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Ahmed Samir
Ahmed Maher Teaching Hospital

Asim M. Herz-Allah
El Mataria Teaching Hospital

Mohamad T. Yusuf
El Mataria Teaching Hospital, drmohtaha@gmail.com

Mohamed M. Gouda
El Mataria Teaching Hospital

Mourad I. Alkhouly
National Institute of Diabetes

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Original Article

Once-daily versus twice-daily enoxaparin for the initial treatment of acute deep venous thrombosis: a case–control study

Mohamad T. Yusuf[a], Mohamed M. Gouda[a], Asim M. Herz-Allah[a], Mourad I. Alkhouly[b], Ahmed Samir[c]

[a]Department of Vascular Surgery, El Mataria Teaching Hospital, [b]National Institute of Diabetes, [c]Department of Vascular Surgery, Ahmed Maher Teaching Hospital, Cairo, Egypt

Abstract

Background

In the initial treatment of deep venous thrombosis (DVT), enoxaparin is administered twice daily. A once-daily treatment regimen is more convenient for the patients and may optimize home treatment. However, it is not clear whether a once-daily treatment regimen is as safe and effective as a twice-daily treatment regimen.

Purpose

Our objective is to assess and compare the efficacy (in terms of recurrent venous thromboembolism) and safety (i.e. major hemorrhagic events) of once-daily versus twice-daily administration of enoxaparin for the initial treatment of DVT.

Patients and methods

A case–control study was conducted. We studied the efficacy and safety of an enoxaparin regimen, 1.5 mg/kg once daily, as a bridge to warfarin for the treatment of acute DVT. We undertook a case–control design. We enrolled 40 acute DVT cases prospectively and matched them by age, sex, and location of venous thromboembolism to 40 previously treated controls. Only hospitalized patients were enrolled; no outpatients were studied. All controls had received enoxaparin 1 mg/kg twice daily. We followed the cases for 30 days. We discontinued enoxaparin after we achieved the target international normalized ratio between 2.0 and 3.0.

Results

One (2.5%) case and two (5%) controls had recurrent venous thromboembolic events. There were no major bleeding complications in the case group, compared with one (2.5%) in the control group.

Conclusion

Once-daily enoxaparin, 1.5 mg/kg, as a bridge to warfarin is as effective with a similar safety profile as twice-daily enoxaparin, 1 mg/kg, for initial treatment of acute DVT. Results showed no statistically significant differences between the two treatment regimens.

Keywords: Deep venous thrombosis, enoxaparin, venous thromboembolic event

Introduction

Venous thromboembolism (VTE) is a common disease with an annual incidence of approximately three cases per 1000 of populations. VTE is a combination of pulmonary embolism (PE) and deep vein thrombosis (DVT).

Risk factors for VTE can be acquired through trauma, surgery, periods of immobilization, or can be inherited, for example, factor V Leiden mutation or protein C deficiency. The disease requires immediate anticoagulant therapy, because if left untreated, VTE has high morbidity and can be fatal [1].

Correspondence to: Mohamad T. Yusuf, MD, Assistant Consultant of Vascular Surgery, El Mataria Teaching Hospital, Cairo, Egypt, Tel: 0100167648. E-mail: drmohtaha@gmail.com

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The aims of treatment of DVT include prevention of PE and local extension of the thrombus, as well as a reduction in the long-term complications (post-thrombotic syndrome and chronic pulmonary hypertension) [2]. The low-molecular-weight heparin (LMWH) enoxaparin can be used in initial and medium to long-term treatment of DVT [3].

The administration of enoxaparin at therapeutic doses during DVT treatment may be carried out in single or double daily doses. The Food and Drug Administration has approved enoxaparin 1 mg/kg twice daily for inpatient treatment of DVT with or without PE and outpatient treatment of acute DVT without PE as a bridge to warfarin [4].

A once-daily treatment regimen is more convenient for the patient and may optimize home treatment. The American College of Chest Physicians suggests once-daily over twice-daily administration (grade 2 C), but this recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (i.e. the once-daily injection contains double the dose of each twice-daily injection). This is not the case for enoxaparin, where the once-daily dose, according to Sanofi-Aventis [5], is a dose only 50% (1.5 mg/kg) higher than each twice-daily injection (1.0 mg/kg) [6]. However, it is not clear whether a once-daily treatment regimen is as safe and effective as a twice-daily treatment regimen [7].

In this study, we compared the effectiveness and safety of the two different dosing strategies of enoxaparin (enoxaparin 1.5 mg/kg subcutaneously once daily vs. 1 mg/kg subcutaneously twice daily) in the initial therapy of patients with acute DVT.

Patients and methods

Patients

Ethical approval and consent was taken. We undertook a case–control design. A total of 40 Egyptian patients with symptomatic acute DVT with confirmed diagnosis by a venous ultrasound duplex were enrolled in this study. The cases were matched by age, sex, and location of venous thrombosis to 40 previously treated controls. Only hospitalized patients were enrolled, and no outpatients were studied. Enrollment began in October 2016 and was completed in March 2018 in Mataria Teaching Hospital, Ahmed Maher Teaching Hospital, and National Institute of Diabetes.

Baseline data

The following parameters were recorded when the episode of DVT was diagnosed: patient's sex; age; body weight; presence of coexisting conditions such as diabetes, peripheral artery disease, chronic lung disease, chronic heart failure, mental disorders, chronic liver disease, and recent major bleeding; concomitant drugs (corticosteroids, NSAIDs, or antiplatelet agents); and laboratory data, including complete blood counts, international normalized ratio (INR), and serum creatinine levels at baseline.

Exclusion criteria

Exclusion criteria were prolonged hospitalization for more than 15 days, PE, high risk of bleeding, renal impairment, pregnancy, and malignancy.

Methods

The cases were treated with 1.5 mg/kg once-daily enoxaparin as a bridge to warfarin. We discontinued enoxaparin after at least 5 days and when we achieved the target INR between 2.0 and 3.0 for 2 consecutive days. Controls were matched by age (less or more 5 years), sex, and location of DVT. The controls had been treated with enoxaparin 1 mg/kg twice daily as a 'bridge' to warfarin. We followed the cases for 30 days. Cases and controls were started on warfarin on day 1, and their INR values were monitored daily. Warfarin doses were adjusted to achieve a target INR between 2.0 and 3.0, then enoxaparin was discontinued, and the patient was discharged.

The assessment of DVT and monitoring of the effectiveness and safety of treatment were carried out by clinical, radiological, and laboratory tests at pre-established times (baseline, 7, and 30 days). After discharge, all patients were followed up weekly in the outpatient clinic. During each visit, any signs or symptoms suggesting DVT recurrences or bleeding were noted. Color Doppler ultrasound was done for suspected DVT recurrence. New DVT events or progression of thrombosis to other veins was diagnosed using color Doppler ultrasound. Thrombocytopenia or adverse events related to major or minor hemorrhages were evaluated and recorded.

The primary endpoint was recurrent VTE or major hemorrhage. Major hemorrhage was defined as overt bleeding that required a transfusion of more than or equal to 2 U of blood, was retroperitoneal, spinal or intracranial, or was fatal.

Results

Cases and controls were well-matched (Table 1). All patients completed the study.

The duration of enoxaparin therapy was longer in patients on a once-daily regimen (7.5 vs. 6.7 days).

One (2.5%) case and two (5%) controls had recurrent VTE events in the form of extension of the thrombus to a more proximal location.

There were no major bleeding complications in the case group, compared with one (2.5%) in the control group that developed lower gastrointestinal bleeding and received 2 U packed red blood cells after stopping enoxaparin.

No symptomatic PE was recorded in both groups.

Discussion

From a theoretical point of view, the twice-daily LMWH results in a more stable level of anticoagulation and thus leads to fewer bleeding complications [8]. This may explain why the twice-daily regimen is preferred in most centers for antithrombotic therapy for VTE.

Table 1: Patients' clinical characteristics and underlying conditions

	n=40 [*n* (%)]	
	Once-daily 1.5 mg/kg enoxaparin	Twice-daily 1 mg/kg enoxaparin
Male	14 (35)	14 (35)
Female	26 (65)	26 (65)
Mean age (years)	59±14	60±15
BMI	32±6	31±8
Risk factors		
Prior VTE	5 (12.5)	5 (12.5)
Trauma	4 (10)	4 (10)
Immobilization	2 (5)	2 (5)
Surgery	3 (7.5)	3 (7.5)
COCP	2 (5)	2 (5)
Comorbidities		
COPD	1 (2.5)	1 (2.5)
Heart disease	2 (5)	2 (5)
Varicose veins	4 (10)	4 (10)
Type of VTE		
Ileofemoral DVT	17 (42.5)	17 (42.5)
Femoropopliteal DVT	21 (52.5)	21 (52.5)
Calf DVT	2 (5)	2 (5)

COCP, combined oral contraceptive pill; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; VTE, venous thromboembolism.

From a large series of patients with acute VTE, in Spain, [9] they found unexpectedly, patients on once-daily enoxaparin therapy had less than half the rate of major bleeding and half the mortality rate, both at 15 and 30 days, compared with patients on enoxaparin twice daily. Trujillo-Santos *et al.* [9] stated that there were no differences in the rate of gastrointestinal bleeding, but no patient receiving once-daily enoxaparin experienced retroperitoneal, cerebral, or fatal bleeding.

Once-daily enoxaparin administration had been compared with a twice-daily regimen, and many studies found it to be as effective and safe as twice-daily dosing [10]. The ACCP guidelines on antithrombotic therapy for VTE suggested that once-daily LMWH administration should be preferred over twice-daily administration because it seems more convenient for patients and may optimize home therapy [4].

Our findings confirmed those obtained in a Cochrane review of trials, suggesting that twice-daily LMWH results in a nonsignificantly lower rate of VTE recurrences and a nonsignificantly higher rate of major bleeding compared with once-daily LMWH [7]. The lower bleeding rate in patients on once-daily enoxaparin regimen may be because they received lower daily doses than those on twice-daily enoxaparin [9]. A meta-analysis of once-daily versus twice-daily LMWH in patients with VTE found no difference in recurrent VTE [11].

Our data are of particular importance, because as once-daily versus twice-daily have similar outcomes, physicians and patients may prefer once-daily enoxaparin. It will halve the number of injections, facilitate outpatient treatment, and reduce health care expenses compared with twice-daily enoxaparin. Our study has some limitations. The sample size was small, and the patients were at low risk for adverse outcomes, which limits the generalizability of our findings. We followed patients for only 30 days because most patients switched to warfarin ~1 week after DVT diagnosis. Moreover, our study design is a case–control study, but it provides the rationale for undertaking a randomized controlled trial comparing the once-daily versus twice-daily enoxaparin for the initial treatment of acute DVT. The results have important implications for future simplification of treatment in otherwise healthy patients with acute DVT.

Conclusion

Once-daily enoxaparin, 1.5 mg/kg, as a bridge to warfarin is as effective with a similar safety profile as twice-daily enoxaparin, 1 mg/kg, for initial treatment of acute DVT. Enoxaparin 1 mg/kg twice daily is not superior to enoxaparin 1.5 mg/kg once daily in low-risk patients. Results showed no statistically significant differences between the two treatment regimens. More randomized controlled studies should confirm our findings.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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