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SCIENTIFIC ARTICLE

Changes in the tumor necrosis factor-α level after an ultrasound-guided femoral nerve block in elderly patients with a hip fracture

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KEYWORDS
Cytokines;
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Tumor necrosis factor alpha

Abstract
Background and objectives: An ultrasound guided femoral nerve block is an established analgesic method in patients with a hip fracture. Elevated cytokine levels correlate with poor patient outcomes after surgery. Hence, the aim of the study was to describe the levels of tumor necrosis factor-α after an ultrasound-guided femoral nerve block in elderly patients having a femoral neck fracture.
Methods: A total of 32 patients were allocated into two treatment groups: 16 patients (femoral nerve block group; ultrasound-guided femoral nerve block with up to 20 mL of 0.3 mL.kg^{-1} of 0.5% bupivacaine and intravenous tramadol) and 16 patients (standard management group; up to 3 mL of 0.9% saline in the femoral sheath and intravenous tramadol). Tumor necrosis factor-α and visual analogue scale scores were evaluated immediately before the femoral nerve block and again at 4, 24, and 48 h after the femoral nerve block. All surgery was performed electively after 48 h of femoral nerve block.
Results: The femoral nerve block group had a significantly lower mean tumor necrosis factor-α level at 24 (4.60 vs. 8.14, $p < 0.001$) and 48 h (5.05 vs. 8.56, $p < 0.001$) after the femoral nerve block, compared to the standard management group. The femoral nerve block group showed a significantly lower mean visual analogue scale score at 4 (3.63 vs. 7.06, $p < 0.001$) and 24 h (4.50 vs. 5.75, $p < 0.001$) after the femoral nerve block, compared to the standard management group.

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Conclusions: Ultrasound-guided femoral nerve block using 0.3 mL.kg^{-1} of 0.5% bupivacaine up to a maximum of 20 mL resulted in a significant lower tumor necrosis factor-α level.

PALAVRAS-CHAVE
Citocinas;
Nervo femoral;
Fratura de quadril;
Resposta inflamatória;
Fator de necrose tumoral alfa

Alterações no nível de TNF-α após bloqueio do nervo femoral guiado por ultrassom em idosos com fratura de quadril

Resumo
Justificativa e objetivos: O bloqueio do nervo femoral guiado por ultrassom é um método analgésico estabelecido em pacientes com fratura de quadril. Níveis elevados de citocinas estão correlacionados com resultados desfavoráveis para o paciente após a cirurgia. Portanto, o objetivo do estudo foi descrever os níveis do fator de necrose tumoral alfa após bloqueio do nervo femoral guiado por ultrassom em pacientes idosos com fratura do colo de fêmur.
Métodos: No total, 32 pacientes foram alocados em dois grupos de tratamento: 16 pacientes (grupo bloqueio do nervo femoral; bloqueio do nervo femoral guiado por ultrassom com até 20 mL de bupivacaína a 0,5% (0,3 mL.kg^{-1}) e tramadol intravenoso) e 16 pacientes (grupo tratamento padrão, até 3 mL de solução salina a 0,9% na bainha femoral e tramadol intravenoso). Os escores do fator de necrose tumoral alfa e da Escala Visual Analógica foram avaliados imediatamente antes do bloqueio do nervo femoral e novamente em 4, 24 e 48 horas pós-bloqueio do nervo femoral. Todas as cirurgias foram realizadas de forma eletiva após 48 horas de bloqueio do nervo femoral.
Resultados: O grupo bloqueio do nervo femoral teve um nível médio de fator de necrose tumoral alfa significativamente menor em 24 (4,60 vs. 8,14, $p < 0,001$) e 48 horas (5,05 vs. 8,56, $p < 0,001$) pós-bloqueio do nervo femoral, comparado ao grupo tratamento padrão. O grupo bloqueio do nervo femoral apresentou uma média significativamente menor no escore da Escala Visual Analógica em 4 (3,63 vs. 7,06, $p < 0,001$) e 24 horas (4,50 vs. 5,75, $p < 0,001$) pós-bloqueio do nervo femoral, em comparação com o grupo tratamento padrão.
Conclusões: O bloqueio do nervo femoral guiado por ultrassom utilizando 0,3 mL.kg^{-1} de bupivacaína a 0,5% até o máximo de 20 mL resultou em um nível significativamente menor de fator de necrose tumoral alfa.

Introduction

Hip fractures are common painful injuries in adults and sources of increasing mortality and morbidity among the elderly.[1] Moreover, geriatric patients are particularly susceptible to profound inflammatory responses to trauma that increase mortality and morbidities, including infectious complications.[2] Thus, minimizing inflammation and pain is important for reducing mortality and morbidity. An ultrasound (US) guided femoral nerve block (FNB) using a single local anesthetic injection is an established and effective analgesic method in patients with a hip fracture. Beaudoin et al. reported that an FNB group using 25 mL of bupivacaine showed significantly reduced pain compared with an intravenous morphine group.[3]

A significant inflammatory response occurs after major musculoskeletal injury.[4] The severity of the inflammatory response is important in many disease states and determines whether the disease resolves or becomes chronic. The role of cytokines in inflammatory dysregulation has been well-established. Recent studies suggested that elevated cytokine levels correlate with poor patient outcomes.[5–7] In particular, one pro-inflammatory cytokine, tumor necrosis factor-α (TNF-α), is an important marker of inflammatory activity.[8] Furthermore, a previous study reported that injured patients with high concentrations of TNF-α were at an increased risk of death.[9]

The aim of this study was to evaluate the change in TNF-α, an important inflammatory cytokine, after a US-guided FNB in Emergency Department (ED) elderly patients with a femoral neck fracture. Our hypothesis was that the level of TNF-α would be significantly altered after the FNB.

Methods

Study design and patient selection

A randomized controlled clinical trial with two study groups was performed. This clinical trial protocol was registered with the Clinical Information Service (available

at: http://cris.nih.go.kr, KCT0001702). The study was approved by our Institutional Review Board and has been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki. Written informed consent was obtained from 34 patients with isolated femoral neck fractures. Patients were eligible if they were aged 60 years and older, had a radiographically proven femoral neck fracture, normal distal neurovascular status, and moderate to severe pain visual analog scale (VAS) score $\geq$5 at the time of enrollment, and were able to consent and actively participate in the study. Patients were excluded if they had refused, had a known history of allergy to the study medicine, prior femoral vascular surgery on the same side as the fracture, and were unable to understand the study protocol. Our study was performed as described by Beaudoin et al.[3] with minor modifications. A total of 36 patients with an isolated femoral neck fracture in the ED were enrolled in this study.

FNB

All procedures were performed by a physician experienced in administering an US-guided FNB. US-guided FNB was performed after the examinations, diagnosis, and consent in the ED. The 16 patients in the FNB group received a US-guided FNB in the supine position using a SonoSite S-nerve instrument (SonoSite Inc., Bothell, WA, USA) with an HFL 38$\times$/13–6 MHz linear array transducer probe. The skin was prepared with a povidone iodine solution. The probe was placed on the side of the affected hip at the level of the groin crease in a transverse orientation for femoral vessels to identify the nerve in cross-section as the hyperechoic structure about 1 cm lateral to the pulsatile artery. A skin bleb was raised 2 cm lateral and distal to the US probe with 2% lidocaine and a 27 gauge needle. After puncturing the wheal, a 22 gauge noncutting spinal needle was introduced at a 45 angle and was advanced under direct vision through the iliopectineal fascia in the immediate proximity of the nerve. Up to 20 mL of 0.3 mL.kg^{-1} of 0.5% bupivacaine was injected along the nerve sheath after initial aspiration. If blood was aspirated, the needle was repositioned. The needle was visualized throughout the procedure to avoid vascular injury and ensure proper drug administration in the correct fascial plane. Local anesthetic was deposited around the femoral nerve sheath and the needle was repositioned if it was outside the desired area. Manual pressure was then applied 1 cm below the injection site for 5 min to facilitate proximal spread of the drug.

The 16 patients in the SM group received a sham injection of normal saline; participants were blinded to the sham injection. The sham procedure was performed as described by Beaudoin et al.[3] and 3 mL of 0.9% saline were injected subcutaneously. Following the injections, intravenous (IV) tramadol was prescribed. The treating physicians were instructed to use IV tramadol and to aim for a 50% reduction in patient discomfort or per-patient request.

Outcome measures

Blood was obtained from a peripheral vein immediately before the FNB to measure the TNF-α level, and again at 4, 24, and 48 h after the procedure. The blood was centrifuged at 3000 rpm for 10 min and the serum was frozen within 30 min at $-70\,^{\circ}$C until the assay was performed. Serum TNF-α was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human TNF-α Quantikine ELISA kit; R&D Systems, Minneapolis, MN, USA).

Pain control was assessed according to an 11 point VAS, which ranged from 0 (no pain) to 10 (most severe pain imaginable), and rescue analgesic use. The VAS score was recorded immediately before the FNB and at 4, 24, and 48 h after completing the procedure. Complications included unwanted signs or symptoms of systemic anesthetic agent use, including vessel puncture (blood aspiration), nerve pain (severe dermatomal pain on injection), hematoma formation, infection, or any adverse events. The amount of rescue analgesia and the occurrence of adverse events (nausea, vomiting, hypotension, desaturation, or pruritis) were measured. Desaturation was defined as room air O_2 saturation <92%. All surgery was performed electively after 48 h of FNB. We reviewed electronic medical records from the ED and recorded the time and dose of analgesics administered. All medication orders were placed in the electronic medical records of the ED. This efficacy variable represented the total amount of opioid received after the study procedure while the patient was in the ED.

Statistical analysis

Sample size was calculated based on a previous study that assessed the effectiveness of an FNB versus standard care with opioids alone.[3] According to that study, 67% of patients who received the FNB showed significant improvement in pain relative to those receiving SM. We estimated that including 32 (16 group) participants would allow us to detect effectiveness with $\alpha = 0.05$, a power of 0.9. All data are expressed as numbers or mean $\pm$ standard deviation. All analyses were performed using SPSS for Windows software (ver. 15.0; SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using Student's *t*-test or the Mann–Whitney *U* test, and categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. TNF-α levels and VAS scores were analyzed by a repeated-measures analysis of variance. *p*-values <0.05 were considered significant.

Results

The median age of the 32 patients was 75 years (range: 61–90 years) and 21 were female. Nineteen patients had a right limb injury whereas the others had a left hip injury. Before the FNB, two patients declined to participate and were excluded. The remaining 34 patients were randomly assigned to one of two groups depending on the use of bupivacaine for the FNB: an FNB using bupivacaine plus intravenous tramadol (FNB group) or a femoral nerve block using saline plus intravenous tramadol (standard management – SM group). After the FNB, two patients were excluded due to hemolysis of the blood sample for the TNF-α assay. Ultimately, 32 patients were included in this study; among them, 16 patients belonged to the FNB group, while the other 16 patients belonged to the SM group (Fig. 1).

All FNB procedures required a single attempt and no complications were observed. A summary of patient

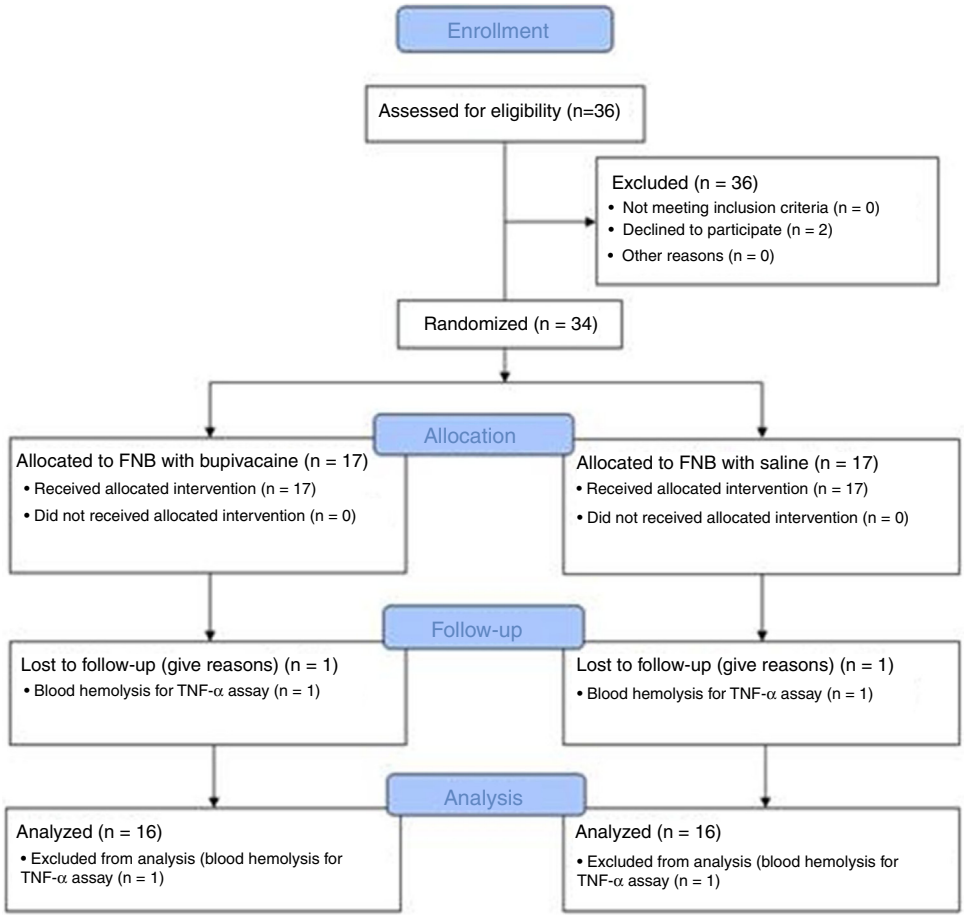

Figure 1 Flow chart of patient enrollment.

Table 1 Patient characteristics and comorbidity. The values represent mean ± standard deviations (range).

	SM ($n = 16$)	FNB ($n = 16$)	p-Value
Male/female	6/10	5/11	1.000
Age (years)	75.2 ± 8.0 (62–88)	76.1 ± 8.9 (61–90)	0.756
Height (cm)	157.3 ± 9.4 (146–171)	156.2 ± 8.2 (145–172)	0.706
Weight (kg)	58.2 ± 9.1 (47–80)	59.3 ± 7.7 (49–72)	0.708
BMI	23.7 ± 4.1 (16–29)	24.4 ± 3.0 (20–29)	0.591
Comorbidity (n)			1.000
Hypertension	6	7	
Diabetes mellitus	5	4	
Coronary heart disease	1	2	
Congestive heart failure	1	1	
Hepatocellular carcinoma	0	1	
Alzheimer's disease	2	1	
Chronic kidney disease	2	2	
Gastric cancer	0	1	
Colorectal cancer	0	1	

SM, standard management; FNB, femoral nerve block; BMI, body mass index; ASA, American Society of Anesthesiologists.

characteristics and comorbidity is presented in Table 1. No differences in age, sex, fracture type or comorbidity were detected between the groups.

The mean VAS score pre-FNB (7.13: FNB group vs. 6.88 SM group, $p = 0.387$) and at 48 h after the FNB (5.13 vs. 5.26, $p = 0.592$) did not differ between the groups. The FNB group had a significantly lower mean VAS score 4 h (3.62 vs. 7.06, $p < 0.001$) and 24 h (4.5 vs. 5.75, $p < 0.001$) after the FNB compared to the SM group (Fig. 2). The mean TNF-α level ($pg.mL^{-1}$) pre-FNB (8.36 vs. 8.15, $p = 0.822$) and at 4 h after

Table 2 Parenteral analgesia, adverse events, and outcome measures.

	SM group	FNB group	*p*-Value
Adverse events			
Nausea/vomiting, *n* (%)	6 (37)	4 (25)	0.446
Hypotension, *n* (%)	4 (25)	2 (12)	0.654
Desaturation, *n* (%)	2 (12)	3 (18)	1.000
Pruritus, *n* (%)	1 (6)	0 (0)	1.000
Parenteral analgesia			
Pre-FNB tramadol (mg) M ± SD	59.4 ± 45.5	62.5 ± 50.0	0.906
Rescue tramadol (mg) M ± SD	53.7 ± 37.7	12.5 ± 9.12	0.001[a]

FNB, femoral nerve block; SM, standard management; M, mean value; SD, standard deviation.
Hypotension was defined as systolic blood pressure <90 mmHg at any time during the study.
Desaturation was defined as room air O_2 saturation <92%.
[a] Statistically significant ($p < 0.05$).

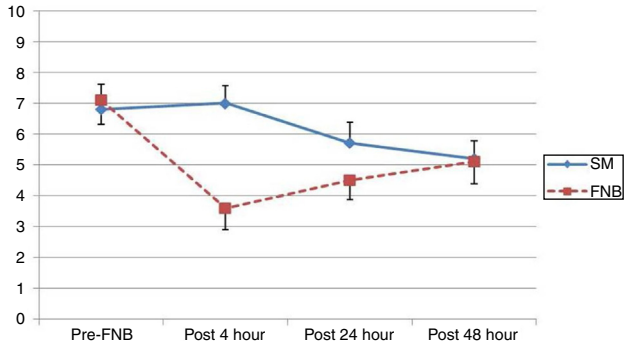

Figure 2 VAS score over time in the FNB and SM groups. Data represent mean ± standard error. FNB, femoral nerve block; VAS, visual analog scale; SM, standard management.

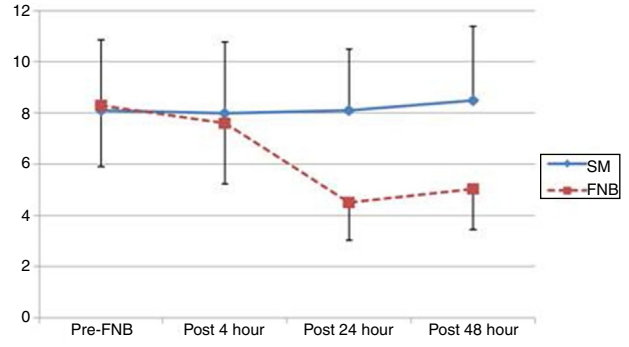

Figure 3 TNF-α levels (pg.mL^{-1}) in the FNB and SM groups. Data represent mean ± standard error. TNF-α, tumor necrosis factor-α; SM, standard management; FNB, femoral nerve block.

the FNB (7.64 vs. 8.08, $p = 0.637$) did not differ between the two groups. The FNB group had a significantly lower mean TNF-α level (pg.mL^{-1}) at 24 (4.60 vs. 8.14, $p < 0.001$) and 48 h (5.05 vs. 8.56, $p < 0.001$) after the FNB, compared to the SM group (Fig. 3).

Parenteral analgesia and adverse events (Table 2)

Patients in the FNB group received significantly less rescue IV tramadol than did patients in the SM group ($p = 0.001$). No difference in adverse events was detected between the groups.

Discussion

In the present study, plasma TNF-α levels decreased significantly 24 and 48 h after the FNB compared with those in the SM group. The lowest value was observed after 24 h, which increased slightly at 48 h but was not significantly different from the 24 h value. The VAS score was the lowest at 4 h but TNF-α began to decrease gradually after 4 h, reaching a minimum at 24 h, which increased slightly at 48 h. This result suggests that the infiltrated bupivacaine in the femoral sheath may have reduced TNF-α at the fracture site, which in turn seems to have slowly decreased the plasma TNF-α concentration after 4 h. The reason for this is that the change in TNF-α level at the local site due to the local anesthetic would have a time delay in affecting the plasma TNF-α level. In a previous study of patients with fractures, the timing of local appearance and concentration gradients of the cytokines IL-6 and IL-8 observed suggested that fracture soft-tissue hematomas and other local sites of tissue injury may be major contributors to systemic cytokine effects.[10] In particular, fracture soft-tissue hematoma serum IL-8 peaked after 46 h and circulating plasma IL-8 appeared after 72 h. Similar to IL-8, our study also suggests that the TNF-α level at the fracture site and plasma TNF-α level may differ at the same time, and that changes in TNF-α level at the fracture site may affect the systemic plasma TNF-α level.

The local response to injury is dominated by inflammatory cells that contribute to the clearance and repair of necrotic tissue.[11] Cytokines released by these inflammatory cells act on sites distant from the origin of their production while a systemic acute-phase response accompanies the local inflammation. The pro-inflammatory cytokine TNF-α is an important marker of inflammatory activity.[8] TNF-α is mainly produced by macrophages and monocytes. It is also produced by T cells after activation and is among the cytokines secreted early after trauma.[12] Increased concentrations of TNF-α are found in acute and chronic inflammatory conditions (e.g., trauma, sepsis, infection, and rheumatoid arthritis).[13] Local anesthetics affect the production of pro-inflammatory cytokines and reduce axonal transport and synthesis of TNF-α.[14] The local anesthetic bupivacaine has a systemic anti-inflammatory effect[15] and reduces cytokine production through local and systemic effects.[16]

The mean onset time of major nerve block using bupivacaine was 20–30 min, and the mean duration was 6–12 h.[17] The duration of bupivacaine is as short as 6–12 h but the VAS score was lower 24 h after FNB than the score in the SM group. The reason for this is that plasma clearance of bupivacaine in elderly patients is lower, so the duration of the effect was longer. In our study, the patients were an average of 75 years old and they had various underlying diseases, such as hypertension, diabetes mellitus, and chronic kidney disease. Sensitivity

to local anesthetics is higher in elderly patients, and the rate of plasma clearance is lower, so the duration of the local anesthetic effect is 2.5-fold longer than that in younger patients.[18–20] The average duration of infiltrated bupivacaine is 6–12 h, but it increases to 40 h in elderly patients. Therefore, bupivacaine remained effective 24 h after FNB, suggesting a lower VAS than that in the SM group. Elderly patients are especially vulnerable to profound inflammatory responses to trauma that would increase mortality and morbidities, including infectious complications.[21] Thus, controlling pain and inflammation in patients by FNB is important to reduce mortality and morbidity.

Study limitation

Our study has several limitations. First, we only measured TNF-α as a pro-inflammatory cytokine. However, TNF-α is involved in systemic inflammation and plays a key role in modulating the acute-phase reaction during infection. Thus, TNF-α is considered a reliable indicator of inflammation. Second, the VAS scoring system is subjective. However, previous studies of preemptive regional blocks for pain control generally adopted the VAS score. Third, we did not evaluate the postoperative level of TNF-α, VAS scores, and complications. Further study is required to define whether decreasing the inflammatory response through an FNB would decrease mortality and complications following a hip fracture postoperatively.

Summary

A US-guided FNB using 0.3 mL.kg^{-1} of 0.5% bupivacaine up to a maximum of 20 mL resulted in significantly lower levels of TNF-α at 24 and 48 h after the FNB. Decreased levels of TNF-α may indicate a low risk of inflammation-induced complications. Additionally, the FNB at the dose in this study provided sufficient analgesic effects.

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Conflicts of interest

The authors declare no conflicts of interest.

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