The effects of early femoral nerve block intervention on preoperative pain management and incidence of postoperative delirium geriatric patients undergoing trochanteric femur fracture surgery: A randomized controlled trial

Ali İhsan Uysal, M.D.,1 Başak Altıparmak, M.D.,4 Eylem Yaşar, M.D.,1 Mustafa Turan, M.D.,4 Umut Canbek, M.D.,2 Nigar Yılmaz, M.D.,3 Semra Gümüş Demirbilek, M.D.4

1Department of Anesthesiology and Reanimation, Muğla Sıtkı Koçman University Training and Research Hospital, Muğla - Turkey
2Department of Orthopedics and Traumatology, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla - Turkey
3Department of Biochemistry, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla - Turkey
4Department of Anesthesiology and Reanimation, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla - Turkey

ABSTRACT

BACKGROUND: Hip fracture is a common clinical problem which causes severe pain in geriatric patients. However, severe pain following fracture may bring on mental disorders and delirium. A neuroinflammatory response with IL-6 and IL-8 has been shown to be associated with the pathophysiology of delirium. In this study, our primary hypothesis is that preoperative femoral nerve block (FNB) intervention in geriatric patients will more effectively attenuate pain following trochanteric femur fracture than the preoperative paracetamol application. Our secondary hypothesis is that interleukin levels (IL-6, IL-8) in cerebrospinal fluid (CSF) will be lower in the femoral nerve block group than the paracetamol group. Our tertiary hypothesis is that the incidence of postoperative delirium will be lower in the femoral nerve block group.

METHODS: The patients over 65 years of age with ASA status II-IV and admitted to the Emergency Service for femur fracture were included in this study. Recommendations of the “delirium prevention table” were applied to all of the patients at arrival. In the first group, 15 mg/kg paracetamol was administered intravenously every eight hours. In the second group, femoral nerve blockage was performed, and a catheter was placed. Then, 0.5 mL/kg bupivacaine 0.25% was applied every eight hours. In both groups, pain scores four hours after interventions were recorded. All patients were operated within 48 hours under spinal anesthesia. During spinal anesthesia, 2 mL of CSF samples were taken from all patients for analysis of IL-6 and IL-8 cytokines, and pain scores during positioning were recorded.

RESULTS: VAS scores four hours after the first preoperative pain treatment and during the positioning for regional anesthesia were significantly lower in the femoral nerve block group. IL-8 levels are significantly lower in the femoral nerve block group but not in IL-6 levels. The incidence of delirium was less in the femoral nerve block group, but the difference was not statistically significant.

CONCLUSION: The femoral nerve block was more effective in preoperative pain management of trochanteric femur fracture and preventing pain during regional anesthesia application. The mean IL-8 level was lower in the femoral nerve block group when compared to the paracetamol group. There is no difference in the postoperative delirium incidence between groups.

Keywords: Delirium; femoral nerve block; hip fracture; interleukin 8.
INTRODUCTION

Hip fracture is a common clinical problem in geriatric patients with a high mortality rate. The incidence of severe pain in the first 24 hours after femur fractures is 50–70%.[1] Previous studies[2,3] reported that the majority of patients with hip fracture had received inadequate pain treatment and almost 40% of the patients have never received any analgesic drugs in the preoperative period. However, it has been suggested that adequate pain treatment should be commenced before admission to the hospital[4] since the severe pain following fracture may cause mental disorders and delirium.[5] Preoperative health status and cognitive functional capacity of the patients, neurotoxic effects of anesthetic agents, perioperative events during surgery and the used cement for prosthetic implantation are associated with postoperative cognitive problems.[6]

Delirium is one of the most common complications in hospitalized elderly patients. Previous studies have shown that delirium is associated with both short and long-term poor outcomes. It is a medical condition that must be treated urgently because it significantly increases morbidity and mortality, prolongs the length of hospital stay, and may lead to a decrease in functional capacity.[7] The pathophysiological mechanisms of delirium are not precise, a neuroinflammatory response is suggested to play a role.[8] Up to date, many studies have analyzed different serum inflammatory markers in order to elucidate the pathophysiology of delirium. IL-6 and IL-8 have been shown to be associated with delirium.[9,10]

In this study, our primary hypothesis is that preoperative femoral nerve block (FNB) intervention in geriatric patients will more effectively attenuate pain following trochanteric femur fracture than the preoperative paracetamol application. Our secondary hypothesis is that interleukin levels (IL-6, IL-8) in cerebrospinal fluid (CSF) will be lower in the femoral nerve block group than the paracetamol group. Our tertiary hypothesis is that the incidence of postoperative delirium will be lower in the femoral nerve block group.

MATERIALS AND METHODS

After the approval of the Muğla Sıtkı Koçman University, Clinical Research Ethics Committee in 17.05.2016 with a decision number 2016/50, 114 patients who were over 65 years of age with ASA status II-IV and admitted to the Emergency Department due to trochanteric femur fracture were included in this study. Patients with preexisting delirium at the admission to emergency service, femur fracture due to metastatic carcinoma, bupivacaine allergy, cholinesterase inhibitors or levodopa medication, parkinsonism or epilepsy, and a contraindication for nerve blockage were excluded from this study.

Anesthesia Procedure

All patients were operated within 48 hours after admission to the hospital. If the operation was delayed more than 48 hours, the patients were excluded from this study. In the operation room, ECG, pulse oximeter and noninvasive blood pressure monitoring were performed. All patients were positioned for the spinal-epidural combined block. The pain occurred during positioning was assessed using VAS and recorded. During spinal anesthesia, 2 mL of CSF samples were taken from all of the patients. These samples were stored at -80º until the CSF specimens were analyzed for IL-6 and IL-8 cytokines using the enzyme-linked immunoassay method (sandwich method) in the Biochemistry Laboratory. For spinal anesthesia, 10 mg bupivacaine + 20 mcg fentanyl were administered intrathe-
The effect of early femoral nerve block on postoperative pain and delirium cally. Following spinal anesthesia, femoral nerve catheters of patients in Group II were removed. After the operation, all patients received 0.125% bupivacaine + 100 mcg fentanyl through the epidural catheter with an infusion rate of 5 ml/h for postoperative pain control. Pain levels of patients were evaluated at the postoperative 1st, 4th, 12th and 24th hours by 100-mm VAS. The delirium status of patients was assessed using “Delirium Rating Scale-R-98 (DRS-R-98)” in the postoperative period for three days.

Evaluation of the Data
The power analysis of the study was based on studies investigating the development of delirium after femur fracture operation. After the calculations were made with $\alpha=0.05$ and 80% power ($1-\beta=0.8$), the number of patients required in each group was found to be 45. It was assumed that there could be a 20% drop out during the study; therefore, 55 patients were included in each group. For the statistical analysis, Statistical SPSS 20.0 (statistical package for social sciences for Windows 16.0) program was used. The normality tests of the distributions of the variables were performed using the Kolmogorov-Smirnov test. For numerical values with a normal distribution, the difference between the averages of the variables was evaluated using one-way ANOVA or Independent Sample t-test. The Wilcoxon test was used for the analysis of the abnormally distributed variables. For all statistical tests, $p<0.05$ was considered statistically significant. Chi-square analysis was applied for categorical variables. Pearson test was applied for correlation.

RESULTS
All in all, 110 patients were included in this study. Fourteen patients were excluded due to delay in the operation time, three patients died in the early postoperative period, and two patients were excluded due to change in anesthesia procedure. Consequently, 45 patients in Group I and 46 patients in Group II completed the study (Fig 1). The demographic variables of the patients are listed in Table 1. There was no significant difference between groups.

Mean VAS scores at the 4th hour after first preoperative pain treatment and during the positioning for regional anesthesia were significantly lower in Group II ($p<0.01$). None of the patients’ required rescue analgesic in Group II. However, seven patients needed rescue analgesic in Group I ($p\leq0.05$) during the preoperative period (Table 2). There was no significant difference regarding VAS scores during the postoperative period between groups ($p>0.05$) (Table 2).

![Figure 1. Operation chart.](#)
According to assessment with DRS-R-98, the occurrence of delirium was less in group II (9 patients in Group I, five patients in Group II) in the early postoperative period. However, the difference was not statistically significant between groups (p>0.05).

IL-8 levels were significantly lower in Group II than Group I (p<0.01). The mean level of IL-8 in patients who developed delirium in Group I was 0.1885±0.13 and in Group II was 0.111±0.025. The IL-6 levels were similar between groups (p>0.05) (Table 3).

A negative correlation was detected between preoperative MMT scores and postoperative 1st, 2nd, 3rd hour delirium scores in both groups. This relation was statistically significant (1st day: r=-0.47, p<0.001, 2nd day: r=-0.49, p<0.001, 3rd day: r=-0.52, p<0.01).

DISCUSSION

In the present study, early intermittent FNB was found to be more effective than intravenous paracetamol administration for pain management of geriatric patients following femur trochanteric fracture. However, there was no significant difference between groups concerning delirium development. Although mean IL-8 levels were significantly lower in the FNB group, mean IL-6 levels were similar between groups.

One of the main problems after hip fracture is severe pain. Up until now, various methods have been used for both preoperative and postoperative pain management.[12] In the preoperative period, intravenous administration of non-steroid drugs and opioids[13,14] and performing nerve blocks[15,16] have been frequently used for pain control. However, pain after femur fracture may not arise solely from the hip joint. The damaged soft tissue after surgery is also a severe pain source, and intravenous agents may be inadequate in postoperative pain treatment. Therefore, the use of peripheral blocks in the preoperative period has gained popularity in recent years. Some previous studies reported that the fascia iliaca block could provide effective analgesia after femur fracture in the elderly.[16,17]

Moreover, Kassam et al.[18] found the fascia iliaca block to provide a morphine-sparing effect in the preoperative period. In the present study, we aimed to apply an intermittent nerve block (instead of a single-shot block) by placing a nerve catheter; therefore, we preferred to perform FNB and provided bet-

### Table 1. Preoperative features of the patients

| Group I (n=45) | Group II (n=46) |
|---------------|----------------|
| Age           | 82.04±6.83     | 81.41±8.06    |
| Gender (Female/Male) | 25/20          | 26/20         |
| Preop Minimental Test score | 16.12±6.11     | 17.05±6.44    |
| Preop delirium score | 3.52±3.12     | 1.75±2.14    |

### Table 2. Preoperative, intraoperative, postoperative VAS scores and the number of patients who required preoperative rescue analgesic among the groups

|                      | Group I       | Group II      | p   |
|----------------------|---------------|---------------|-----|
| VAS scores at the 4th hour | 4.47±1.06    | 3.32±0.92     | <0.01|
| Preoperative rescue analgesic need (n) | 7          | 0            | 0.05 |
| VAS scores during positioning | 5.55±1.77    | 4.02±1.80     | <0.01|
| VAS scores at postop 1st hour | 3.30±1.06    | 3.12±1.09     | 0.47 |
| VAS scores at postop 4th hour | 3.22±1.12    | 3.45±0.71     | 0.28 |
| VAS scores at postop 12th hour | 3.17±0.74    | 3.07±0.79     | 0.56 |
| VAS scores at postop 24th hour | 3.12±0.72    | 2.82±0.67     | 0.06 |

VAS: Visual Analogue Scale.

### Table 3. Number of patients with delirium among groups and IL-6, IL-8 levels in CSF samples

|                      | Group I       | Group II      | p   |
|----------------------|---------------|---------------|-----|
| Delirium             | 9 (20.0%)     | 5 (10.9%)     | 0.227|
| Interleukin levels-6 | 3.30±1.57     | 3.12±1.44     | 0.57 |
| Interleukin levels-8 | 73.15±73.35   | 43.23±38.52   | 0.017|
| Interleukin levels-8 (with delirium) | 0.1885±0.13 | 0.111±0.025 | 0.213|
| Interleukin levels-6 (with delirium) | 2.29±1.10     | 3.14±0.57     | 0.213|

IL: Interleukin levels; CSF: Cerebrospinal fluid.
shown to reduce the postoperative delirium incidence.\[21\] In starting from the early preoperative period was previously of postoperative delirium. Moreover, adequate pain control ture. They found the incidence of delirium 16% and reported that severe pain was highly associated with the development of postoperative delirium. Moreover, adequate pain control starting from the early preoperative period was previously shown to reduce the postoperative delirium incidence.\[21\] In our study, preoperative pain scores were significantly lower in the cyclic FNB group. Although the postoperative delirium inc

Delirium is one of the most common postoperative complications in elderly patients with an incidence of 5% and 61% after femur fracture surgery.\[20\] The underlying pathophysiology is not fully understood; however, postoperative pain is believed to trigger delirium development in elderly patients. Morrison et al.\[13\] assessed 541 patients with a femur fracture. They found the incidence of delirium 16% and reported that severe pain was highly associated with the development of postoperative delirium. Moreover, adequate pain control starting from the early preoperative period was previously shown to reduce the postoperative delirium incidence.\[21\] In our study, preoperative pain scores were significantly lower in the cyclic FNB group. Although the postoperative delirium inc

Central nervous system inflammation that arises from systemic inflammation is another blamed hypothesis for delirium development after femur fracture. Previously, IL-6 and IL-8 were reported to be higher in geriatric patients who developed delirium after femur fracture operation.\[9,10\] In the study of MacLullich et al.,\[22\] the increase of IL-8 levels in the CSF was reported to be associated with postoperative delirium. Similarly, elevated IL-6 level was also reported as the signature of post-stroke delirium in a recent study.\[23\] In the present study, IL-8 levels were found significantly lower in the FNB group. We think that the most likely reason for this result is the attenuation of the inflammatory response by effective pain management with FNB. On the other hand, we did not detect any differences in IL-6 levels between groups. Similar to our results, Lemstra et al.\[24\] did not find any association between preoperative IL-6 and the incidence of delirium after a hip surgery. We think that the data concerning IL-6 and IL-8 are still limited and conflicting.

The preoperative cognitive function level of patients are thought to play an essential role in the development of delirium.\[25,26\] Our results are consistent with the current literature, we detected a negative correlation between preoperative MMT scores and the incidence of delirium in the first three postoperative days. Moreover, there was a positive correlation between preoperative MMT scores and delirium scores.

Limitations
Our study has some limitations: (1) Although the sample size is large enough to meet the primary outcome, our study is probably underpowered to detect a relation between the incidence of delirium and cytokine levels, or incidence of delirium and femoral nerve block. (2) The release of IL-6 and IL-8 may also be affected by other factors, such as the current metabolic condition, the usage of previous medications, the previous story of fractures and operations. Therefore, we may not be able to standardize these factors during the study period because of the comorbidities of patients. (3) Preoperative erythrocyte transfusion to some patients according to the “delirium prevention program” may affect cytokine responses.

Conclusions
We found that intermittent femoral nerve block was more effective in preoperative pain management of trochanteric femur fracture and preventing pain during regional anesthesia application. Moreover, the mean IL-8 level was lower in the femoral nerve block group when compared to the paracetamol group. However, we could not find a difference in the postoperative delirium incidence between groups.

Ethics Committee Approval: Approved by the local ethics committee (date: 17.05.2016, no: 2016/50).

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES
1. Mouzopoulos G, Vasiladis G, Lasanianos N, Nikolaras G, Morakis E, Kaminaris M. Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study. J Orthop Traumatol 2009;10:127−33. [CrossRef]
2. Holdgate A, Shepherd SA, Hudson S. Patterns of analgesia for fractured neck of femur in Australian emergency departments: Original Research. EMA - Emerg Med Australas 2010;22:3−8. [CrossRef]
3. Simpson PM, Bendall JC, Tiedemann A, Lord SR, Close JC. Provision of out-of-hospital analgesia for older fallers with suspected fractures: Above par, but opportunities for improvement exist. Acad Emerg Med 2013;20:761−8.
4. Aronsson K, Björkheldh I, Wäreklint Sundström B. Prehospital emergency care for patients with suspected hip fractures after falling - older patients’ experiences. J Clin Nurs 2014;23:3115−23. [CrossRef]
5. Julieb V, Krogsseth M, Skovlund E, Engedal K, Ranhoff AH, Wylle TB. Delirium is not associated with mortality in elderly hip fracture patients. Dement Geriatr Cogn Disord 2010;30:112−20. [CrossRef]
6. Sïcari D, Cattano D, Hussain M, Rosenstein A. Perioperative management of proximal hip fractures in the elderly: The surgeon and the anes-
Inouye SK, Westendorp R, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911–22. [CrossRef]

Cunningham C, MacLullich AM. At the end of the psychoneuroimmunological spectrum: Delirium as a maladaptive sickness behavior response. Brain Behav Immun 2013;28:1–13. [CrossRef]

van Munster BC, Koevoet JC, Zwijnderman AH, Levi M, Wiersinga WJ, De Rooy SE. Time-course of cytokines during delirium in elderly patients with hip fractures. J Am Geriatr Soc 2008;56:1704–9. [CrossRef]

de Rooy SE, van Munster BC, Koevoet JC, Levi M. Cytokines and acute phase response in delirium. J Psychosom Res 2007;62:521–5. [CrossRef]

Björkelund KB, Hommel A, Thorngren KG, Gustafsson L, Larsson S, Lundberg D. Reducing delirium in elderly patients with hip fracture: A multi-factorial intervention study. Acta Anaesthesiol Scand 2010;54:5678–88. [CrossRef]

Cryer B, Pageau P, Woo MY, Perry JJ. Regional nerve blocks for hip and femoral neck fractures in the emergency department: A systematic review. Can J Emerg Med 2016;18:37–47. [CrossRef]

Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci 2003;58:76–81. [CrossRef]

Cryer B, Barnett MA, Wagner J, Wilcox CM. Overuse and Misperception of Nonsteroidal Anti-Inflammatory Drugs in the United States. Am J Med Sci 2016;352:472–80. [CrossRef]

Nie H, Yang YX, Wang Y, Liu Y, Zhao B, Luu B. Effects of continuous fascia iliaca compartment blocks for postoperative analgesia in patients with hip fracture. Pain Res Manag 2015;20:210–2. [CrossRef]

Castillon P, Veloso M, Gómez O, Salvador J, Bartra A, Anglés F. Fascia iliaca block for pain control in hip fracture patients. [Article In English, Spanish] Rev Esp Cir Ortop Traumatol 2017;61:383–9. [CrossRef]

Ansoy D, Gardner MJ, Amanatullah DF, Huddleston JJ 3rd, Goodman SB, Maloney WJ, et al. Continuous femoral nerve catheters decrease opioid-related side effects and increase home disposition rates among geriatric hip fracture patients. J Orthop Trauma 2017;31:186–9. [CrossRef]

Kassam AM, Gough AT, Davies J, Yalagadda R. Can we reduce morphine use in elderly, proximal femoral fracture patients using a fascia iliaca block? Geriatr Nurs 2018;39:84–7. [CrossRef]

Ranjit S, Pradhan BB. Ultrasound guided femoral nerve block to provide analgesia for positioning patients with femur fracture before subarachnoid block: Comparison with intravenous fentanyl. Kathmandu Univ Med J 2016;14:125–9.

Robertson BD, Robertson TJ. Postoperative delirium after hip fracture. J Bone Joint Surg Am 2006;88:2060–8. [CrossRef]

Hamrick I, Meyer F. Perioperative management of delirium and dementia in the geriatric surgical patient. Langenbecks Arch Surg 2013;398:947–55. [CrossRef]

MacLullich AMJ, Edelshain BT, Hall RJ, de Vries A, Howie SEM, Pearson A, et al. Cerebrospinal fluid interleukin-8 levels are higher in hip fracture patients with peri-operative delirium versus controls. JAGS 2015;59:1151–3. [CrossRef]

Kowalska K, Klimiec E, Weglarczyk K, Pera J, Slowik A, Siedlar M, et al. Reduced ex vivo release of pro-inflammatory cytokines and elevated plasma interleukin-6 are inflammatory signatures of post-stroke delirium. J Neuroinflammation 2018;15:111. [CrossRef]

Lemstra AW, Kaliavarst KJ, Vreeswijk R, van Gool WA, Eikelenboom P. Pre-operative inflammatory markers and the risk of postoperative delirium in elderly patients. Int J Geriatr Psychiatry 2008;23:943–8. [CrossRef]

MacLullich AMJ, Ferguson KJ, Miller T, de Rooij SEJA, Cunningham C. Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses. J Psychosom Res 2008;65:229–38. [CrossRef]

Adogwe O, Elsamadicy AA, Vuong FD, Fialkoff J, Cheng J, Karikari JO, et al. Association between baseline cognitive impairment and postoperative delirium in elderly patients undergoing surgery for adult spinal deformity. J Neurousurg Spine 2018;28:103–8. [CrossRef]