hospital.

Participants • A total of 100 elderly patients with proximal femur fractures who underwent lumbar anesthesia between January 2022 and January 2023.

Intervention • Participants were divided into two groups: the ketamine group (n=49) and the fentanyl group (n=51). The ketamine group received ketamine combined with dexmedetomidine, while the fentanyl group received fentanyl combined with dexmedetomidine.

Outcome Measures • The following outcome measures were assessed and compared between the two groups: (1) hemodynamic indexes; (2) visual analogue scale (VAS) scores; (3) stress reaction indexes; (4) Incidence of adverse effects. These comparisons were made using the random number table method.

Results • No significant differences were observed in systolic blood pressure (SBP), transcutaneous oxygen saturation (SPO_2), and heart rate (HR) between the two groups at each time point ($P > .05$). SBP and HR of both groups were lower than baseline (T_0) from T_1 onwards. Throughout the surgery, SBP and HR exhibited a decreasing trend with operation time, followed by an increase post-operation. SPO_2 showed minimal fluctuations during surgery in both groups. Preoperatively, VAS scores were comparable between groups ($P > .05$). However, at 12h, 24h, and 48h post-surgery, VAS scores were significantly lower in the ketamine group ($P < .05$). Stress indicator levels were similar preoperatively ($P > .05$), but postoperatively, serum cortisol (Cor), epinephrine (E), and norepinephrine (NE) levels were lower in the ketamine group ($P < .05$).

Conclusion • Dexmedetomidine combined with ketamine demonstrates safety and efficacy in the elderly. It significantly reduces postoperative pain and stress reactions while decreasing the incidence of adverse reactions. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Fractures of the proximal femur, which include both femoral neck and intertrochanteric fractures, represent a frequent occurrence in clinical practice, especially among the elderly population. Approximately 90% of these fractures occur in individuals aged 65 years and older.[1] Surgical intervention remains the primary treatment in managing proximal femur fractures among the elderly. Lumbar anesthesia, in comparison to general anesthesia, has demonstrated advantages, including reduced mortality rates and lower incidences of deep vein thrombosis during the initial postoperative month. Moreover, it has shown efficacy specifically in the elderly patient population.[2]

The utilization of analgesic medications like morphine is constrained by age-related tissue and organ degeneration, alongside chronic comorbidities and physiological instability among elderly patients.[3] These factors heighten the risk of adverse events and diminish patients' quality of life.[3,4] Notably, severe postoperative pain, particularly upon positional changes, emerges as a primary complication in elderly individuals with proximal femur fractures.[5]

Clinical studies have explained the significant role of dexmedetomidine in alleviating postoperative anxiety and pain among orthopedic surgery patients.[5,6] However, dexmedetomidine monotherapy exhibits limitations in managing pain associated with positional changes.[6] Fentanyl, an opioid agonist, emerges as a potent narcotic analgesic extensively employed for intraoperative and postoperative pain management.[7]

In contrast, ketamine, a phencyclidine derivative, acts on peripheral opioid receptors, thereby exerting a notable peripheral analgesic effect.[8] However, the significant effects of dexmedetomidine-ketamine and dexmedetomidine-fentanyl combinations have been demonstrated in pediatric surgery, adult orthopedic surgery, and gastroscopy.[6-12] However, there is a lack of clinical observations regarding the effects of dexmedetomidine-ketamine or dexmedetomidine-fentanyl combinations in lumbar anesthesia for proximal femoral fractures in the elderly.

To address the scarcity of literature on the subject, we conducted a prospective comparison of the effects of dexmedetomidine-ketamine and dexmedetomidine-fentanyl in lumbar anesthesia for proximal femoral fractures in elderly patients. Our objective was to establish a reliable reference for optimizing anesthesia and postoperative analgesia in the elderly patient population.

METHODS

Study Design

This study employed a prospective, randomized controlled trial (RCT) design to evaluate the effects of different anesthesia regimens on elderly patients with proximal femur fractures. A total of 100 participants were included, undergoing lumbar anesthesia at Beijing Jishuitan Hospital over a one-year period. They were randomly assigned to two groups: the ketamine group (n=49) and the fentanyl group (n=51). Each group received a combination of either ketamine or fentanyl with dexmedetomidine. Ethical approval was obtained from the hospital's medical ethics committee, and all participants provided informed consent. This design allowed for a comparative assessment of the efficacy and safety of these anesthesia protocols among the elderly patient population.

Inclusion and Exclusion Criteria

Patients meeting the following criteria were included in the study: (1) age ≥ 65 years; (2) confirmation of proximal femur fracture diagnosis through imaging; and (3) American Society of Anesthesiologists (ASA) classification Grade I-III.[13] Exclusion criteria encompassed the following: (1) severe cardiac disease, (2) hepatic or renal dysfunction, (3) coagulation disorders, (4) back infection, (5) psychiatric disorders, or (6) documented allergic reactions to the study drugs.

Anesthesia Protocol

Patients in both groups underwent standard pre-operative procedures, including disinfection and monitoring for ECG, blood pressure, oxygen saturation, and electroencephalographic bifrequency index (BIS), upon entering the operating room.

Drug Administration. Ketamine (1mg/kg) and fentanyl (1mg/kg) were diluted with saline to a volume of 10ml. In the ketamine group, a dose of 1mg/kg ketamine was administered intravenously, with administration halted after 10 minutes. Conversely, in the fentanyl group, a dose of 1mg/kg fentanyl was administered intravenously and also ceased after 10 minutes. Additionally, both groups received dexmedetomidine (1mg/kg) infusion via a separate syringe pump concurrently with the injection. This was followed by a continuous drip of dexmedetomidine (0.6mg/kg/h) over 20 minutes, with the drip rate adjusted (0.2~0.6 mg/kg/h) based on the patient's hemodynamic parameters and BIS changes.

Lumbar Puncture and Ropivacaine Administration. After the administration of ketamine or fentanyl, the patient is positioned laterally, with the fracture site facing upward and the hip and lumbar spine flexed. Subsequently, the anesthetist performs a lumbar puncture at the L3~4, L4~5, or L5~S1 level. Upon confirmation of free flow of cerebrospinal fluid, intrathecal ropivacaine is injected at a dosage of 10~15 mg.

Intraoperative Management. During anesthesia, hemodynamic parameters were continuously monitored in real time. If the mean blood pressure (MBP) dropped below 60 mmHg, ephedrine was administered intravenously at a dosage of 5 mg. Similarly, if the heart rate fell below 50 beats/min, atropine was administered intravenously at a dosage of 0.5 mg. Supplemental oxygen was provided via a face mask at a rate of 6L/min if the oxygen saturation fell below 90%. In cases of intraoperative moaning, fentanyl was administered intravenously at a dosage of 50 mg. Additionally, if the patient exhibited intraoperative anxiety, isoproterenol was administered intravenously at a dosage of 10 mg IV.

Observation Indicators

Haemodynamic Parameters. Mean arterial pressure (MAP), heart rate (HR), and respiration rate (RR) were monitored at multiple time points: before the procedure (T_0), at the start (T_1), 10 minutes post-procedure (T_2), and 30 minutes post-procedure (T_3). These parameters provide insights into cardiovascular stability and respiratory function during the perioperative period.

Pain Assessment. Patients' pain levels were evaluated preoperatively, as well as at 12 hours, 24 hours, and 48 hours postoperatively, using a visual analogue scale (VAS).[14] The VAS score, ranging from 0 to 10, allows for the quantification of pain severity, with higher scores indicating greater pain intensity.

Stress Indicators. Serum levels of cortisol (Cor), epinephrine (E), and norepinephrine (NE) were measured using radioimmunoassay before surgery and 24 hours postoperatively. These stress markers provide insights into the physiological stress response elicited by surgical trauma and anesthesia.

Adverse Reactions. The occurrence of perioperative adverse reactions in both study groups was systematically recorded, and the incidence rate was calculated. This comprehensive assessment helped to identify potential complications associated with the anesthesia regimen and surgical intervention.

Table 1. Demographic and Clinical Characteristics of Patients Undergoing Lumbar Anaesthesia ($\bar{x}\pm$s)/[n (%)]

Variable		Ketamine Group (n=49)	Fentanyl Group (n=51)	χ^2/t	*P* value
Age (years)		75.42±6.31	76.19±6.24	0.614	.541
Male/Female (n)		29/20	28/23	0.187	.666
Weight (kg)		52.21±7.69	53.07±7.75	0.557	.579
ASA Classification (1/2/3) (n)		0/34/15	0/36/15	0.017	.896
Type of Fracture [n (%)]	Femur Neck Fracture	26 (53.06)	27 (52.94)	0.000	.990
	Intertrochanteric Fracture	23 (46.94)	24 (47.06)		

Note: This table presents the demographic and clinical characteristics of patients who underwent lumbar anesthesia for proximal femoral fractures. Data are expressed as mean±standard deviation ($\bar{x} \pm s$) or [n (%)]. Comparison between groups was conducted using the Chi-square test (χ^2) or *t* test (*t*), as appropriate. $P < .05$ were considered statistically significant.

Abbreviation: ASA, American Society of Anesthesiologists.

Statistical Analysis

The statistical analysis was conducted using SPSS version 21.0 (International Business Machines, Corp., Armonk, NY, USA) for data processing and GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA) for graphical representation. Count data were presented as frequencies and percentages [n (%)] and analyzed using the chi-square test (χ^2). Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared using the *t* test, analysis of variance (ANOVA), and LSD test. Statistical significance was set at $P < .05$, indicating meaningful differences between groups.

RESULTS

Comparision of Baseline Characteristics

Baseline demographic characteristics and clinical parameters exhibited no significant differences between the two groups ($P > .05$), see Table 1, indicating comparability in terms of patient profiles and baseline health status.

Hemodynamic Stability Analysis

No significant differences were observed in SBP, SPO_2, and HR between the two groups at each time point ($P > .05$). Throughout the surgical procedure, both groups exhibited a declining trend in SBP and HR compared to baseline (T_0). Additionally, SBP and HR increased postoperatively. Notably, both groups demonstrated minor fluctuations in SPO_2 levels during surgery, see Figure 1.

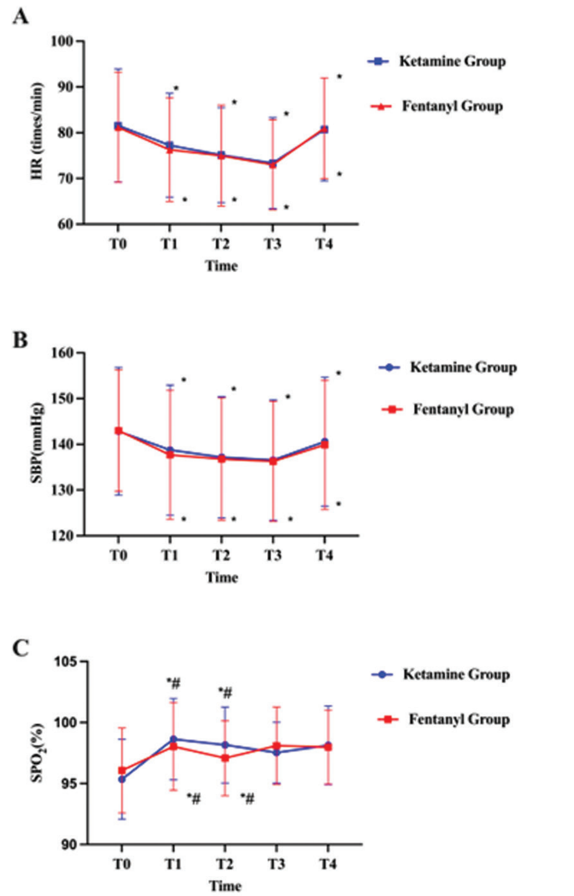
Postoperative Pain Assessment

Prior to surgery, VAS scores did not differ significantly between the two groups ($P > .05$). However, at 12 hours, 24 hours, and 48 hours postoperatively, VAS scores were significantly lower in both study groups compared to baseline (T_0), with the ketamine group exhibiting lower scores than the fentanyl group ($P < .05$), see Figure 2.

Stress Indicator Levels

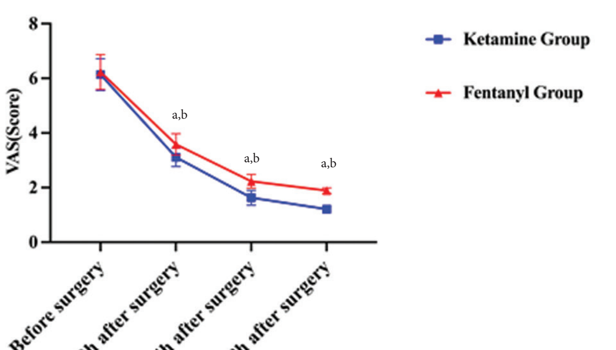
Before surgery, there were no significant differences in stress indicator levels between the two groups ($P > .05$). However, postoperatively, Cor, epinephrine, and NE levels increased in both groups. Notably, these levels were lower in

Figure 1. Comparison of Haemodynamic Parameters Between the Two Groups. (A) Change in Systolic Blood Pressure (SBP); (B) Comparison of Oxygen Saturation (SPO_2); (C) Comparison of Heart Rate (HR).



Note: This figure illustrates the comparison of hemodynamic parameters between the ketamine and fentanyl groups throughout the surgical procedure. Changes in SBP, SPO_2, and HR are depicted to evaluate the variations between the two groups.

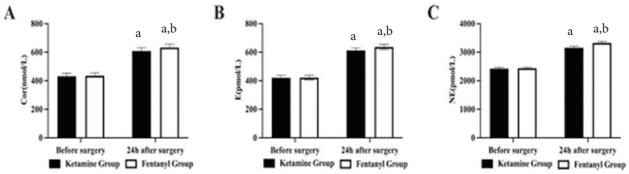
Figure 2. Comparison of Visual Analogue Scale (VAS) Scores between the Two Groups.



[a]indicates significance compared to the preoperative values
[b]denotes significance compared to the fentanyl group.

Note: This figure illustrates the comparison of Visual Analogue Scale (VAS) scores between the ketamine and fentanyl groups of patients.

Figure 3. Comparison of Stress Response Indicators between the Two Groups. (A) Comparison of Cortisol (Cor); (B) Comparison of Epinephrine (E); (C) Comparison of Norepinephrine (NE). This figure depicts the comparison of stress response indicators, including cortisol (Cor), epinephrine (E), and norepinephrine (NE), between the ketamine and fentanyl groups.



[a]indicates significance compared to the preoperative values
[b]denotes significance compared to the fentanyl group.

Table 2. Incidence of Adverse Reactions in the Two Groups [n (%)]

Variable	Ketamine Group (n=49)	Fentanyl Group (n=51)	χ^2	*P* value
Dizziness	1 (2.04)	3 (5.88)		
Drowsiness	1 (2.04)	2 (3.92)		
Nausea And Vomiting	1 (2.04)	4 (7.84)		
Respiratory Depression	0 (0.00)	2 (3.92)		
Total	3 (6.12)	11 (21.57)	4.952	.026

Note: This table presents the incidence of adverse reactions observed in the ketamine and fentanyl groups during the study. Data are presented as [n (%)]. The Chi-square test (χ^2) was used to compare the incidence of adverse reactions between the two groups. $P < .05$ were considered statistically significant.

the ketamine group compared to the fentanyl group ($P < .05$), see Figure 3.

Incidence of Adverse Reactions

The ketamine group exhibited a significantly lower incidence of adverse reactions compared to the fentanyl group ($P < .05$), see Table 2. This finding suggests that the anesthesia regimen involving dexmedetomidine combined with either ketamine may lead to a reduction in perioperative complications.

DISCUSSION

Fractures of the proximal femur represent major surgical procedures, often associated with intense pain and psychological stress. This surgical trauma triggers the sympathetic-adrenergic medullary system, leading to the release of various substances such as theophylline and aldosterone.[12-15] Additionally, it activates other physiological systems, promoting the secretion of antidiuretic hormones and glucocorticoids. These responses can result in tachycardia and, in severe cases, cardiovascular complications, particularly pronounced in elderly patients, thus posing significant risks.[15]

Elderly individuals with proximal femur fractures necessitate postoperative rehabilitation exercises to mitigate complications like thrombosis and joint stiffness. Consequently, they demand detailed attention to anesthetic analgesia management.[16] Dexmedetomidine, an imidazole derivative, is a potent α2A adrenergic agonist recognized for its strong analgesic, sedative, and anxiolytic properties.[16] Research indicates that upon administration, dexmedetomidine interacts with α2A receptors located both presynaptically and postsynaptically in neuronal synapses. This interaction leads to the inhibition of norepinephrine synthesis and secretion, thereby interrupting the transmission of pain signals.[16,17]

Although dexmedetomidine exhibits significant analgesic properties, achieving adequate pain control for proximal femoral fractures solely with dexmedetomidine can be challenging. Therefore, a combination of medications is frequently employed in clinical anesthesia.[17] Ketamine and fentanyl are frequently utilized as intravenous anesthetic agents. In our study, we observed that the analgesic efficacy of the dexmedetomidine-ketamine combination surpassed that of the dexmedetomidine-fentanyl combination.

Ketamine's efficacy results from its selective inhibition of the medial thalamic nucleus, which impedes the ascending transmission of the spinal cord's reticular tract while stimulating the limbic system, resulting in potent anesthetic effects. Additionally, ketamine administration intravenously can extend postoperative analgesia duration, lower the required dosage of postoperative analgesics, and serve in the acute management of pain.[18]

Research indicates that elevated doses of ketamine may reduce synaptic plasticity, impair learning and memory functions, and heighten the likelihood of postoperative cognitive impairment. Hence, careful dosage adjustments for ketamine are imperative in clinical practice.[19] Furthermore, dexmedetomidine exhibits pronounced synergistic effects with ketamine while also mitigating ketamine's cardiac stimulatory effects and adverse impacts on the central nervous system.[20]

Fentanyl, a potent narcotic analgesic commonly administered during perioperative periods for fracture surgery, possesses an analgesic potency 80 times greater than morphine.[21] Its efficacy establishes within 1 to 2 minutes following intravenous injection, offering rapid onset but brief duration.[19,20] Despite the combination of dexmedetomidine with fentanyl in the study, the analgesic effect remained relatively short-lived, accompanied by a higher incidence of postoperative adverse effects compared to the dexmedetomidine-ketamine combination. It reiterates the efficacy and safety of dexmedetomidine-ketamine in alleviating pain associated with proximal femur fractures in the elderly.

It has been noted that the analgesic efficacy of fentanyl and ketamine correlates with plasma concentration. Compared to a rapid single injection, a slower administration allowing the plasma concentration to reach the target level results in fewer side effects and greater overall benefit.[22] Hence, in clinical settings, a gradual infusion of fentanyl can be considered to optimize its anesthetic effect and extend its analgesic duration.

The stress response index serves as a tangible measure of the body's reaction to surgical trauma. Our findings indicate that the combination of dexmedetomidine and ketamine is notably superior in mitigating the body's stress response. This observed efficacy is closely linked to the sustained and potent analgesic properties of dexmedetomidine when used concomitantly with ketamine.

In terms of hemodynamics, both groups in this study exhibited comparable levels of relevant indicators, suggesting that the dexmedetomidine-ketamine combination did not confer a significant advantage over the dexmedetomidine-fentanyl combination in terms of hemodynamic stabilization. Specifically, from T_1 onwards, both groups experienced a decrease in SBP and HR compared to baseline (T_0). Throughout the operation, SBP and HR displayed a declining trend in both groups, correlating with the duration of the procedure, and showed a subsequent increase at the end of the operation.

Both groups exhibited minor fluctuations in SPO_2 throughout the operation, a phenomenon likely attributed to dexmedetomidine's role in reducing norepinephrine release and inhibiting central sympathetic excitability. However, we are inclined to believe that the dexmedetomidine-ketamine combination promotes hemodynamic stability. The reason for this result may be related to the limited sample size, and we plan to validate our hypothesis by increasing the sample size and minimizing statistical variability in future studies.

Elderly patients with proximal femur fractures face unique challenges due to potential exacerbation of underlying conditions like hypertension and heart disease, leading to increased organismal stress and a poorer prognosis postoperatively. Our findings reveal that the ketamine group exhibited a lower incidence of adverse reactions compared to the fentanyl group, indicating that the dexmedetomidine-ketamine combination offers a superior safety profile over the dexmedetomidine-fentanyl combination.

It has been demonstrated that ketamine effectively augments the sedative properties of dexmedetomidine and counteracts its sympathetic depressant effects, thereby lowering the occurrence of adverse reactions.[23] Additionally, the anxiolytic properties of ketamine have been documented in the literature,[24] proving effective in mitigating the impact of surgical and anesthetic stimuli on patients' vital signs. However, our findings indicate that precautions should be exercised to mitigate potential adverse effects when employing the dexmedetomidine-ketamine combination.

Study Limitations

There are several limitations to consider in this study. Firstly, the relatively small sample size, while representative of typical clinical patients, may introduce statistical variability. Secondly, the assessment of postoperative pain levels relied on subjective VAS scores and lacked objective measures such as pain biomarkers. Additionally, patient-reported perceptions of analgesic efficacy were not incorporated into the analysis. Finally, the dosing and infusion duration of dexmedetomidine and ropivacaine were not standardized and were subject to individual anesthesiologist judgment, potentially influencing study outcomes. These limitations should be addressed in future studies.

CONCLUSION

In conclusion, the combination of dexmedetomidine and ketamine demonstrates remarkable efficacy in anesthesia for proximal femur fractures in elderly patients. This combination substantially alleviates postoperative pain and stress while also lowering the occurrence of adverse reactions. Importantly, it proves to be both safe and effective, underscoring its potential as a preferred approach in managing such fractures in the elderly population.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

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Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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