Use of new oral anticoagulants (Rivaroxaban and Dabigatran Etexilate) in postoperative thromboprophylaxis after hip hemiarthroplasty in patients with fracture neck of femur

Thesis

Submitted for Partial Fulfillment of the Master Degree in

Orthopedic Surgery

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2016

List of Abbreviations

DVT	Deep Vein Thrombosis
VTE	Venous Thromboembolism
PE	Pulmonary Embolism
PTS	Post Thrombotic Syndrome
ATIII	Anti Thrombin III
CYP3A4	Cytochrome P3A4
LMWH	Low Molecular Weight Heparin
DIC	Disseminated Intravascular Coagulopathy
NICE	National Institute for Health &Clinical Excellence
DTIs	Direct Thrombin Inhibitors
NOACs	New Oral Anticoagulants
P-gp	P-glycoprotein
FFP	Fresh Frozen Plasma
PCCs	Prothrombin Complex Concentratres
Cmax	Maximal Plasma Concentration
ASA	American society of anaesthesiologists
HFS	Hip fracture surgery
THR	Total hip replacement
TKR	Total knee replacement
RCTs	Randomized controlled trials
CI	Confidence interval
RR	Relative risk

Aim of the work

The purpose of this study is to review and study the available clinical data with regard to the safety profiles of these two new oral anticoagulants ,namely Dabigatran Etexilate a Direct Thrombin Inhibitor and Rivaroxaban, a Direct Factor Xa inhibitor. Specific areas of focus include : bleeding events, deep venous thrombosis and pulmonary embolism incidence.

Abstract

Introduction:

Patients who undergo major orthopaedic surgeries are particularly at high risk of venous thromboembolism (VTE). New oral anticoagulants (NOACs) are being developed to improve the efficacy and safety of pharmacological VTE prophylaxis. Evolution in the development of oral anticoagulants to offset the drawbacks of Warfarin has led to the introduction of two new oral anticoagulants ,namely Dabigatran Etexilate a Direct Thrombin Inhibitor and Rivaroxaban, a Direct Factor Xa inhibitor.

Patients and Methods:

The study includes 40 patients who met the inclusion criteria. They were divided to twenty patients received postoperative Dabigatran Etexilate and twenty patients received postoperative Rivaroxaban for thromboprophylaxis. Patient outcomes included total drain output, bleeding events, deep venous thrombosis (DVT) and pulmonary embolism(PE) incidence.

Results:

Of the 40 patients , only 1 patient in the Rivaroxaban group developed asymptomatic silent DVT discovered at the end of prophylaxis regimen. No patient in both groups had neither major nor minor bleeding event.

Introduction

Patients who undergo major orthopaedic surgeries are at high risk of venous thromboembolism (VTE). Therefore, prophylaxis against VTE is considered a standard of care(1).

However, controversies exist with regard to the most clinically relevant and the safest pharmacological prophylaxis in orthopaedic patients. Low molecular weight heparin (LMWH) is considered to be among the most clinically efficacious pharmacological prophylaxis and is used as the standard of care in many medical communities(2).

New oral anticoagulants are being developed to improve the efficacy and safety of pharmacological VTE prophylaxis. Currently, several oral anticoagulants are in advanced stages of clinical development and regulatory approval process. Most clinical trial data have demonstrated equal or superior efficacy in comparison to LMWH based on venographic endpoints. Bleeding complications, however, have been reported to occur as frequently, or more frequently than, with LMWH. Other potential complications, such as liver enzyme elevation have also been reported with these newer agents. Thus, it remains to be established if newer oral anticoagulants will be better alternatives to the current standard of care in clinical practice(3).

Evolution in the development of oral anticoagulants to offset the drawbacks of Warfarin has led to the introduction of two new oral anticoagulants, namely Dabigatran Etexilate a direct Thrombin Inhibitor and Rivaroxaban, a direct factor Xa inhibitor. The clinical and cost effectiveness of both Dabigatran Etexilate and Rivaroxaban have been appraised by the National Institute for Health and Clinical Excellence (NICE). According to the technology appraisal of their efficacy and cost effectiveness, both drugs are licensed for the prevention of VTE in patients undergoing elective hip and knee replacement surgery(4).

The purpose of this study is to review and study the available clinical data with regard to the safety profiles of these newer oral anticoagulants. Specific areas of focus include : bleeding events, deep venous thrombosis and pulmonary embolism incidence.

Anatomy

Lower extremity venous anatomy

Although much thinner walled than arteries, veins are also composed of intimal, medial, and adventitial layers. The intimal monolayer rests on the basement membrane and is actively antithrombogenic, producing prostaglandin and glycosaminoglycan cofactors of antithrombin and thrombomodulin (5).

In comparison with arteries, veins have a weaker muscular layer and less elastic tissue. The adventitia is the thickest layer of the veins wall (Fig.1), containing proportionately more collagen and rendering veins stiffer than the arteries(6).

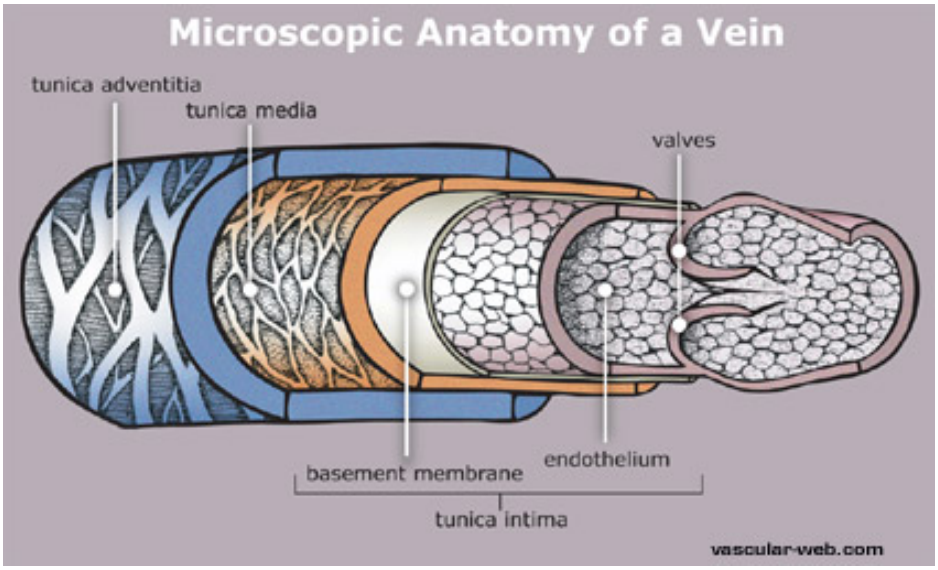

Figure 1 : Microscopic Anatomy of a vein (6).

The venous system of the lower extremities includes :

1-The deep veins which lie beneath the muscular fascia and drain the lower extremity muscles.

2- The superficial veins which lie above the deep fascia and drain the cutaneous microcirculation.

3- The perforating veins that penetrate the muscular fascia and connect the superficial and deep veins.
Communicating veins connect veins within the same system (i.e., deep to deep, superficial to superficial)(7).

The Superficial Veins

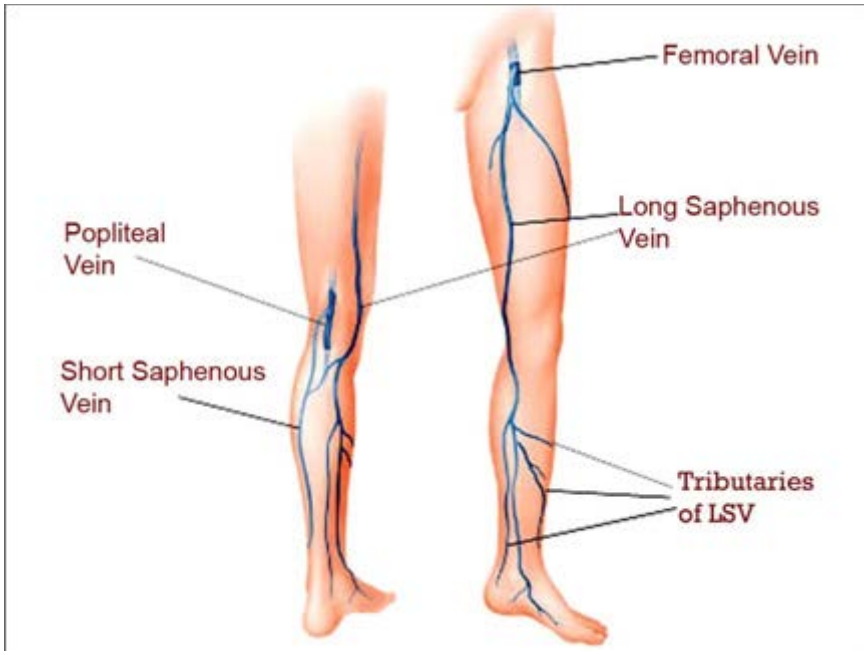

Figure 2: Superficial venous system (8).

The superficial venous system includes the reticular veins as well as the great (greater) and small (lesser) saphenous veins and their tributaries (8).

The great saphenous vein arises from the medial aspect of the dorsal pedal venous arch and ascends anterior to the medial malleolus, crossing the tibia at the junction of the distal and middle third of the calf to pass posteromedial to the knee (Fig.2).

The vein then ascends medially in the thigh to perforate the deep fascia and join the common femoral vein 3 to 4 cm (two fingerbreadths) inferior and lateral to the pubic tubercle(8).

A valve is present at the saphenofemoral junction. The main trunk of the great saphenous vein usually has at least six valves. The saphenous nerve lies anterior to the great saphenous vein in the calf and may be injured by procedures extended into the calf(9).

The small saphenous vein, formerly known as the short or lesser saphenous vein, arises from the dorsal pedal arch and ascends posterolaterally from behind the lateral malleolus to a variable termination in the popliteal vein. The small saphenous vein usually has 7 to 10 closely spaced valves. The sural nerve ascends immediately lateral to the vein, which usually lies on and then beneath the muscular fascia prior to its termination. Approximately 60% of small saphenous veins join the popliteal vein within 8 cm of the knee joint, 20% join the great saphenous vein via anterior or posterior tributaries, and 20% join the femoral, deep femoral, or internal iliac veins. The reticular veins, a network of veins parallel to the skin surface and lying between the saphenous fascia and dermis, drain the lower extremity skin and subcutaneous tissue (8).

The Deep Veins

The major deep veins of the lower extremity (Fig.3) follow the course of the associated arteries and, with the exception of the femoral vein, are named accordingly. However, there is significant variability and the classic anatomy may be present in as few as 16% of limbs(9).

The deep venous system of the calf includes the tibial and peroneal veins as well as the soleal and gastrocnemial veins. The anterior tibial, posterior tibial, and peroneal veins are the venae comitantes of the corresponding arteries, the paired veins

communicating in a plexiform arrangement around the artery. The muscular venous sinuses are the principal collecting system of the calf muscle pump(6).

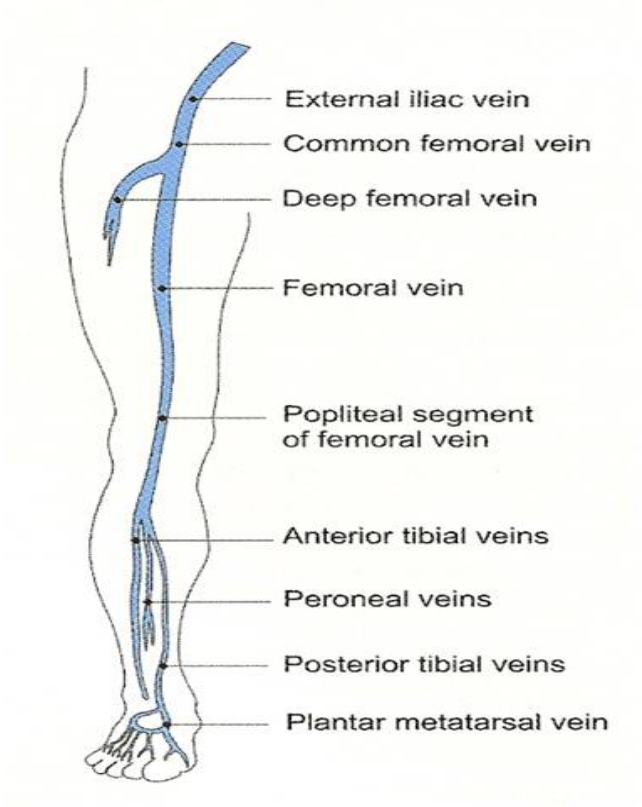

Figure 3 : The Deep Venous System of the lower limb(9).

There are 1 to 18 soleal sinuses that are numerically of greater importance than those present in the gastrocnemius muscles. The soleal sinuses communicate with the posterior tibial vein in the proximal calf, while the gastrocnemial network coalesces to form the paired gastrocnemial veins draining into the popliteal vein. The popliteal vein is formed by the confluence of the calf veins. The femoral vein is continuation of popliteal vein and it ends at the inferior margin of the inguinal ligament. The deep femoral vein(profund femoris vein) receives blood from the inner thigh and proceeds superiorly and medially alongside the profund femoris artery to join the femoral vein. The femoral vein accompanies the femoral artery within the femoral sheath in the femoral triangle(6).

The femoral triangle:

The femoral triangle is the space which occupies the upper third of the front of the thigh(Fig.4).

Borders : As this area is a triangle, it has three borders:

- Superior border which is formed by the inguinal ligament, a ligament that runs from the anterior superior iliac spine to the pubis tubercle.
- Lateral border which is formed by the medial border of the sartorius muscle.
- Medial border which is formed by the medial border of the adductor longus muscle. The rest of this muscle forms part of the floor of the triangle(10).

It also has a floor and a roof:

- Anteriorly, the roof of the femoral triangle is formed by the fascia lata.
- Posteriorly, the base of the femoral triangle is formed by the pectineus, iliopsoas and adductor longus muscles(10).

Contents:

The femoral triangle contains some of the major neurovascular structures of the lower limb. Its contents (from lateral to medial) are:

- Femoral nerve which innervates the anterior compartment of the thigh, and provides sensory branches for the leg and foot.
- Femoral artery which is responsible for the majority of the arterial supply to the lower limb.
- Femoral vein and the great saphenous vein drains into the femoral vein within the triangle.

- Femoral canal : A structure which contains deep lymph nodes and vessels. The femoral artery, vein and canal are contained within a fascial compartment known as the femoral sheath(10).

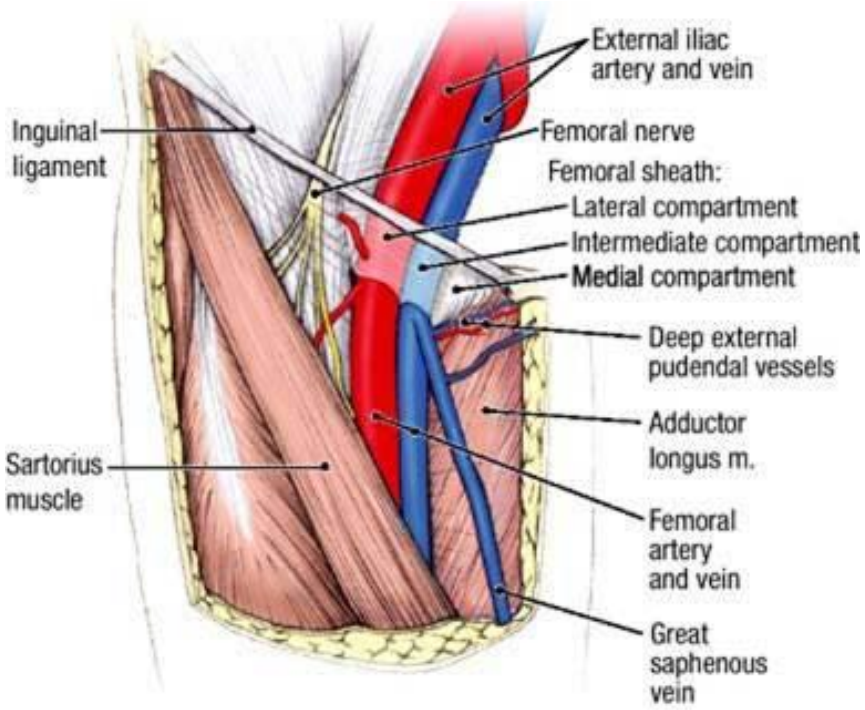

Figure 4: Anatomy of femoral triangle(11).

To avoid confusion with the superficial venous system, the phrase “superficial femoral vein” has been abandoned in current nomenclature. The deep vein extending from the popliteal vein to the common femoral vein is now referred to as the femoral vein rather than the superficial femoral vein(12).

The anatomy of the iliac veins has been less thoroughly described than that of the infrainguinal veins. A single internal iliac trunk usually drains into the external iliac vein to form the common iliac vein. However, a duplicated internal iliac vein may be present in up to 27% of extremities. The common iliac veins unite on the right side of the fifth lumbar vertebrae to form the inferior vena cava. The right common iliac vein ascends along a relatively