SAFETY OF FEMORAL NERVE BLOCKADE FOR HIP FRACTURES IN ADULT PATIENTS TREATED WITH ANTI-XA DIRECT ORAL ANTICOAGULANTS: A PILOT STUDY

Roy Rafael Dayan MD1, Yosef Ayzenberg MD1,2*, Tzachi Slutsky MD1,2, Ela Shaer MD1,2, Alon Kaplan BMedSc1, and Vladimir Zeldetz MD1,2
1Faculty of Health Sciences, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
2Department of Emergency Medicine, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

ABSTRACT

Background: Limited data exist regarding the safety of ultrasound-guided femoral nerve blockade (US-FNB) in patients with hip fractures treated with anti-Xa direct oral anticoagulants (DOAC).

Objectives: To compare the safety outcomes of US-FNB to conventional analgesia in patients with hip fractures treated with anti-Xa DOAC.

Methods: This observational exploratory prospective study included 69 patients who presented to our emergency department (ED) in 3 years with hip fracture and who were treated with apixaban or rivaroxaban. Patients received either a US-FNB (n=19) or conventional analgesics (n=50) based on their preference and the presence of a trained ED physician qualified in performing US-FNB. Patients were observed for major bleeding events during and 30 days after hospitalization. The degree of preoperative pain and opioid use were also observed.

Results: We found no significant difference in the number of major bleeding events between groups (47.4% vs. 54.0%, P = 0.84). Degree of pain measured 3 and 12 hours after presentation was found to be lower in the US-FNB group (median visual analog scale of pain improvement from baseline of -5 vs. -3 (P = 0.002) and -5 vs. -4 (P = 0.023), respectively. Opioid administration pre-surgery was found to be more than three times more common in the conventional analgesia group (26.3% vs. 80%, P < 0.0001).

Conclusions: Regarding patients treated with Anti-Xa DOAC, US-FNB was not associated with an increase in major bleeding events compared to conventional analgesia, although it was an effective means of pain alleviation. Larger scale randomized controlled trials are required to determine long-term safety and efficacy.

KEY WORDS: anesthesia, anticoagulation, anti-Xa direct oral anticoagulants (DOAC), femoral nerve block, ultrasound-guided femoral nerve blockade (US-FNB)

IP fractures are known as one of the most frequent orthopedic emergencies among the elderly [1]. They have detrimental effects on quality of life and level of function and also carry an unacceptably high mortality rate [2]. Surgical correction is the treatment of choice in most cases, usually within 24 to 48 hours, which is thought of as the time window for intervention [3]. Since hip fractures can be extremely painful, patients usually require urgent adequate analgesia until definitive care. While olovanalgesia is a familiar problem in the emergency department (ED) [4], using multiple doses of opioids to control severe pain until surgical correction may cause deleterious effects [5]. Opioids can cause various known complications (e.g., delirium state, urinary retention), especially among the elderly, which is the most common population presenting with hip fractures [6,7].

In this setting, ultrasound-guided femoral nerve block (US-FNB) is a relatively quick, safe, and effective alternative for managing acute hip pain in the ED [8,9]. This treatment was also found to reduce additional periprocedural analgesia and carried fewer adverse systemic events without offering a higher complication rate [10,11]. Anti-Xa direct oral anticoagulants (DOAC), such as apixaban and rivaroxaban, are non-vitamin K antagonist oral anticoagulants, which are becoming more common because they are considered convenient to administer with respect to warfarin due to their fixed dosing without the need for routine coagulation monitoring [12].

In contrast to central neuraxial anesthesia in the presence of anticoagulant treatment, there have been no prospective studies that assessed the safety and outcomes of peripheral nerve blocks in patients treated regularly with anticoagulants such as anti-Xa DOAC. Due to lack of evidence and in the presence of numerous reports suggesting significant morbidity related to hematomas following peripheral nerve blockade in patients on antithrombotic therapy [13,14], the American Society of Regional Anesthesia and Pain Medicine recommends the same guidelines for peripheral nerve blocks as for neuraxial procedures [15]. To the best of our knowledge, no evidence exists on the safety, frequency of complications, or outcomes of US-FNB in patients.
with acute hip fractures regularly treated with anti-Xa DOAC. We evaluated the safety of US-FNB compared to conventional analgesia, specifically in the anti-Xa DOAC population.

PATIENTS AND METHODS

STUDY POPULATION
The study was conducted at Soroka University Medical Center, a large regional trauma center in the south of Israel. Sixty-nine patients presented to the ED between January 2015 and July 2018 with confirmed hip fracture and who were treated with anti-Xa DOAC were observed and analyzed [Table 1]. Inclusion criteria included patients above the age of 18 years, who had radiographically confirmed proximal femur fracture (extracapsular or intracapsular) with no additional injuries, were under regular anti-Xa DOAC (apixaban or rivaroxaban) treatment, and were able to give full conscious verbal consent to the study trial. All participants were treated with anti-Xa DOAC for stroke prophylaxis due to atrial fibrillation and high CHADS2-VAS score. Also, all patients received anticoagulation during the 24 hours before presenting to the ED. Only hemodynamically stable patients with no signs of pending shock or circulatory/respiratory compromise were eligible to participate. Exclusion criteria included absolute contraindications for local anesthesia, such as known allergy to local anesthetics or infection/hematoma overlying the femoral triangle (injection site). The medical ethics board and the Helsinki committee of the Soroka University Medical Center approved the study protocol.

STUDY DESIGN
This trial was a single-center, observational exploratory prospective cohort study. A total of 69 participants presented to the ED with acute hip fracture and who were on prior regular anti-Xa DOAC treatment were included. Participants received either an ultrasound-guided, single-injection, femoral nerve block (see supplementary for full technique description) administered by emergency physicians at the ED (n=19) or conventional analgesics (acetaminophen, dipyrone, or opioids) (n=50) based on patient preference and the presence and availability of experienced certified ED physician qualified in performing this procedure. In our facility, the ED is only occupied by trained ED specialists who are skilled in US-guided minimally invasive procedures; hence, US-FNB was offered to all comers only during this time frame rather than during night shifts. Both groups were observed for the occurrence of major bleeding events (defined according to the International Society on Thrombosis and Hemostasis current definition [16]) and for the level of preoperative pain both during hospitalization and for 30 days after discharge. The degree of pain was quantified subjectively by the 1–10 visual analog scale validated pain scoring system (VAS) [17] at three sequential points in time: at presentation, 3 hours, and 12 hours after treatment (femoral anesthesia vs. medical treatment). For either group, an add-on analgesic treatment was at the ED physician’s discretion, based on his clinical judgment. The percentage of patients receiving opioids before surgery was recorded as well. The anti-Xa DOAC was discontinued at presentation and resumed 48–72 hours after surgery. All patients had surgical correction (open reduction and internal fixation or total/ hemiarthroplasty), most patients within the appropriate 48-hour timeframe (78%). In concordance with local protocols, oral anticoagulation was stopped at first medical contact and was initiated once more 12 hours after surgery.

STATISTICAL ANALYSES
Statistical analyses were based on non-parametric tests due to the relatively small sample size. Differences within groups at various time points, compared to baseline, were analyzed by the Friedman or Wilcoxon test, depending on the number of time points. To examine the differences between the groups, we used the Mann-Whitney test or Pearson chi-square test, as appropriate. Multiple logistic regression was used as a sensitivity analysis for the primary outcome. Results are presented as means ± standard deviation unless otherwise stated. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). All P values were two-sided, and P < 0.05 was considered statistically significant.

<table>
<thead>
<tr>
<th>Table 1: Basic characteristics of the study population (N=69)</th>
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<tr>
<td>Sex (male)*</td>
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<td>Age (years)</td>
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<td>International normalized ratio</td>
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<td>Hemoglobin level (g/dl) at presentation</td>
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<tr>
<td>Anti-Xa DOAC (rivaroxaban/apixaban)*</td>
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<td>VAS score at admission**</td>
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<td>Charlson score**</td>
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<td>HAS-BLED score**</td>
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<td>OHADS2 score**</td>
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*Cases (percentages)  
**Median (range)  
DOAC = direct oral anticoagulant, VAS = visual analog scale
RESULTS

A total of 69 patients with hip fracture and chronic anti-Xa DOAC treatment were observed and analyzed. For acute pain management, 19 patients received US-FNB, while 50 patients received conventional analgesia, mostly parenteral opioids [Table 2]. There was no significant difference observed in the number of major bleeding events during hospitalization and in the 30 days post-discharge between patients receiving US-FNB and patients receiving conventional analgesia (47.4% vs. 54%, P = 0.622). In addition, there was no significant difference noticed in the need for blood transfusions (26.3% vs. 20%, P = 0.745), change in hemoglobin levels compared to baseline (-2.2 mg/dl vs. -1.9 mg/dl, P = 0.282) hospital length of stay (median 6 to all, P = 0.849), or rate of death after 30 days (5% vs. 12%, P = 0.664). Other adverse events such as delirium during hospitalization, wound infections, hematomas, or sepsis were also found to be without significant difference between treatment strategies. Improvement in the level of pain 3 hours and 12 hours after treatment initiation (assessed by the VAS scoring difference from baseline) was shown to be more pronounced in the US-FNB group compared to the conventional analgesia group: median -5 vs. -3 at 3 hours (P = 0.002) and -5 vs. -4 at 12 hours (P = 0.023) [Figure 1]. Furthermore, opioid administration before surgery was found to be three times more common in patients who received conventional analgesia (26.3% vs. 80%, P < 0.0001).

DISCUSSION

US-FNB in patients presenting with hip fracture is now familiar as a quick, relatively simple, and effective strategy for managing severe hip pain in the ED [18]. Minimal-to-no adverse events are expected with femoral nerve blockade when performed by a skilled physician, compared to those found with the usage of opioids, such as severe constipation, nausea, and increase risk for delirium [19-21]. Nonetheless, studies have yet to confirm the safety of peripheral nerve anesthesia with patients on continuous DOAC treatment.

DOAC includes direct thrombin inhibitors and direct factor Xa inhibitors, which block major procoagulant activities involved in forming a fibrin clot.

Direct factor Xa inhibitors (i.e., anti-Xa DOAC) bind directly to factor Xa and prevent it from cleaving prothrombin to thrombin, a significant player in the clotting cascade [22]. DOAC therapy has become the cornerstone treatment for stroke prophylaxis in high-risk patients due to its fixed dosage, reliable dose-response effect, and the fact that no laboratory coagulation monitoring is necessary [23]. As the population ages, the prevalence of atrial fibrillation is expected to rise [24]. By default, an increase in the number of elderly patients receiving DOAC daily is anticipated. Therefore, physicians should expect to be facing elderly patients on regular DOAC treatment who present with hip fractures more frequently than in the past. With no previous

<table>
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<tr>
<th>Table 2. Comparison of safety outcomes between groups</th>
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<tr>
<td>Conventional analgesic group (N=50)</td>
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<tr>
<td>Time to surgical correction (hours)</td>
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<td>Surgical correction performed within 48-hour window*</td>
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<td>Absolute change in hemoglobin level (g/dl)***</td>
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<td>Major bleeding events*</td>
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<td>Decrease in hemoglobin level of 2g/dl or more***</td>
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<td>Transfusion of two or more units of packed red blood cells*</td>
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<td>Critical site bleed*</td>
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<td>Fatal bleed*</td>
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<td>Wound Hematomas*</td>
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<td>Wound infection*</td>
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<td>Delirium*</td>
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<td>Sepsis*</td>
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<td>Preoperative opioid administration*</td>
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<td>Length of hospital stay (days)**</td>
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<tr>
<td>Reoperation*</td>
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<td>Readmissions*</td>
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<td>Death after 30 days*</td>
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*cases (percentages)  
**Median (range)  
***Change in hemoglobin level after surgery, compared to admission

Major bleeding events during hospitalization and 30 days post-discharge were defined according to the international society on thrombosis and hemostasis. They are defined as fatal bleeding or bleeding that is symptomatic and occurs in a critical area or organ such as intracranial, intraspinal, intracranial, retroperitoneal, or pericardial in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon, or extra-surgical site bleeding causing a fall in hemoglobin level of 2 g/dl (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.
LIMITATIONS
As a first exploratory trial, this study has several limitations. First and foremost, a relatively small sample size makes it difficult to conclude a long-term safety profile without additional large-scale trials. Second, there was no randomization between groups, although baseline characteristics (including age, gender, and co-morbidities assessed by Charlson score) were similar. Femoral anesthesia was offered to all qualifying patients during the morning and afternoon in contrast to during night shifts when a trained ED specialist was not readily available. Nevertheless, we speculate that patients who present to the ED during the day are similar to those who arrive at night. Also, anti-Xa drug levels in the blood have not been tested before the procedure, although all patients received their usual oral dosage in the past 24 hours. This fact, and since the half-life of the anti-Xa DOACs is about 12 hours [23], reassures us about the participants’ antiocoagulated status while performing the procedure. Last, patients were offered a femoral nerve block, and by definition selection bias could potentially have affected the results.

CONCLUSIONS
This study is a pioneer study to examine the safety of US-guided femoral nerve anesthesia in patients with hip fractures who are being treated with anti-Xa DOAC. To the best of our knowledge, our study is the first to show that peripheral nerve anesthesia among anti-Xa DOAC patients does not carry a higher risk for major bleeding events. Additional, larger-scale randomized controlled trials are mandatory to determine the long term safety of these semi-invasive procedures in the presence of the growing population of anti-Xa DOAC patients.

Correspondence
Dr. R.R. Dayan
Faculty of Health Sciences, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva 8410501, Israel
Fax: (972-8) 647-7630
email: royday@post.bgu.ac.il

References


**Capsule**

TCR detection of citrullinated epitopes

The autoreactive T cell repertoire driving disease activity in rheumatoid arthritis (RA) includes CD4+ T cells that recognize major histocompatibility complex–bound peptides with arginine residues posttranslationally modified to citrulline. Some human leukocyte antigen–DRB1 proteins have a shared susceptibility epitope associated with increased RA incidence. Lim et al. analyzed the repertoire, binding properties, and structure of multiple T cell receptors (TCRs) derived from humanized mice reactive with citrullinated peptides presented by HLA-DR4. TCR repertoire analysis revealed a citrullinated antigen–specific motif that was conserved in both mice and humans. X-ray crystal structures revealed direct contact of the TCR with the shared epitope on N-terminal tau in cerebrospinal fluid resulting in discontinuation of the open-label, long-term extension. Unbound N-terminal tau in cerebrospinal fluid decreased by 98% with gosuranemab and increased by 11% with placebo (P < 0.0001). Incidences of adverse events and deaths were similar between groups. This well-powered study suggests that N-terminal tau neutralization does not translate into clinical efficacy.

**Capsule**

Safety and efficacy of anti-tau monoclonal antibody gosuranemab in progressive supranuclear palsy: a phase 2, randomized, placebo-controlled trial

In a randomized, double-blind, placebo-controlled, 52-week study (no. NCT03068468), Dam et al. evaluated gosuranemab, an anti-tau monoclonal antibody, in the treatment of progressive supranuclear palsy (PSP). In total, 486 participants dosed were assigned to either gosuranemab (n=321) or placebo (n=165). Efficacy was not demonstrated on adjusted mean change of PSP Rating Scale score at week 52 between gosuranemab and placebo (10.4 vs. 10.6, P=0.85, primary endpoint), or at secondary endpoints, resulting in discontinuation of the open-label, long-term extension. Unbound N-terminal tau in cerebrospinal fluid decreased by 98% with gosuranemab and increased by 11% with placebo (P < 0.0001). Incidences of adverse events and deaths were similar between groups. This well-powered study suggests that N-terminal tau neutralization does not translate into clinical efficacy.

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Eitan Israeli