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Review

Are Anticoagulants required after High Tibial Osteotomy to Prevent Venous Thromboembolism Events? A Systematic Review

Frank R Noyes[1], Sue D Barber-Westin[1]*, and Martin S Levy[2]

[1]Cincinnati Sports medicine and Orthopaedic Center, Noyes Knee Institute, The Jewish Hospital-Mercy Health, Cincinnati, Ohio, USA

[2]Operations and Business Analytics and Information Systems, Lindner College of Business, University of Cincinnati, Cincinnati, Ohio, USA

Abstract

Introduction

High Tibial Osteotomy (HTO) is an operation that, although well-established, may be associated with complications including venous thromboembolism events. There is no consensus regarding postoperative thromboprophylaxis, including the routine use of anticoagulants. This review investigated two questions: (1) what are the incidence rates of venous thromboembolism events after HTO, and (2) what is the routine use of anticoagulants required in standard-risk patients?

Methods

We conducted a systematic review of PubMed and Cochrane databases from 1999 through 2014 using search terms high tibial osteotomy, HTO complications, HTO DVT, opening wedge osteotomy and closing wedge osteotomy. One-hundred and seven studies were included (opening-wedge osteotomy 3923 knees and closing-wedge osteotomy 3172 knees).

Results

The overall incidence rates of deep venous thrombosis and pulmonary embolism were 1.24% and 0.11%, respectively. Anticoagulants were used in 1,110 patients and aspirin was used in 312 patients. The relative risk of DVT was higher in patients that used anticoagulants compared with patients that did not use any form of chemoprophylaxis (1.99% and 1.11%, respectively; P = 0.02). The risk of DVT was higher in closing-wedge osteotomies compared with opening-wedge osteotomies regardless of the use of anticoagulants.

Conclusion

The incidence of venous thromboembolism events was very low after HTO, regardless of the use of chemoprophylaxis. Therefore, the necessity for anticoagulation after HTO in patients who do not have significant risk factors is questioned considering the side effects that may occur with these agents.

***Corresponding author:** Sue D Barber-Westin, Cincinnati Sports Medicine and Orthopaedic Center, Noyes Knee Institute, The Jewish Hospital-Mercy Health, Cincinnati, Ohio, USA, Tel: +1 5133479999; E-mail: sbwestin@csmref.org

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Introduction

High Tibial Osteotomy (HTO) is an operation that, although well-established, may be associated with complications [1,2] including Deep Venous Thrombosis (DVT) that may occur in up to 5% of patients [2-5]. Several authors have recommended postoperative thromboprophylaxis programs for HTO that are similar to those used after Total Knee Arthroplasty (TKA) [2-5]; however, the appropriate program is not supported by clinical studies. Whether anticoagulants should be routinely used postoperatively in patients who do not have significant risk factors for DVT is unknown. In addition, the role of aspirin, mechanical compressive devices, early mobilization and exercises such as immediate range of knee motion in decreasing the incidence of venous thromboembolism events after HTO has not been addressed.

This study was designed to address two primary questions: (1) What are the incidence rates of DVT and Pulmonary Embolism (PE) after modern HTO and (2) is the routine use of anticoagulants required in patients who do not have significant risk factors for venous thromboembolism events? Significant risk factors include personal or family history of DVT, obesity, use of oral contraceptives, and well-recognized hereditary disorders such as protein C deficiency, protein S deficiency and antithrombin III deficiency. In addition, secondary questions were developed to address comparisons between and within opening- and closing-wedge osteotomy studies and postoperative rehabilitation factors (Table 1).

Research Question	
Primary: All studies	What is the incidence of DVT and PE after modern HTO?
Primary: All studies	Is the use of anticoagulants required for thromboembolic prophylaxis in patients who do not have significant risk factors for DVT?
Secondary: Comparison opening-versus closing-wedge osteotomies	Is there a difference between opening- and closing-wedge osteotomy studies in the incidence of DVT when no chemoprophylaxis is used postoperatively?
Secondary: Comparison opening-versus closing-wedge osteotomies	Is there a difference between opening- and closing-wedge osteotomy studies in the incidence of DVT when chemoprophylaxis is used postoperatively? Does the type of chemoprophylaxis (anticoagulants vs. aspirin) affect the incidence rate?
Secondary: Opening-wedge studies only	In the opening-wedge osteotomy studies, did the use of anticoagulants or aspirin after surgery significantly reduce the incidence of DVT?
Secondary: Closing-wedge studies only	In the closing-wedge osteotomy studies, did the use of anticoagulants or aspirin after surgery significantly reduce the incidence of DVT?
Secondary: Effect of postoperative rehabilitation factors	Do mechanical compressive devices, early partial weight-bearing, and immediate range of knee motion exercises significantly reduce the incidence of DVT?

Table 1: Primary and Secondary Study Questions.

Abbreviations: DVT-Deep Venous Thrombosis; HTO-High Tibial Osteotomy; PE-Pulmonary Embolism

PRISM guidelines were followed in conducting this study [6]. An online search was performed using Medline and Cochrane databases from April 1999 through April 2014. Search terms included High Tibial Osteotomy, HTO complications, HTO DVT, opening wedge osteotomy and closing wedge osteotomy. The resulting titles and abstracts were screened to determine eligibility. The full text was retrieved and reviewed if the abstract suggested that this might be a study in our topic of interest. The references of each article that met the inclusionary criteria were searched to find any other articles not otherwise obtained.

The online search initially identified 382 original research articles. A total of 275 were excluded for the reasons shown in table 2. This left 107 research investigations (Appendix 1) that met the following inclusionary criteria: (1) English language, (2) opening-wedge or closing-wedge osteotomy clinical studies of all evidence levels and (3) postoperative incidence rates of DVT and/or PE provided.

Exclusionary Criteria	Number of Studies
Off topic	87
Study related to biomechanics or anatomy only	39
Review article, no discussion of thromboprophylaxis protocol	48
HTO clinical study:	
Thromboprophylaxis protocol or incidence rates of DVT/PE not reported	36
Rate of DVT/PE not reported according to type of osteotomy	5
Prophylaxis program used, but not described	8
Study on radiographic or computer navigation data only	30
HTO technique paper	17
Other	5

Table 2: Exclusionary criteria of 382 original research studies identified.

Abbreviations: DVT-Deep Venous Thrombosis; HTO-High Tibial Osteotomy; PE-Pulmonary Embolism

Exclusionary criteria were as follows: (1) articles that were off topic (2) articles that failed to achieve the inclusionary criteria listed previously (3) studies that did not provide any information regarding thromboprophylaxis or incidence rates of DVT and/or PE (4) studies that only provided radiologic or intra operative measurement data (5) investigations on other types of osteotomy such as dome and hemicallotasis and (6) other types of articles such as case reports, abstracts and technical notes.

Each study that met the inclusion criteria was abstracted for information regarding the following: (1) the level of evidence as determined by the journal of publication [7,8], (2) number of patients and knees (3) number of males and females (4) age at osteotomy (5) months or years of follow-up (6) type of osteotomy (opening-wedge or closing-wedge) (7) number of DVT (either calf, distal thigh, or site not given) and PE events (8) outcome of treatment for venous thromboembolism events (9) any recommended thromboprophylaxis protocol (10) time when partial weight-bearing was allowed postoperatively and (11) time when range of knee motion exercises began postoperatively. The findings were reviewed by two of the authors (FRN and SBW) and agreement reached regarding the data extracted.

The thromboprophylaxis protocols were divided into three subgroups according to the usage of chemoprophylaxis agents: none, anticoagulants (heparin, warfarin, or low-molecular-weight-heparin) and anti platelets (aspirin). One of us (MSL) calculated Odds Ratios (OR), 95% Confidence Intervals (CI) and *P* values to compare the magnitude of risk for the development of DVT between closing-wedge and opening-wedge osteotomies with and without chemoprophylaxis. In addition, the effects of anticoagulants versus aspirin in reducing the risk were determined between and within the two types of osteotomies. Because there were patients that underwent staged bilateral HTOs, the percent rates were calculated according to the number of knees and not the number of patients.

Results

The level of evidence was I in 13% of the studies, II in 9%, III in 12%, and IV in 66%. The overall incidence rates of DVD and PE after HTO were 1.24% and 0.11%, respectively (Table 3).

Anticoagulants were used in 1,110 patients and aspirin was used in 312 patients (Table 4). The relative risk of DVT was higher in patients that used anticoagulants compared with patients that did not use any form of chemoprophylaxis (1.99% and 1.11%, respectively; P = 0.02). There was no significant difference in the incidence rates of DVT between patients who used aspirin and patients who used no chemoprophylaxis agents, or between patients who used anticoagulants and those who used aspirin.

The risk of DVT was higher in patients who underwent closing-wedge osteotomy compared with those who underwent opening-wedge osteotomy when no chemoprophylaxis was used (P<0.0001; Table 5). When anticoagulants were used postoperatively, the risk of DVT was also higher in closing-wedge osteotomy studies (P = 0.03). However, when aspirin was used postoperatively, there was no significant difference in the risk of DVT between closing-wedge and opening-wedge osteotomy studies.

The use of anticoagulants or aspirin did not significantly reduce the incidence of DVT within closing-wedge or opening-wedge studies (Table 6).

It was not possible to analyze the potential effect of the postoperative rehabilitation program with regard to the use of mechanical compressive devices and the initiation of range of knee motion exercises and mobilization on the risk of DVT. Nearly one-third of the studies did not provide specific information on these factors. Although the closing-wedge osteotomy studies were generally performed in an earlier time period (2000 to 2008), it cannot be assumed that these rehabilitation factors were different than those used in the more recently published opening-wedge studies.

Discussion

There is no consensus regarding postoperative thromboprophylaxis, including the routine use of anticoagulants, after HTO. This study was designed to address two primary questions. First, what is the incidence of DVT and PE after modern HTO? Second, is the routine use of anticoagulants required in patients who do not have significant risk factors for venous thromboembolism events?

This study found that the overall incidence of PE after HTO was exceedingly low (0.11%) regardless of the use of chemoprophylaxis. Only one fatal PE was reported in the 7095 knees that occurred 2 weeks postoperatively in a study in which warfarin had been administered, but the dosage, duration and risk factors were not provided [9]. The overall incidence of DVT was also low (1.24%). For unknown reasons, when all osteotomy studies were combined, the patients that

Type of Osteotomy	Number of Studies	Number of Knees	Gender		Age (Years)		Number of Knees with DVT (%)	Number of Knees with PE (%)
			Men	Women	Mean	Range		
Closing-wedge, chemoprophylaxis used	8#	799	443	236	49	16-77	20 (2.5)	6 (0.75)
Opening-wedge, Chemoprophylaxis used	14#	623	367	243	45	15-67	5 (0.80)	1 (0.16)
Closing-wedge, chemoprophylaxis not used	35^	2373	651	744	53	19-81	48 (2.0)	1 (0.04)
Opening-wedge, chemoprophylaxis not used	57^	3300	1245	936	48	10-84	15 (0.45)	0
Total	107	7095	2706	2159	47	10-84	88 (1.24)	8 (0.11)

Table 3: Study demographics and incidence rates of deep venous thrombosis and pulmonary embolism.

^Includes 5 studies that compared opening-wedge with closing-wedge osteotomy in which venous thromboembolism event data were given for each type of osteotomy.

#Includes 2 studies that compared opening-wedge with closing-wedge osteotomy in which venous thromboembolism event data were given for each type of osteotomy.

Abbreviations: DVT-Deep Venous Thrombosis; PE-Pulmonary Embolism

Chemoprophylaxis (No. of Knees)	Number of Knees with DVT (%)	Odds Ratio	95% CI	P
Anticoagulants (1110) None (5673)	22 (1.99) 63 (1.11)	1.8	1.10-2.94	0.02
Aspirin (312) None (5673)	6 (1.92) 63 (1.11)	1.75	0.75-4.06	NS
Anticoagulants (1110) Aspirin (312)	22 (1.99) 6 (1.92)	1.03	0.41-2.57	NS

Table 4: Risk of DVT according to chemoprophylaxis used postoperatively.

Abbreviations: CI-Confidence Interval; DVT-Deep Venous Thrombosis; NS-Not Significant

Chemoprophylaxis	Type osteotomy (No. of Knees)	Number of Knees with DVT (%)	Odds Ratio	95% CI	P
None	Closing-wedge (2373) Opening-wedge (3300)	48 (2.02) 15 (0.45)	4.52	2.53-8.09	<0.0001
Anticoagulants	Closing-wedge (737) Opening-wedge (373)	20 (2.71) 2 (0.54)	5.17	1.20-22.26	0.03
Aspirin	Closing-wedge (62) Opening-wedge (250)	3 (4.84) 3 (1.20)	4.19	0.82-21.27	NS

Table 5 : Comparison DVT incidence rates: opening- versus closing-wedge osteotomies

Abbreviations: CI-Confidence Interval; DVT-Deep Venous Thrombosis

Type of Osteotomy	Chemoprophylaxis (No. of Knees)	Number of Knees with DVT (%)	Odds Ratio	95% CI
Opening-wedge	Aspirin (250) None (3300)	3 (1.20) 15 (0.45)	2.66	0.76-9.25
Opening-wedge	Anticoagulants (373) None (3300)	2 (0.54) 15 (0.45)	1.18	0.27-5.18
Opening-wedge	Aspirin (250) Anticoagulants (373)	3 (1.20) 2 (0.54)	2.25	0.37-13.58
Closing-wedge	Aspirin (62) None (2373)	3 (4.84) 48 (2.02)	2.46	0.75-8.13
Closing-wedge	Anticoagulants (737) None (2373)	20 (2.71) 48 (2.02)	1.35	0.80-2.29
Closing-wedge	Aspirin (62) Anticoagulants (737)	3 (4.84) 20 (2.71)	1.82	0.53-6.31

Table 6: Risk of DVT according to chemoprophylaxis used and type of osteotomy performed*.

Abbreviations: CI-Confidence Interval; DVT-Deep Venous Thrombosis.

*None of the comparisons were statistically significant.

used anticoagulants postoperatively had a higher incidence of DVT. In addition, the risk of DVT was higher in closing-wedge osteotomy studies compared with opening-wedge studies regardless of the use of anticoagulants. This finding necessitated an analysis of the effect of anticoagulants and aspirin for each type of osteotomy separately. No significant difference was found in the risk of DVT in either

opening-wedge or closing-wedge studies between knees that used anticoagulants or aspirin and those that did not. Because the incidence of venous thromboembolism events was very low regardless of the use of chemoprophylaxis, the necessity for anticoagulation after HTO in patients who do not have significant risk factors for venous thromboembolism events is questioned.

The indications for HTO have expanded to include patients who require correction of varus malalignment before meniscus transplantation, articular cartilage procedures, and knee ligament reconstruction [10,11]. The potential use of a thromboprophylaxis program may be justified in patients who undergo osteotomy due to the magnitude of the procedure; however, there are no recommendations from governing bodies or orthopaedic societies regarding a thromboprophylaxis program after HTO. A few authors have recommended that the thromboprophylaxis standards for TKA would be appropriate for HTO [2-4]. The American Academy of Orthopaedic Surgeons (AAOS) published a moderate recommendation for TKA in 2012 for the "use of pharmacologic agents and/or mechanical compressive devices" for patients who are not at elevated risk [12]. However, a specific prophylactic regimen after routine TKA could not be recommended based on current evidence [12,13]. The AAOS guidelines also stated that current evidence is unclear regarding whether factors other than a personal history of previous venous thromboembolism increase the risk of venous thromboembolism [14].

Erickson et al., recently reviewed the rates of symptomatic DVT and PE after HTO, distal femoral osteotomy, and tibial tubercle osteotomy in 141 patients who did not receive postoperative chemical prophylaxis [15]. Forty-seven of these patients underwent HTO. One patient developed a bilateral DVT after a medial opening-wedge osteotomy that progressed to PE; this woman died 3 days after surgery. She was using oral contraceptives at the time of surgery and was subsequently found to have a maternal-side family history of DVT. Neither the patient nor her family physicians were aware of this history. For the entire series of 141 patients, the postoperative rates of DVT and PE were 1.42% and 0.71% respectively.

Significant risk factors for DVT include personal or family history of DVT, obesity, use of oral contraceptives and well-recognized hereditary disorders such as Factor V Leiden (FVL) mutation, prothrombin G20210A mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency [16-21]. van der Meer et al. [22] reported that the risk of thromboembolism was increased seven-fold in individuals who were heterozygous for FVL and eight-fold for individuals who were homozygous for FVL. Other studies have observed that, while the presence of a genetic variant alone may not produce a venous thromboembolism, the addition of other risk factors such as oral contraceptive use [23,24], hormone replacement therapy [25] and smoking [26] will magnify the risk. The use of oral contraceptives was reported to be associated with venous thromboembolism in data derived from 201 studies by Wu et al. [21]. The highest risk has been observed in women with Factor V Leiden (FVL) (OR - 15.62), followed by those with deficiencies in antithrombin (OR - 12.60), protein C (OR - 6.33) and protein S (OR - 4.88). The discontinuation of oral contraceptives before surgery was not discussed in the osteotomy studies in this review. Pharmaceutical companies recommend that patients discontinue all estrogen products 4 to 6 weeks before any operation that has an increased risk of thromboembolism.

The use of aspirin for prophylaxis of venous thromboembolism events has gained recent interest after TKA [27-30] and from the American College of Chest Physicians for patients undergoing major orthopaedic surgery [31]. A recent study of 4,651 primary total joint arthroplasty patients reported that low-dose aspirin (81 mg twice daily for 4 weeks) was not inferior to high-dose aspirin (325 mg twice daily for 4 weeks) for venous thromboembolism prophylaxis [29]. However, whether the routine use of aspirin after HTO in patients who do not have significant risk factors for venous thromboembolism events is justified remains unknown. We recommend that future HTO studies provide a description of prophylaxis programs (including dosage, duration and timing of medications) that include the use of compressive devices and early postoperative exercises. We have previously reported our program that includes intermittent pneumatic compression devices in both extremities for the first 24 hours, immediate knee range of motion exercises, early ambulation and partial weight-bearing, antiembolism stockings, and ankle pumps performed for 5 minutes every hour the patient is awake [32]. For surgeons who wish to use some form of chemical prophylaxis, we empirically recommend aspirin (325 mg/twice a day for 10 days). A Doppler ultrasound is immediately obtained with any suspicion of a DVT including abnormal calf tenderness, a positive Homan sign or increased lower extremity edema.

This literature review had several limitations. Of the 107 studies, 78% were Level-III or Level-IV investigations. There were no randomized high-level studies that compared different prophylaxis protocols. It was not possible to identify the number of patients in each study that were at increased risk of DVT. Even though some investigators did not describe a specific prophylaxis protocol in their study, they may have used medications, compressive devices or other measures to prevent venous thromboembolism events. There was a lack of agreement among the protocols published in regard to chemoprophylactic agents and their indications. While some protocols only used medications [9,33-38], others also incorporated compressive devices and/or early knee motion and strengthening exercises [10,32,39-42]. The number of cases that used multiple prophylactic measures was too small to perform a valid comparison with those that used only chemoprophylaxis. In addition, a few studies only prescribed chemoprophylactic agents in patients with a history of DVT [41,43]. The limited number of knees in the subgroups shown in table 6 precludes definitive conclusions to be reached regarding our third and fourth questions. For instance, a post-hoc sample size analysis demonstrated that, in the opening-wedge aspirin versus anticoagulant comparison, a total of 17,497 knees would be required for statistical significance ($P<0.05$, 80% probability) to be obtained. In the closing-wedge aspirin versus anticoagulant comparison, a total of 12,136 knees would be required for statistical significance to be reached.

Conclusion

Our study found that the incidence of venous thromboembolism events was very low after HTO, regardless of the use of chemoprophylaxis. Therefore, the necessity for anticoagulation after HTO in standard-risk patients is questioned considering the side effects that may occur with these agents.

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Appendix 1: Studies included in systematic review

Studies that did not mention prophylaxis for deep venous thrombosis

Closing-wedge high tibial osteotomy [1-30]

Opening-wedge high tibial osteotomy [31-82]

Closing-wedge and opening-wedge high tibial osteotomy [83-87]

Studies that provided prophylaxis for deep venous thrombosis

Closing-wedge high tibial osteotomy [88-95]

Opening-wedge high tibial osteotomy [94-107]

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