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Research Article

Thromboprophylaxis Following Hip Fracture: A Multicenter Comparative Study of Dabigatran Versus Enoxaparin

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Abstract

Introduction: Venous Thromboembolism (VTE) is a leading cause of mortality among hospitalized patients [1]. In the United States, Pulmonary Embolus (PE) causes almost 300,000 deaths per year [2]. 12% of annual deaths are due to VTE [3]. Major orthopaedic surgery (e.g., hip or knee replacement) is associated with a high risk for postoperative VTE [1,4,5]. In hip fracture surgery without thromboprophylaxis, the incidence of VTE reported is 35% with venography, and symptomatic VTE is about 3% [6].

Because the clinical diagnosis of VTE is unreliable and its first manifestation may be a life-threatening PE, it is recommended that patients undergoing hip or knee replacement receive routine thromboprophylaxis with anticoagulant therapy after surgery unless they have contraindications to anticoagulant therapy [1,4,7,8].

This study quantifies the efficacy and safety of enoxaparin (LMWH) versus dabigatran (Indirect Anti-X) in patients with hip fractures.

Material and Methods: This prospective randomized study compared daily doses of LMWH 40 mg subcutaneously with Indirect Anti-X 220 mg orally in consecutive patients with hip fractures. Patients were evaluated with Doppler scans for deep DVT on postoperative days 5 and 30 and with a clinical evaluation on postoperative days 30, 45, 90, and 120.

Results: 330 study patients. *LMWH Group*: 165 patients (males 38%). Average age 72.4 years (range 32 to 84 years). Day 5 postoperative Doppler scan detected 1 asymptomatic distal DVT. Another patient later (in the period between day 5 to 30 day control) presented with signs of a PE and had a Doppler scan positive for proximal DVT. The V/Q scan was positive and the patient was treated per standard guidelines. Day 30 Doppler scan detected 11 DVTs (3 proximal and 8 distal). 4 of these were symptomatic (1 proximal and 3 distal). All were evaluated in the emergency department. After diagnosis, 2 were readmitted for studies and treatment, and 2 were discharged home. All 4 of these patients were started on LMWH as suggested by local guidelines. The overall incidence of PE in this group was 0.6%. Doppler scan detected DVTs in 6.6% (symptomatic 2.4%) of the LMWH group. 2 patients returned for the evaluation of bleeding, 2 for superficial wound infections and 3 for thigh hematomas.

Anti-X Group: 165 patients (males 43.3%) enrolled. Average age 69.3 years (range 18 to 73 years). Day 5 postoperative Doppler scan detected no DVTs. The postoperative day 30 Doppler scan detected 5 DVTs (1 proximal and 4 distal). An additional patient was diagnosed with a PE (V/Q scan positive, Doppler scan negative). 2 symptomatic patients (one with distal DVT who developed symptoms during in-hospital rehabilitation and one with a proximal DVT) were readmitted and treated per standard guidelines. The incidence of PE in this group was 0.68%, with Doppler scan-detected DVTs 3% (1.2% symptomatic). 1 patient had an hematoma involving 2/3 of the thigh, 1 had a wound infection, and 2 had a rash.

There were no significant differences between the two thromboprophylactic treatments, and the Fishers exact test was not significant for any individual complication or total number of complications. No patient died during the study period.

Conclusion: Both LMWH and Anti-X appear to be equally effective prophylactic medications for the prevention of deep venous thrombosis after proximal femur fracture surgery. The cost benefits of using Anti-X may be considerable.

Introduction

Venous Thromboembolism (VTE) is a leading cause of mortality among patients in hospital [1]. In the United States, pulmonary embolus (PE) causes almost 300,000 deaths per year [2]. 12% of annual deaths are due to VTE [3]. Major orthopaedic surgery (e.g., hip or knee replacement) is associated with a high risk for postoperative venous thromboembolism [1,4,5].

Without thromboprophylaxis, the DVT incidence is 42 to 57% on venography and PE incidence is 0.9 to 28%, after primary Total Hip Arthroplasty (THA) [1]. In hip fracture surgery without

thromboprophylaxis, the incidence of VTE reported is 35%, and symptomatic VTE to be about 3% [6].

Because the clinical diagnosis of VTE is unreliable and its first manifestation may be a life-threatening PE, it is recommended that patients undergoing hip or knee replacement receive routine thromboprophylaxis with anticoagulant therapy after surgery unless they have contraindications to anticoagulant therapy [1,4,7,8].

Guidelines recommend extended thromboprophylaxis for up to 28 to 35 days after surgery for patients undergoing hip replacement [8]. There is evidence that extended thromboprophylaxis after hospital discharge is effective for reducing the risk of VTE among patients who undergo hip replacement [9].

A failure to prevent VTE may result in hospital read mission, delayed hospital discharge, patient discomfort, and long term morbidity sequelae, such as pulmonary hypertension, recurrent thrombosis or post-thrombotic syndrome [10].

Low Molecular Weight Heparin (LMWH) is standard thromboprophylaxis after hip fracture surgery. The most widely used LMWH is enoxaparin 40 mg once a day, starting on admission and continued up to 30 days postoperatively [1].

New oral anticoagulants regimens for throboprophylaxis after hip fracture surgery would improve efficacy with less risk of bleeding. In [our country], Dabigatran (Pradaxa, Boerhingher AG, Germany) has been approved for use in lower limb fractures. It has now been approved in Canada, Europe, and the United States for thromboprophylaxis after hip and knee replacement surgery [1].

Dabigatran is an oral, indirect Factor Xa inhibitor with high bioavailability, a rapid onset of action, and predictable pharmacokinetics.

Material and Methods

From June 2013 to December 2014, we conducted a prospective comparative study on consecutive patients with hip fractures admitted in 2 medical centres. The goal was to include 25% of the total number of hip fracture patients seen annually in these institutions. The study was authorized by local ethical committee and performed in accordance with Ethical standards of 1964 Declaration of Helsinki revised in 2000.

We enrolled 330 patients in the study who, after providing informed consent, were randomly assigned to treatment with LMWH or Anti-X. There were 165 treated with LMWH and 165 with Anti-X, there were no significant differences between the two groups' demographics, treatment or anaesthesia (Table 1).

Upon arrival at the hospital, residents or attending physicians described the study to eligible patients with a diagnosis of hip fracture. They signed a written consent before inclusion in the study. Exclusion criteria were a previous history of DVT, stroke, malignancy, renal insufficiency, or recent myocardial infarction , politrauma.

Study patients were randomly divided into two groups: enoxaparin 40 mg once daily subcutaneous administration, or dabigatran 110 mg twice a day oral. A departmental secretary controlled randomization.

Physicians who were unaware of which medication had been given evaluated both groups using a Doppler scan on postoperative days 5 (day the patients return home and entered in domiciliary medicine care) and 30 (when domiciliary medicine care is discontinuead and the indication for the thromboprophylaxis is finished), and had a clinical evaluation at postoperative days 30, 45, 90, and 120.

The Doppler scan included examination of bilateral common femoral, superficial femoral, popliteal, anterior tibial, and posterior tibial veins. They were assessed for flow, visualized thrombus, compressibility, and augmentation. Diagnosis of DVT was made where there was visualization of thrombosis, absence of flow, lack of compressibility or lack of augmentation.

Statistics were analyzed using Statistix 7.0 Analytical software 2000 (Informer Technologies, Inc.). Fishers exact test was used for stadistic evaluation.

The study protocol was approved by the institutional review board of each study centre.

Results

LMWH Group: 165 patients (males 38%) enrolled . Average age 72.4 years (range 32 to 84 years). They waited between 1 and 5 days (average 1.6 days) before they had surgery. Their surgical procedures included 78 total hip replacements (32 cemented, 25 hybrids, and 21 uncemented), 52 endomedular devices, and 35 dynamic hip screws systems. Epidural anaesthesia was used on 151 of these patients and general anaesthesia on 14.

The day 5 postoperative Doppler scan detected 1 asymptomatic distal DVT. Another patient later (in the period between day 5 to 30 day control) presented with signs of a PE and had a Doppler scan positive for proximal DVT. The V/Q scan was positive and the patient was treated per standard guidelines.

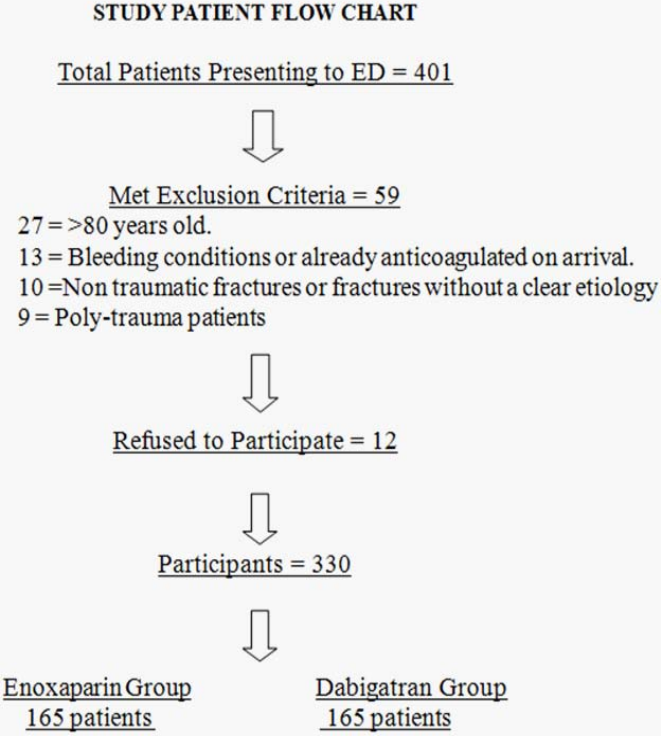
The postoperative day 30 Doppler scan detected 11 DVTs (6.6% of the group) (3 proximal and 8 distal). 4 of these were symptomatic (1 proximal and 3 distal). All were evaluated in the emergency department. After diagnosis, 2 were readmitted for studies and treatment, and 2 were discharged home. All 4 of these patients were started on LMWH as suggested by local guidelines.

The overall incidence of PE in this group was 0.6%. Doppler scan detected DVTs in 6.6% (symptomatic 2.4%) of the LMWH group.

2 patients returned for the evaluation of bleeding problems requiring laboratory evaluation and the discontinuation of enoxaparin. 2 superficial wound infections required surgical debridement, and there were 3 thigh hematomas (no specific treatment was performed for the hematomas; . and resolved during rehabilitation).

Table 1: Demographic Data of Enrolled Patients.

	Enoxaparin	Dabigatran	P
N	165	165	-
Men	63 (38%)	67 (40.6%)	0.735
Age	72.4 (32-79)	69.3 (19-74)	0.452
Pre operative days	3 (1-5)	3 (1-6)	1
Total hip replacement	78	65	0.182
Endomedular	52	51	1
Dinamyc hip screw	35	49	0.1
Epidural anaestesia	151	155	0.526



Anti-X Group: 165 patients (males 43.3%) enrolled. Average age 69.3 years (range 18 to 73 years). They waited between 1 and 6 days (average 1.8 days) before they had surgery. Their surgical procedures included 65 total hip replacements (35 uncemented, 21 hybrid and 9 cemented); 51 endomedular systems, and 49 dynamic hip screws. Epidural anaesthesia was used on 155 of these patients and general anaesthesia on 10 (Flow chart).

The day 5 postoperative Doppler scan detected no DVTs. The postoperative day 30 Doppler scan detected 5 DVTs (3% of the group) (1 proximal and 4 distal). An additional patient was diagnosed with a PE (V/Q scan positive, Doppler scan negative). 2 symptomatic patients (with distal DVT who developed symptoms during in-hospital rehabilitation and one with a proximal DVT) were readmitted and treated per standard guidelines. The incidence of PE in this group was 0.68%, with Doppler scan-detected DVTs 3% (1.2% symptomatic).

As shown in Table 2, one patient in this group had a hematoma involving 2/3 of the thigh, another had a wound infection that required surgical debridement, and two had a rash that resolved after dabigatran was discontinued.

Table 2: Results.

	Enoxaparin	Dabigatran	P
DVT 5 days	2	0	0.498
EP 5 days	1	0	1
DVT 30 days	11	5	0.199
EP 30days	0	0	1
Bleeding	2	0	0.499
Infection	2	1	1
Hematomas	3	1	1

There were no significant differences between the two thromboprophylactic treatments. The Fishers exact test was not significant for any individual complication or the total number of complications.

No patient died during the study period.

Discussion

The standard thromboprophylaxis uses LMWH or vitamin K antagonists. While effective, these medications are limited by the need for parenteral administration or laboratory dependency. LMWH administration can be problematic, especially during the postoperative period. Professionally administered injections can be costly and some trials of self-injection demonstrated poor compliance [11].

Vitamin K antagonists, more commonly used in the United States, require routine anticoagulation monitoring and dose adjustment, with numerous food and drug interactions [12].

Ultrasound has been shown to be highly sensitive and specific for occlusive proximal DVT, but it may be less sensitive for the detection of distal or non-occlusive proximal thrombi [13,14].

Warwick, et al. in 1995 investigated 1162 patients with THA in whom compression stockings had been used for prophylaxis; there was a readmission rate of 1.4% within 28 days [13]. Seagroatt, *et al.* reported readmission of 0.73% of over 8000 patients with THA and no specified prophylaxis [14].

Post-hip fracture VTEs, as well as VTEs after THA and TKA represent serious economic burdens to the healthcare system. In many cases, VTE is preventable with the use of adequate thromboprophylaxis. Thromboprophylaxis use has been shown to be cost-effective compared with no prophylaxis.

Estimated U.S. costs for treating symptomatic VTEs range from $9,805 to $14,146 per event [15]. The potential cost savings related to thromboprophylaxis may be considerable, since the number of hip fractures in the United States could reach 650,000 by 2050 and, by 2030, there should be more than 570,000 total hip replacements and nearly 3.5 million total knee replacements performed annually [16,17].

Compared with enoxaparin, the current standard of care, the new oral anticoagulant dabigatran has the potential to further reduce healthcare costs, particularly those associated with drug administration and VTE management [18]. These cost reductions relate to patients' reduced hospital stays, drug self administration, and increased patient compliance with the medication regimen. With increased compliance comes decreased costs related to rehabilitation, morbidity and mortality, and the long-term effects of post-thrombotic syndrome. Wolowacz, *et al* reported the cost for dabigatran as £ 137 and £ 237 for enoxaparin (need for nurse visit and drug injection, lab tests). According to the UK NHS the costs using dabigatran are highly reduced [19], and in similar cost study (NICE), the reduction was 726 Euros per patient using dabigatran with 98% compliance [20].

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