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Original article

A comparative study in patients with fractures of the lower limbs between rivaroxaban versus enoxaparin and its impact on bone healing time

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ABSTRACT. ***Background:*** **Each year it is estimated in the United States an approximate of 8 million fractures; 5 to 10% develop delayed union or absence of periosteal new bone. There are several factors that can cause delay in fracture healing, among the well known, is the use of prophylactic antithrombotic therapy for deep vein thrombosis (DVT). DVT appears in 40 to 60% of the patients undergoing orthopedic surgery without prophylactic antithrombotic therapy. The goal of this study was to assess whether there is a difference in time of bone healing in lower limb fractures (femur and tibia) comparing rivaroxaban to enoxaparin as the prophylactic antithrombotic management.** ***Material and methods:*** **We present a retrospective observational and analytic study in a sample of cases. It is a cross-sectional study with patient data from the database of the American British Cowdray (ABC) Medical Center. We included patients with femur and tibia fractures under antithrombotic prophylactic management with rivaroxaban or enoxaparin during the period of January 2011 to December 2012. Our sample included 32 patients separated into two groups. Student's t-test was used for comparing parametric variables and the Mann-Whitney U test for nonparametric variables. Linear regression model was preformed considering the variables related to the time it took the fracture to heal.** ***Results:*** **All fractures consolidated in a time of 13 and 14 weeks**

RESUMEN. ***Antecedentes:*** **En Estados Unidos se presentan aproximadamente ocho millones de fracturas anuales y de ellas entre cinco y 10% desarrollan retraso o ausencia en la consolidación ósea. Existen diferentes factores bien conocidos que promueven este retraso, entre los cuales se encuentra el uso de los antitrombóticos como terapia profiláctica de la trombosis venosa profunda, la cual aparece de 40 a 60% en pacientes que no los utilizan y son sometidos a cirugías ortopédicas. El objetivo de este estudio fue evaluar si existe diferencia en el tiempo de consolidación de las fracturas de los huesos de las extremidades pélvicas (fémur y tibia) en pacientes sometidos a terapia profiláctica antitrombótica comparando rivaroxabán con enoxaparina.** ***Material y métodos:*** **Presentamos un estudio descriptivo y analítico con muestreo a conveniencia de casos retrospectivos. Es un estudio transversal con datos recolectivos. Se revisó la base de datos del Centro Médico ABC y se incluyeron pacientes con diagnóstico de fracturas de fémur y tibia sometidos a manejo profiláctico antitrombótico con rivaroxabán o enoxaparina durante el periodo de Enero 2011 a Diciembre de 2012. La muestra total se constituyó de 32 pacientes divididos en dos grupos. Se utilizó la prueba T de Student para comparar variables paramétricas y la prueba U de Mann-Whitney para las no-paramétricas. Se realizó un modelo de regresión lineal considerando las variables relacionadas**

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for rivaroxaban and enoxaparin respectively (p = 0.67). *Discussion:* We found no difference in bone healing time for lower limb fractures in patients receiving antithrombotic prophylaxis treatment comparing rivaroxaban with enoxaparin.

Key words: Femur fractures, tibia fractures, bone healing, antithrombotic prophylaxis, rivaroxaban, enoxaparin.

con el tiempo de consolidación ósea. *Resultados:* Todas las fracturas consolidaron, presentando un tiempo de 13 semanas con rivaroxabán y de 14 semanas (p = 0.67) con enoxaparina. *Discusión:* No encontramos diferencia en el tiempo de consolidación de las fracturas de los huesos de las extremidades pélvicas (fémur y tibia) en pacientes que reciben antitrombóticos como profilaxis comparando rivaroxabán con enoxaparina.

Palabras clave: Fracturas de fémur, fracturas de tibia, consolidación ósea, antitrombóticos, rivaroxabán, enoxaparina.

Introduction

Each year it is estimated in the United States an approximate of 8 million fractures; 5 to 10% of which develop delayed union or absence of periosteal new bone.[1,2,3] In order to minimize or eliminate these damages, it is necessary to study the concepts of molecular aspects of bone healing.[4,5,6] There are several factors that can cause delay in fracture healing, among the well known is the insufficient stability in osteosynthesis, nutritional deficiencies (low protein, mineral, calcium or vitamins C, D, K intake), unhealthy habits (smoking, alcoholism) and some prescribed medicine such as nonsteroidal anti-inflammatory drugs (NSAIDs), antifungals, antibiotics (ciprofloxacin) and antithrombotic therapy.[7,8,9,10]

Antithrombotic therapy is currently used for the prevention of deep vein thrombosis (DVT). Without thromboprophylaxis, an increased incidence of DVT is observed after lower limb fracture surgery in 30 to 80% of the patients,[11] while the risk of developing fulminant pulmonary embolism is 1-2%.[12]

The use of thromboprophylaxis for the prevention of DVT includes the administration of antithrombotic agents; the most common is the low molecular weight heparin (LMWH), which can be applied intravenously or subcutaneously.[13]

Several studies suggest that prolonged use of LMWH induces osteoporosis by modifying the bone metabolism, suggesting it as a risk factor causing delay in bone healing in 2-5% of the patients.[13,14] Studies have demonstrated that LMWH reduces the incidence of osteoporosis and osteopenia when compared with unfractionated heparin.[14]

Rivaroxaban is an oral anticoagulant used for antithrombotic therapy approved by the European Commission of the Pharmaceutical Industry in 2008 as a treatment for the prevention of DVT in adults undergoing hip and knee surgery.[15] This drug is a selective inhibitor of Factor Xa and is recommended as an alternative to enoxaparin for antithrombotic prophylactic management. Rivaroxaban has the advantage that it is taken orally, making it an effective, safe and easy-to-use treatment. The recommendation for duration of rivaroxaban therapy is five weeks after hip joint replacement and two weeks after knee replacement.[16,17] There has been no consistent protocol in the literature for management of patients with fractures.

Studies have demonstrated that rivaroxaban also inhibits the formation of osteoblasts without affecting the bone mineralization process.[18] Several investigations *in vitro* have shown a negative effect on osteoblast function with the use of rivaroxaban in comparison to enoxaparin.[19,20] However, at the moment we conducted the present research, we did not find any published paper assessing such comparison in humans.

The purpose of this study was to assess whether there is a difference in time of bone healing in lower limb fractures (femur and tibia) comparing rivaroxaban to enoxaparin as the prophylactic antithrombotic management in patients undergoing surgical treatment.

Material and methods

We present a retrospective observational and analytic study in a sample of cases. It is a cross-sectional report patient data from the database on both campuses of the American British Cowdray Medical Center. We included patients with femur (31A, 32A, 32B, 32C, 33A, 33B, 33C AO classification) and tibia (41A, 41B, 41C, 42A, 42B, 42C, 43A, 43B, 43C AO classification) fractures under antithrombotic prophylactic management during the period of January 2011 to December 2012. Our sample involved 32 patients who received antithrombotic prevention with 40 mg of enoxaparin administered via subcutaneous or 10 mg rivaroxaban taken orally every 24 hours.

The Research Ethics Board and the Electronic Record Committee of the hospital approved the protocol. We used the OnBase electronic document system and searched for medical records with the diagnosis codes ICD-9: 79.5, 79.16, 79.35, 79.36.

The exclusion criteria were: patient age under 18 years old, incomplete clinical and radiographic record, 10 year

history of tobacco use, ingestion of ketorolac, under previous bisphosphonate therapy, any musculoskeletal disorder that affected bone healing, intracapsular femoral fractures (31B, 31C AO Classification), malleolar fractures (44A, 44B, 44C AO Classification), open fractures, victims of polytrauma with an Injury Severity Score (ISS) > 16, walking disability prior to the fracture and patients with previous administration of > 40 mg of enoxaparin via subcutaneous or > 10 mg of rivaroxaban taken orally once daily.

We included a consecutive sample of patients for this study. Given the fact that there are no previous studies, we consider this as a pilot study. Further research can use the data presented herein in order to make a power and sample-size calculation in order to avoid a type-II error. The 32 patients included in the study were divided into two groups: those under antithrombotic prophylactic therapy with rivaroxaban and those using enoxaparin *(Figure 1)*.

The electronic medical record integrated the analysis of the patient identification, admission note, surgery note, discharge summery and prescription. With this information we obtained variables to time of bone healing related in age, sex, body mass index (BMI), mechanism of injury, the kind of implant used for osteosynthesis, type of fracture reduction (open or closed), duration of antithrombotic treatment and the length of hospital stay.

We studied the radiographic records of the subjects who met the selection criteria in different time intervals: preoperative, immediate postoperative period, at weeks 7th and 8th postoperative and then every two weeks to determine the healing status of the bone. Each radiograph was measured until it achieved a grade III of bone healing according to the classification of Montoya.[2,21]

Data analysis was performed with IBM SPSS Statistics for Windows (V 12.0). Continuous variables were subjected to normality tests (Kolmogorov-Smirnov). Demographic characteristics are described as mean and standard deviation (SD) for parametric variables and as median, minimum and maximum for nonparametric variables. Categorical variables were described as absolute and relative frequencies (expressed as a percentage).

The comparison between the parametric variables was performed using the Student´s t-test and the Mann-Whitney U Test to calculate the nonparametric variables. A binomial exact test was used to compare proportions. Linear regression model was preformed considering the variables related to the time it took the fracture to heal. A two-tailed p-value of 0.05 was considered significant in order to avoid a type-I error.

Results

A total of 370 patients were initially screened for the study, 338 were ineligible for the following reasons: malleolar fractures (140 patients); intracapsular proximal femur fractures (40); open fractures (10); an Injury Severity Score >16 (3); without antithrombotic prophylactic therapy (10); positive history of tobacco use (40); ingestion of ketorolac (25); the use of antithrombotic prophylactic therapy other than enoxaparin or rivaroxaban (13); incomplete radiographic record (57). The study group consisted of the remaining 32 patients divided in two equal groups.

The rivaroxaban group consisted of 16 patients. The average age was 63 years (± 21.36 DS); 7 were female (43.75%) and 9 were male (56.25%); the average BMI was 25.09 (± 3.93 DS); the average length of hospital stay was 4 days (min: 2, max: 8); and the average length of the antithrombotic prophylactic therapy was 30 days (range 7-35) *(Table 1)*.

The enoxaparin group consisted of 16 patients. The average age was 73.56 years (± 17.14 DS); 9 were female (56.25%) and 7 were male (43.75%) the average BMI was 23.68 (± 3.74 DS); the average length of hospital stay was 4 days (min: 2, max: 11); and the average length of the antithrombotic prophylactic therapy was 29 days (range 14-30) *(Table 1)*.

Different trauma mechanisms were observed in the patients. Considering both groups: 13 patients (40.60%) had secondary trauma due to a fall from standing height; 7 (21.80%) had a fall greater than 2 meters; 2 (6.35%) had direct trauma; and 10 (31.25%) were caused after suffering a car accident.

According to the topography and extent of bone lesion, the fractures were classified using the AO System.

The 16 fractures in the rivaroxaban group were classified as follows: 6 (37.5%) were 31A; 3 (18.75%) were 32A; 3 (18.75%) were 41C; 1 (6.25%) was 33C; 1 was 41B; 1 was 42A; and 1 was 42B. Seven (43.75%) of these fractures were treated with open reduction and internal fixation and 9 (56.25%) patients with closed reduction and internal fixation.

The 16 fractures in the enoxaparin group were classified as follows: 9 (56.25%) were 31A; 3 (18.75%) were 32A; 1 (6.25%) was 33C; 1 was 41B; 1 was 41C; 1 was 42A. Six (37.5%) of these fractures were treated with open reduction and internal fixation and 10 (62.5%) patients with closed reduction and internal fixation.

A grade III in Montoya's healing classification was observed in all (100%) of the cases at an average time of 14.87 weeks (range 7-35 weeks); the rivaroxaban group had a median time of 13 weeks (7 min, 35 max), while the enoxaparin group had a median time of 14 weeks (7 min, 28 max) (p = 0.67) *(Table 2)*.

Discussion

Nowadays in the multidisciplinary treatment of fractures it has increased the importance of the widespread use of antithrombotic therapy as a basis for prevention of major complications.

The introduction of new antithrombotic drugs in the market in the last years has made it easier for patients to have better adherence and to avoid incidence of

complication along the treatment. Rivaroxaban comes in an oral presentation and studies have reported less side effects compared to the use of enoxaparin, considered the gold standard for thromboprophylaxis medication.

Several investigations[19] *in vitro* have shown a negative effect on osteoblast function with the use of rivaroxaban in comparison to enoxaparin; but no study has questioned the clinical effects *in vivo*.

To our knowledge this is the first retrospective study of its kind. The analysis found no difference comparing rivaroxaban with enoxaparin bringing us the pattern to start its use in a routine manner.

With a linear regression model it was possible to observe that independent variables such as age, gender and BMI do not relate directly to the time it takes bone to consolidate (statistically non-significant). However we found a delay in time in patients with a BMI > 25 and > 75 years old, which could reveal that other factors such as BMI and age influence on time of bone healing rather than the use of an antithrombotic prophylactic drug.

Table 1. Demographic table.

	Rivaroxaban (n =16)	Enoxaparin (n = 16)	p
Age	63 (± 21.36)	73.56 (± 17.14)	0.15
Sex			
Female	7 (43.75%)	9 (56.25%)	0.36
Male	9 (56.25%)	7 (43.75%)	0.36
BMI	25.09 (± 3.93)	23.68 (±3.74)	0.23
Length of hospital stay	4 (2-8)	4 (2-11)	0.72
Fracture reduction			
Open	7 (43.75%)	6 (37.5%)	0.64
Closed	9 (56.25%)	10 (62.5%)	0.64
Length of antithrombotic treatment	30 (7-35)	29 (14-30)	0.25

Values expressed in: mean (+ SD), median (min.-max.), absolute frequency (%). p-values were obtained with Student's T-test and Mann-Whitney's U test and exact binomial test.

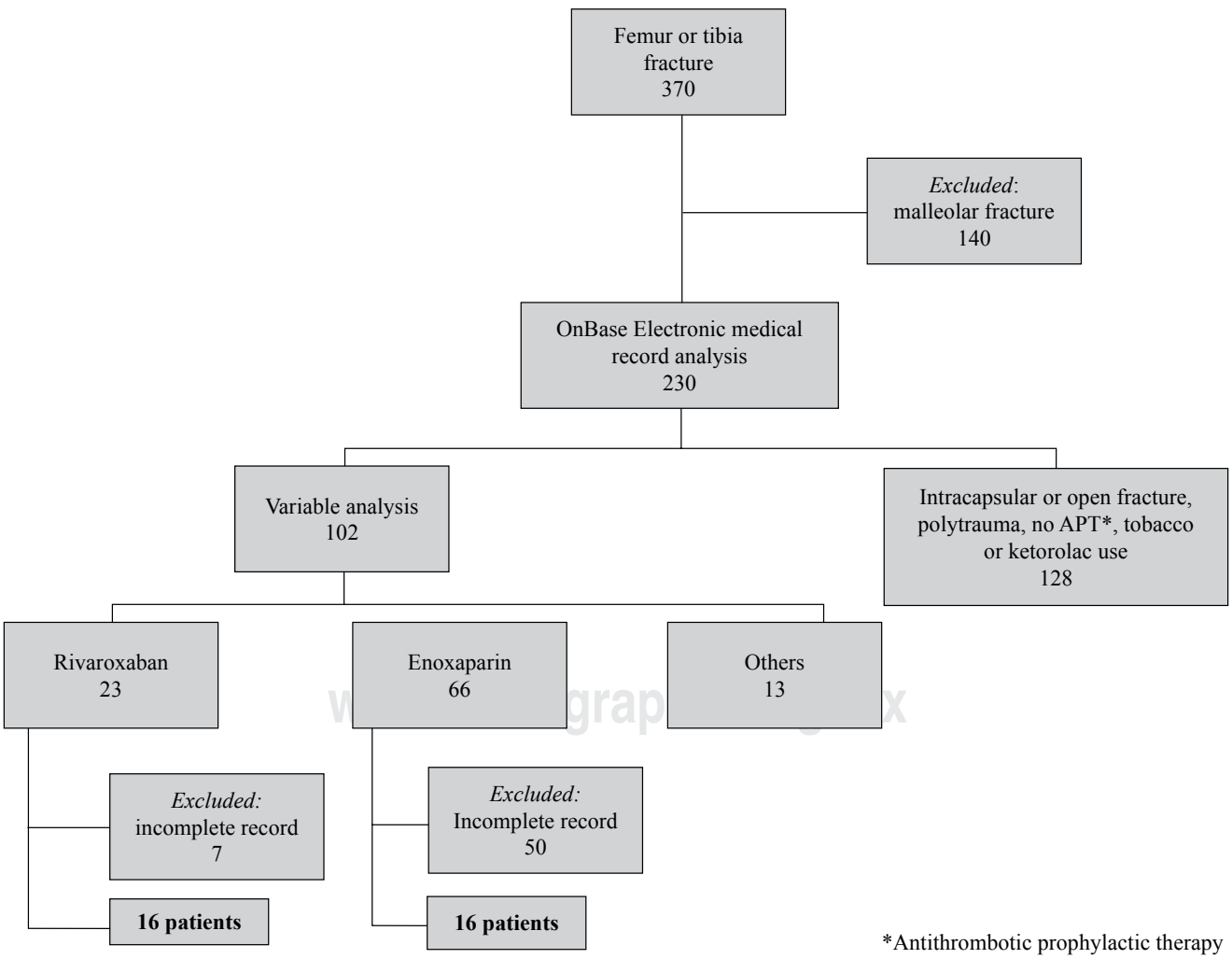

Figure 1. Selection of electronic medical records.

Table 2. Time of fracture healing.

	Rivaroxaban (n = 16)	Enoxaparin (n = 16)	p*
Weeks	13 (7-35)	14 (7-28)	0.67

Values expressed in: median (min.-max.). * Mann-Whitney's U.

The identified limitations of this study are: it´s a retrospective analysis, the sample could not be calculated because there are no previous studies and the sample size is too small. There was a lack of radiographic techniques standardization. Multiple orthopaedic implants were used, this could represent bias, however it is always a challenge trying to standardize trauma implants due to the great variety of fracture patterns. The fact that no statistical significance was found could be secondary to the sample size. More research is needed in the future to reach a conclusion on the safety switching to an oral route of antithrombotic preventive management related to the fractures treatment.

Any of the authors of this paper has or had along the study development any economic or professional relation with the pharmaceutical product research and manufacturers of the both antithrombotic medication.

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