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Review Article

Use of Anticoagulation Following Anterior Cruciate Ligament Reconstruction: A Systematic Review

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Received: June 13, 2016; **Published:** July 13, 2016

Abstract

Background: Use of chemical and mechanical anticoagulation for venous thromboembolic (VTE) disease prophylaxis following anterior cruciate ligament (ACL) reconstruction has not been well documented.

Hypothesis: The most common protocol of VTE prophylaxis following ACL reconstruction would be aspirin and early ambulation.

Methods: A systematic review was registered with PROSPERO and performed using PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines using three publicly available databases. All studies describing the use of mechanical and/or chemical prophylaxis to prevent VTE disease following ACL reconstruction were eligible for inclusion. All study, subject and surgical data were analyzed. Descriptive statistics were calculated.

Results: Of the 2002 studies identified in the initial search, one study was identified that met the inclusion criteria. A total of 140 patients (82 males), mean age 30.1 +/- 7.1 years without concomitant pathology or use of a tourniquet underwent ACL reconstruction using a bone patellar tendon bone autograft. Patients received either subcutaneous once daily placebo or subcutaneous 40mg once daily enoxaparin for 20 days after hospital discharge. Two patients (2.8%) in the enoxaparin group and 28 patients (41.2%) in the placebo group had a magnetic resonance venography (MRV) proven deep vein thrombosis (DVT) ($p < 0.001$) at 23 to 28 days post-operatively, with no symptomatic pulmonary embolus in either group.

Conclusion: There is a significant deficit in the literature regarding use of anticoagulation for VTE prophylaxis after ACL reconstruction. Enoxaparin reduces rates of DVT compared to placebo, but does not reduce the rate of symptomatic PE.

Keywords: *Deep Venous Thrombosis (DVT); Pulmonary Embolus (PE); Prophylaxis (PPx); Anterior Cruciate Ligament (ACL) Reconstruction; Thromboembolic disease*

Introduction

Anterior cruciate ligament (ACL) reconstruction is one of the most common surgeries performed by Orthopedic Surgeons and the number of reconstructions performed each year continues to rise [1]. It is estimated that there are over 250,000 ACL tears annually, over half of which undergo reconstruction. This amounts to an annual cost of approximately one billion dollars to the health care industry [2-4]. As the number of ACL reconstructions continues to rise, despite a reduction in the complication rate, the overall number of complications

increases as well [5]. Complications include infection, re-rupture, venous thromboembolism (VTE) (including both deep venous thrombosis [DVT] and pulmonary embolism [PE], among others [6]. The rates of VTE have been highly scrutinized around other types of knee surgery, including total knee arthroplasty. However, the rates of VTE following ACL reconstruction have been less well studied [5,7-9].

Given the potential morbidity and mortality of VTE regardless of etiology and the lack of evidence investigating the routine use of perioperative VTE prophylaxis for ACL reconstruction, the topic is controversial, poorly defined, and demonstrates a need for study. There are some surgeons who advocate for routine use of VTE prophylaxis following various arthroscopic knee procedures, ranging from a baby aspirin to low molecular weight heparin (LMWH) and even rivaroxaban [6,9]. However, there are many ACL reconstruction studies in the literature with no mention of the use VTE prophylaxis, either mechanical or chemical [10-14]. As chemical VTE prophylaxis is not without complications including hemarthrosis, surgical site infections, and medication reactions, the treating surgeon must weigh the risk of VTE with the morbidity of taking chemical anticoagulation [15-17].

The purpose of this investigation was to perform a systematic review and meta-analysis of the entire ACL reconstruction literature to determine what proportion of subjects receive VTE prophylaxis following ACL reconstruction and the most common protocol of VTE prophylaxis (chemical, mechanical, dose, duration) after ACL reconstruction. We hypothesized that most patients would not receive VTE prophylaxis after ACL reconstruction and the most common type of anticoagulation used following ACL reconstruction would be aspirin.

Methods

A systematic review was conducted according to PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses) using a PRISMA checklist [18]. Systematic review was registered in the PROSPERO International prospective register of systematic reviews (registration number CRD42014013116) on (July 8, 2014) [19]. Two reviewers independently conducted the search on August 6, 2014 using the following databases: Medline, Cochrane Central Register of Controlled Trials, SportDiscus, and CINAHL. The electronic search citation algorithm utilized was:

(Anterior cruciate ligament reconstruction [Title/ Abstract]) and knee [Title/ Abstract]) not (cadaver [Title/ Abstract]) not (shoulder [Title/ Abstract]) not hip [Title/ Abstract]. English language Level I-IV evidence (2011 update by the Oxford Centre for Evidence-Based Medicine [20]) clinical studies were eligible. No conference abstracts were eligible for inclusion. All references within included studies were cross-referenced for inclusion of any studies missed by the initial search. Duplicate subject publications within separate unique studies were not reported twice. The study with the higher number of patients was included. Level V evidence reviews, letters to the editor, basic science, biomechanical studies, and classification studies were excluded.

A total of 2002 studies were identified on the initial search (Figure 1). The inclusion and exclusion criteria were applied and then the following information was recorded for the study: Type of anticoagulation (chemical, mechanical), dose of anticoagulation, duration of anticoagulation, number of venous thromboembolic events (PE and DVT) minor bleeding events, major bleeding events, reoperations, and side effects to medications. There was no minimum follow-up or rehabilitation requirement. Study and subject demographic parameters analyzed included year of publication, years of subject enrollment, presence of study financial conflict of interest, number of subjects and knees, gender, age, body mass index (BMI), and diagnoses treated. Study methodological quality was evaluated using the MCMS (Modified Coleman Methodology Score) [21].

Statistical analysis

Study descriptive statistics were calculated. Continuous variable data were reported as mean +/- standard deviation from the mean. Weighted means and standard deviations were calculated for all subject, knee, and surgical parameters. Categorical variable data was reported as frequency with percentages. Statistical analysis was not reported in this study due to the fact that only one study was found to meet the inclusion/exclusion criteria, which eliminates any means of comparing data.

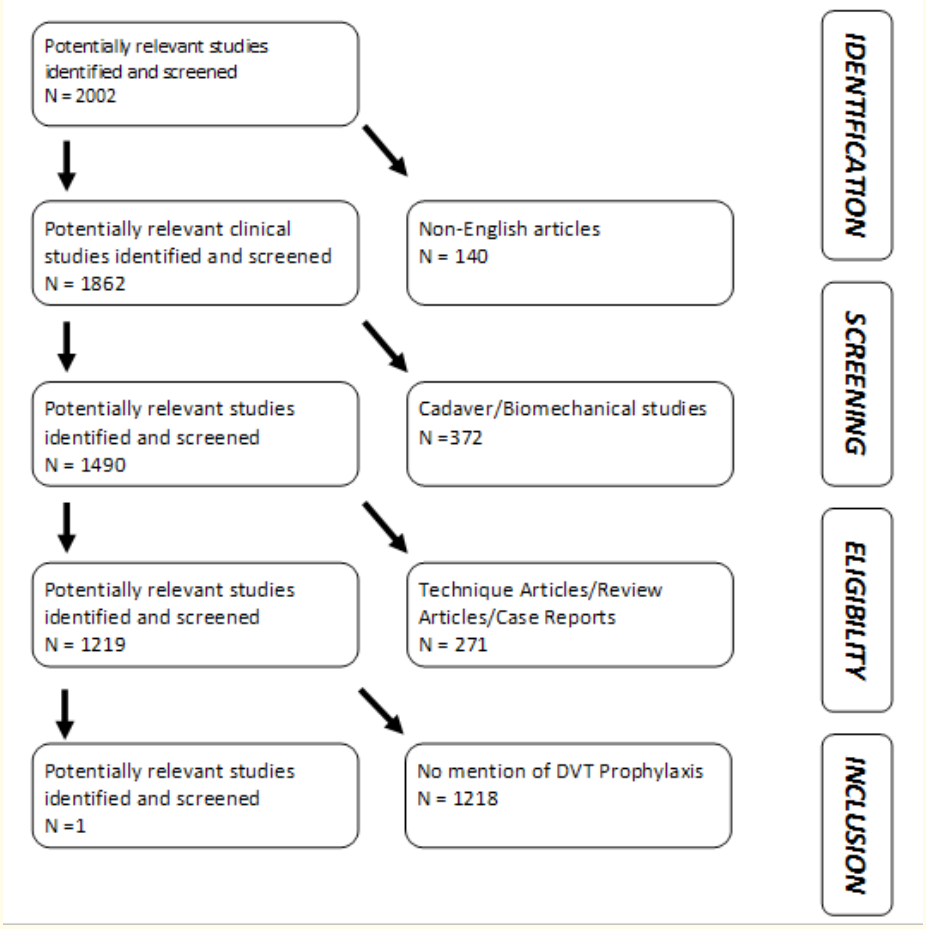

Figure 1: *PRISMA Flowchart.*

Results

Of the 2002 studies initially identified, only one study remained for inclusion in this review after implementation of the inclusion criteria as only one study evaluated solely patients who underwent ACL reconstruction and not other knee arthroscopic procedures (Figure 1) [22]. Marlovits., *et al*. was a single center, level I, double-blind, randomized controlled trial, with a potential financial conflict of interest, conducted in France, published in 2007, with an MCMS of 69 [22]. A total of 140 patients, 82 males and 58 females, mean age 30.1 +/- 7.1 years, mean body weight 72.7 +/- 12.3 kg, mean height 174 +/- 8 cm underwent ACL reconstruction using a bone patellar tendon bone autograft and were included in the intent to treat analysis. Every patient received one dose of enoxaparin 40mg subcutaneously (SC) preoperatively and while in the hospital. Upon discharge the group was randomized to receive 40 mg of subcutaneous enoxaparin or subcutaneous placebo once daily for 20 days after discharge.

No patient had radiographic (as defined by magnetic resonance venography (MRV)) evidence of a DVT prior to surgery or at time of discharge from the hospital. At the final follow up, two patients (2.8%) in the enoxaparin group and 28 patients (41.2%) in the placebo group had an MRV proven DVT ($p < 0.001$), while no patient had a symptomatic PE. There were 13 patients (2.5%) in the enoxaparin group and 10 patients (2.0%) in the placebo group who experienced minor bleeds ($p = 0.595$). Minor bleeds were differentiated from major bleeding events which included fatal bleeding, intracranial, intraspinal, or retroperitoneal bleeding, bleeding leading to reoperation

or transfusion of 2 or more units of packed red blood cells, bleeding involving a critical organ, and overt bleeding with a bleeding index of two or more. Immobilization prior to surgery and age > 30 years were noticed to be independent risk factors for DVT following ACL reconstruction.

Discussion

ACL reconstruction has become a common surgery for both sports medicine fellowship trained and general orthopaedic surgeons [5]. However, the decision on whether to anticoagulate patients post-ACL reconstruction has varied opinions. The purpose of this study was to perform a systematic review of the current literature to determine the most common type of VTE prophylaxis following ACL reconstruction as well as the trends in use of VTE prophylaxis following ACL reconstruction. As only one study met the inclusion criteria, it is difficult to confirm or reject our hypotheses that aspirin would be the most common anticoagulant and that the trend in the literature would be to avoid anticoagulation after ACL reconstruction. However, as the included study was the highest quality evidence possible (level I evidence: a double blind randomized control trial), the authors' hypotheses were rejected as enoxaparin was the anticoagulant of choice, and a lower rate of DVT was seen in the treatment group compared to the placebo group [22]. However, despite the higher incidence of DVT in the placebo group, there was no difference in symptomatic PE rates.

Prophylaxis against VTE following ACL reconstruction is a controversial topic. While some surgeons may routinely use some form of anticoagulation or VTE prophylaxis, based on the results of this literature search it appears that the majority do not use VTE prophylaxis, or if they do it is not reported in the literature. While VTE prophylaxis, both mechanical and chemical, is routinely performed after arthroplasty procedures, the indications for VTE prophylaxis following arthroscopic surgery, specifically ACL reconstruction, are less well defined [23,24]. There have been several studies that have evaluated VTE prophylaxis after arthroscopic surgery of the knee [6,25-28]. Wirth., *et al*. randomized 262 patients who underwent outpatient arthroscopic knee surgery (meniscectomy, loose body removal, but not ACL reconstructions) to receive low-molecular weight heparin (LMWH) or nothing for VTE prophylaxis [26]. Five patients (4.1%) in the group who did not receive prophylaxis and one patient (0.85%) in the LMWH group developed a DVT, and no patients sustained a major bleeding complication. No patient in either group suffered a symptomatic PE. Munoa., *et al*. randomized 467 patients to either rivaroxaban or bemiparin for VTE prophylaxis who underwent either a meniscectomy (363 patients), ACL reconstruction (60 patients), osteochondral graft (16 patients), necrosis perforations (nine patients), or other (19 patients) [6]. No patient in either group developed a DVT or symptomatic PE while they were taking their prophylaxis.

Similarly, Michot., *et al.* randomized 218 patients to receive LMWH or no VTE prophylaxis following arthroscopic knee surgery and found one patient (1.5%) in the low-molecular weight heparin group and 10 patients (15.6%) in the control group had a VTE [27]. Interestingly, the one patient who experienced a DVT in the LMWH group experienced a symptomatic PE while no patient in the control group experienced a symptomatic PE, and patients in the LMWH group had more minor bleeds than the controls group (12% vs. 6%). While these studies showed low rates of VTE in the patients who were treated with some form of chemical VTE prophylaxis following arthroscopic knee surgery, the clinical relevance of these finding are called into question given the traditionally low reported incidence of VTE after arthroscopic knee surgery.

Recent studies are starting to challenge the traditional thought that VTE incidence is low after knee arthroscopy and the emerging data are suggesting that even if the VTE is present it may just be silent and located in the distal calf veins thus rendering the patient asymptomatic [29,30]. The clinical relevance of silent DVT's after knee arthroscopy is unclear and more studies are needed to explore this area. Sun., *et al*. in their review of 537 consecutive patients who underwent a variety of knee arthroscopy procedures and had no VTE prophylaxis, found that the overall incidence of VTE diagnosed with routinely applied venography after arthroscopic knee surgery was 14.9%, of which only 3.7% of cases were symptomatic. Therefore, a majority (11.2%) of the cases of VTE after knee arthroscopy were silent VTE's [29]. Furthermore, 45% (36/80) of the total VTE's found in the study were in patients who had undergone ACL reconstruction and 15.6% of patients who had ACL reconstructions were found to have a DVT. Similarly, Struijk-Mulder., *et al*. showed that incidence

of VTE, diagnosed with complete compression ultrasonography, after arthroscopic ACL reconstruction was relatively high and found that there was a 9% incidence of asymptomatic proximal or distal DVT, with only 4% of the patients having symptomatic DVT [30]. Despite the fact that patients were routinely screened in the above studies, it is not necessary to screen all patients for VTE with imaging studies after ACL reconstruction.

Furthermore, the relevance of silent DVTs and the role of post-operative chemical or mechanical prophylaxis is not clear from the available literature. However, these high rates of asymptomatic DVTs warrant further investigation into the potential use of DVT prophylaxis and the decision-making could possibly be based on individual patient risk factors, but more research will be needed. While DVT is a known complication of total joint arthroplasty and routine prophylaxis against VTE with coumadin, LMWH, aspirin, in these patients is undertaken, the rate of symptomatic PE in these patients is relatively low, [31] similar to the previously mentioned ACL reconstruction studies. Hence, there is more work to be done on cost/benefit analysis of VTE prophylaxis as it relates to ACL reconstruction.

The increased risk of both minor and major adverse reactions with the use of chemical prophylaxis has to be closely weighed against the potential benefits of its use after arthroscopic ACL reconstruction. The rates of minor bleeding events were often higher in the groups of patients treated with chemical prophylaxis and although the risk is generally thought to be low there is also the potential for a major bleed. Postoperative hemarthrosis places a patient at risk for infection and stiffness. Henceforth, there does not seem to be a consensus in the literature as to whether or not patients undergoing arthroscopic knee surgery, and specifically ACL reconstruction, would see a clinically relevant benefit to receiving VTE prophylaxis in the post-operative setting.

The single study included in this review, Marlovits., *et al*. found an increased rate of DVT in patients who did not receive prophylaxis post-operatively (41.2% vs. 2.8%), although the clinical significance of this difference in unknown [22]. The reported rate of DVT in this study was higher than other studies in the literature. It is likely that these rates were higher because Marlovits., *et al*. performed an MRV (sensitivity of 100% and specificity of 96% in detecting a DVT) in all patients, regardless of clinical symptoms, to diagnose DVT while other studies used ultrasonography, and often only when symptoms of DVT (pain, swelling) arose [6,22,26,27]. Marlovits., *et al*. also used indirect signs of DVT rather than direct signs, which may have falsely elevated the number of DVT [22]. While a distal DVT can cause pain, swelling, and some moderate dysfunction, the overall morbidity is low if the clot does not propagate to a more proximal region of the leg leading to persistent pain and swelling, or embolize to the lung resulting in a symptomatic PE. When below the knee, clots will often undergo endogenous fibrinolysis and dissolve before ever becoming symptomatic; therefore, these clots be clinically insignificant, and may never have been picked up without routine screening. Interestingly, in the Marlovits., *et al*. study only 10% of the MRV positive DVT were confirmed by contrast venography, leading to potential over diagnosis of DVT [22]. To positively verify a DVT by MRV, international standards require a constant intraluminal filling defect to be demonstrated on at least two images within different projections [22]. Using these criteria, only direct signs of DVT can be accepted as a verification of DVT, unlike the indirect signs used in the Marlovits study [22]. Furthermore, detection of silent DVT by MRV screening of the lower limbs after knee surgery has not been validated by MRV, a highly relevant point in asymptomatic patients.

Finally, the majority of patients in all of the studies mentioned developed a distal DVT, which may or may not be clinically significant. The lack of studies and eligible patients to include in our analysis highlights the need for further studies looking at the clinical significance and morbidity (inability to participate in rehabilitation secondary to pain, higher likelihood of developing arthrofibrosis, etc.) of developing a DVT in the post-operative setting after an ACL reconstruction. Given the increasing number of ACL reconstructions performed annually, large, double blind, randomized clinical trials, similar to those found in the joint replacement literature, studying the efficacy and safety of DVT prophylaxis in comparison with placebo and using clinical endpoints are essential to improve patient outcomes [5,33,34].

Limitations

The strength of this study is our use of PRISMA guidelines and the inclusion of only level 1 evidence as this was the only study which

met inclusion criteria. Unfortunately, there was only one study that met our inclusion/exclusion criteria, which greatly limits the conclusions that we are able to draw. As this study was a review of the literature, it is subject to the limitations of the included study, although these were minimal as the included study was a level I double blind randomized control trial. The current study is limited by lack of evidence surrounding the subject of VTE prophylaxis following ACL reconstruction. The lack of available literature prevents the formulation of any definitive recommendations about the use of VTE prophylaxis after ACL reconstruction and highlights the need for more research in this area. These finding illustrate the need for further study in this area.

Conclusion

There is a significant deficit in the literature regarding use of anticoagulation for VTE prophylaxis after ACL reconstruction. Enoxaparin reduces rates of DVT compared to placebo, but does not reduce the rate of symptomatic PE.

Bibliography

1. Labella CR., *et al*. "Anterior Cruciate Ligament Injuries: Diagnosis, Treatment, and Prevention". *Pediatrics* 133.5 (2014).

2. Frank CB and Jackson DW. "The science of reconstruction of the anterior cruciate ligament". *The Journal of Bone and Joint Surgery American volume* 79.10 (1997): 1556-1576.

3. Marrale J., *et al*. "A literature review of autograft and allograft anterior cruciate ligament reconstruction". *Knee Surgery, Sports Traumatology, Arthroscopy* 15.6 (2007): 690-704.

4. Griffin LY., *et al*. "Noncontact anterior cruciate ligament injuries: risk factors and prevention strategies". *The Journal of the American Academy of Orthopaedic Surgeons* 8.3 (2000): 141-150.

5. Leroux T., *et al*. "The Epidemiology of Revision Anterior Cruciate Ligament Reconstruction in Ontario, Canada". *The American Journal of Sports Medicine* 42-11 (2014): 2666-2672.

6. Munoa L., *et al*. "Rivaroxaban is as efficient and safe as bemiparin as thromboprophylaxis in knee arthroscopy". *Musculoskeletal Surgery* 98.1 (2014): 21-25.

7. George MS., *et al*. "Current concepts review: revision anterior cruciate ligament reconstruction". *The American Journal of Sports Medicine* 34.12 (2006): 2026-2037.

8. Hettrich CM., *et al*. "The rate of subsequent surgery and predictors after anterior cruciate ligament reconstruction: two- and 6-year follow-up results from a multicenter cohort". *The American Journal of Sports Medicine* 41.7 (2013): 1534-1540.

9. Chahal J LA., *et al*. "A Retrospective Review of Anterior Cruciate Ligament Reconstruction Using Patellar Tendon: 25 Years of Experience". *Orthopaedic Journal of Sports Medicine* 1.3 (2013).

10. Briem K., *et al*. "Altered medial versus lateral hamstring muscle activity during hop testing in female athletes 1-6 years after anterior cruciate ligament reconstruction". *Knee Surgery, Sports Traumatology, Arthroscopy* 24.1 (2016): 12-17.

11. Engelman GH., *et al*. "Comparison of Allograft Versus Autograft Anterior Cruciate Ligament Reconstruction Graft Survival in an Active Adolescent Cohort". *The American journal of sports medicine* 42 .10 (2014): 2311-2318.

12. Koga H., *et al*. "Effect of Notchplasty in Anatomic Double-Bundle Anterior Cruciate Ligament Reconstruction". *The American journal of sports medicine* 42.8 (2014): 813-821.

13. Webster KE., *et al*. "Younger patients are at increased risk for graft rupture and contralateral injury after anterior cruciate ligament reconstruction". *The American journal of sports medicine* 42.3 (2014): 641-647.

14. Rahr-Wagner L., *et al*. "Comparison of hamstring tendon and patellar tendon grafts in anterior cruciate ligament reconstruction in a nationwide population-based cohort study: results from the danish registry of knee ligament reconstruction". *The American journal of sports medicine* 42.2 (2014): 278-284.

15. Wang Z., *et al*. "Surgical site infections and other postoperative complications following prophylactic anticoagulation in total joint arthroplasty". *PLOS ONE* 9.4 (2014): e91755.

16. Raphael IJ., *et al*. "Aspirin: an alternative for pulmonary embolism prophylaxis after arthroplasty?" *Clinical orthopaedics and related research* 472.2 (2014): 482-488.

17. Marengoni A., *et al*. "Understanding adverse drug reactions in older adults through drug-drug interactions". *European journal of internal medicine* 25.9 (2014): 843-846.

18. Liberati A., *et al*. "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration". *Journal of clinical epidemiology* 62.10 (2009): e1-34.

19. The University of York CfRaDP-Iprosr-v. 2013 [2014].

20. The University of Oxford CfEBMOLoES. Oxford Centre for Evidence Based Medicine [2012].

21. Cowan J., *et al. "*Quality of prospective controlled randomized trials. Analysis of trials of treatment for lateral epicondylitis as an example". *The Journal of bone and joint surgery American volume* 89.8 (2007): 1693-1699.

22. Marlovits S., *et al.* "Extended-duration thromboprophylaxis with enoxaparin after arthroscopic surgery of the anterior cruciate ligament: a prospective, randomized, placebo-controlled study". *Arthroscopy* 23.7 (2007): 696-702.

23. Hamilton WG., *et al.* "Mechanical thromboembolic prophylaxis with risk stratification in total knee arthroplasty". *The Journal of arthroplasty* 30.1 (2014): 43-45.

24. Levitan B., *et al.* "Benefit-risk assessment of rivaroxaban versus enoxaparin for the prevention of venous thromboembolism after total hip or knee arthroplasty". *Vascular health and risk management* 10 (2014): 157-167.

25. Chapelle C., *et al.* "Prevention of venous thromboembolic events with low-molecular-weight heparin in the non-major orthopaedic setting: meta-analysis of randomized controlled trials". *Arthroscopy* 30.8 (2014): 987-996.

26. Wirth T., *et al.* "Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): Results of a randomized controlled trial". *Arthroscopy 17.4* (2001): 393-399.

27. Michot M., *et al.* "Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low-molecular weight heparin". *Arthroscopy* 18.3 (2002): 257-263.

28. Sun Y., *et al.* "Deep venous thrombosis after knee arthroscopy: a systematic review and meta-analysis". *Arthroscopy* 30.3 (2014): 406-412.

29. Sun Y., *et al.* "Incidence of symptomatic and asymptomatic venous thromboembolism after elective knee arthroscopic surgery: a retrospective study with routinely applied venography". *Arthroscopy* 30.7 (2014): 818-822.

30. Struijk-Mulder MC., *et al.* "Deep vein thrombosis after arthroscopic anterior cruciate ligament reconstruction: a prospective cohort study of 100 patients". *Arthroscopy* 29.7 (2013): 1211-1216.

31. Sasaki H., *et al*. "Retrospective comparison of three thromboprophylaxis agents, edoxaban, fondaparinux, and enoxaparin, for preventing venous thromboembolism in total knee arthroplasty". *International orthopaedics* 38.3 (2014): 525-529.

32. Somarouthu B., *et al.* "Diagnosing deep vein thrombosis". *Postgraduate Medicine* 122.2 (2010): 66-73.

33. Lazo-Langner A., *et al.* "Rivaroxaban vs. low molecular weight heparin for the prevention of venous thromboembolism after hip or knee arthroplasty: a cohot study". *Journal of thrombosis and haemostasis* 12.10 (2014): 1626-1635.

34. Sheth NP., *et al.* "DVT prophylaxis in total joint reconstruction". *The Orthopedic clinics of North America* 41.2 (2010): 273-280.

Volume 3 Issue 3 July 2016