



Comparison of Generic (Rolexan) and Brand (Clexan) Forms of Enoxaparin in Critically Ill Patients: A Cross Over, Open Label, Randomized Prospective Clinical Trial

Shadi Ziaie^{1,2}, Hanieh Malekmohammadi¹, Mohammad Sistanizad^{1,3*}

¹Department of Clinical Pharmacy, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

²Department of Nephrology and Kidney Transplantation, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

³Prevention of Cardiovascular Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Background: Several generic forms of enoxaparin were introduced to the market after expiring the patent of Clexane. But the main problem with generic forms is its bio-equivalency with brand form as a little difference in active ingredients characteristics, could led to significant clinical differences. For evaluating the efficacy of enoxaparin, it is recommended to measure its activity against Anti Xa. The aim of this study was comparison of Anti Xa Activity of Enoxan® versus Clexane® in critically ill patients with prophylactic doses.

Methods: This was a cross over, open label, randomized prospective study which was performed between September 2016 and December 2017 in intensive care unit of Labbafinezhad hospital, Tehran, Iran. Thirty adult patients, who received enoxaparin for prophylaxis of thromboembolic events, were recruited. Subjects were subsequently randomized to one of the treatment sequences (Generic-brand or brand-generic). The generic drug was enoxaparin sodium 40 mg (4,000 IU anti-FXa/0.4 mL), manufactured by Ronakpharm, Iran; the brand drug was enoxaparin sodium 40 mg (Clexane® 4,000 IU anti-FXa/0.4 mL), manufactured by Sanofi, France.

Results: Anti-Xa activity was assessed with Stago kit. The anti-Xa activity between 0.2 and 0.5 U/mL was defined as prophylaxis. The average Anti-Xa activities of Clexan and Rolexan were 0.3 ± 0.12 and 0.22 ± 0.10 , respectively which reveals statistically no significant difference (P: 0.35). Also Anti-Xa activity in 6 and 11 patients in Clexan and Rolexan groups were under 0.2 (P: 0.16).

Conclusion: Our study showed comparable efficacy of prophylactic doses between Clexan and Rolexan in critically ill patients. Further studies in different patient population are recommended.

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Introduction

Heparin is a highly sulphated and heterogeneous member of the glycosaminoglycan family of carbohydrates consisting of various disaccharide units. The most common disaccharide unit is composed of a 2-O-sulfated α -L-iduronic acid and 6-O-sulfated, N-sulfated α -D-glucosamine, IdoA(2S)-GlcNS(6S). Endogenous heparin is synthesized in the

granules of mast cells and possesses the highest negative charge density of all known biological molecules. Heparin used for therapeutic purposes is sourced from domestic animals, mainly from porcine intestinal mucosa (1).

Low molecular-weight heparins (LMWHs) are derived from unfractionated heparin (UFH) by chemical or enzymatic depolymerization. Thus, the starting material

*Corresponding Author: Dr Mohammad Sistanizad

Address: Emam Hossein Hospital, Madani St., Tehran, Iran. Tel:+982173430, Fax:+982188200087.

Email: Sistanizadm@sbmu.ac.ir

of LMWHs is of biological origin and the manufacturing process defines the characteristics of the drug substance. Compared to UFH, LMWHs have decreased inhibitory activity against thrombin (FIIa) compared to factor Xa (FXa) in animal models, have longer half-lives and more predictable dose-responses, requiring only one or two administrations per day (1-4).

Several generic forms of enoxaparin were introduced to the market after expiring the patent of originator. But the main problem with generic forms is their bio-equivalency with brand form as a little difference in active ingredients characteristics, could led to significant clinical differences. To compare the biosimilar/generic version to the reference LMWH, both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) recommend measurement of the PD activities (5,6). Moreover, measurement of the anti-FXa activity are also recommended by the EMA (5). The aim of this study was comparison of Anti Xa Activity of generic form of enoxaparin versus the brand one, Clexan®, in critically ill patients with prophylactic doses in a randomized crossover study.

Methods

This was a cross over, open label, randomized prospective study which was performed between September 2016 and December 2017 in intensive care unit of Labbafinezhad hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. The clinical study protocol and the informed consent forms were reviewed and approved by the ethics committee of Shahid Beheshti University of Medical Sciences and the Iranian Registry of Clinical Trials (IRCT), with registry number of IRCT2016031910178N9. IRCT is listed as a primary registry at the WHO International Clinical Trials Registry Platform.

Adult patients (age between 18 to 65), who received enoxaparin for prophylaxis of thromboembolic events, recruited by written consent. Exclusion criteria were participation in another study, pregnancy or lactation, receiving an anticoagulant in the previous three months, haemostatic disorders or Glomerular filtration rate (GFR)<40ml/min. Subjects were subsequently randomized using RND function, Excel software, by simple randomization method to one of the treatment sequences (Generic-brand or brand-generic) by SC injection. The generic drug was enoxaparin sodium 40 mg (4,000 IU anti-FXa/1.0 mL), manufactured by Ronakpharm, Iran; the brand drug was enoxaparin sodium 40 mg (Clexane® 4,000 IU anti-FXa/0.4 mL), manufactured by Sanofi, France.

Considering half-life and duration of anti Xa activity of enoxaparin which are 4.5 and 12 hours respectively, the wash out period considered as 24 hours. On Day 1 of the study, subjects were given, a single subcutaneous (SC) injection of the test or the reference drug and after 24 hours of washout period, they were crossed over to receive a single SC dose of the reference or the test drug. Before and 4 hours after administration of 40mg enoxaparin as SC,

blood samples were collected in a citrate collection tube and centrifuged at 2000g for 20 minutes and anti Xa activity was measured in the samples using STA®-Liquid Anti-Xa, Stago, France. For all recruited patients, complete blood count, platelet count and international normalised ratio (INR) were monitored daily, for three days.

The primary objective of the study was Anti-Xa in subjects. As secondary objectives, platelet count and partial thromboplastin time (PTT) were followed. Based on similar studies, sample size was determined as 30 subjects.

Results

Based on defined inclusion and exclusion criteria, 30 patients were recruited. Table 1, reveals demographic data related to study subjects.

Table1. Demographic characteristics of patients.

	Minimum	Maximum	Mean	Std. Deviation
Age	18	57	38.47	11.93
Body Mass Index	18.03	30.09	24.86	3.49
APACHEII Score	5	26	16.27	5.61
Sex (m); N(%)	23(76.7)			

The anti-Xa activity between 0.2 and 0.5 U/mL was defined as prophylaxis. The average Anti-Xa activities of Clexan and Rolexan were 0.30 ± 0.12 (95% CI, 0.22 to 0.31) and 0.22 ± 0.10 (95% CI, 0.20 to 0.27), respectively which reveals statistically no significant difference (independent sample t-test, P: 0.35). Also Anti-Xa activity in 6 and 11 patients in Clexan and Rolexan groups were under 0.20 (Chi square test, P: 0.16). Data are shown in Table 2.

Table 2. Number of subjects with therapeutic, sub or supra-therapeutic Anti-Xa activity in patients receiving Clexan or Rolexan.

Anti-Xa Activity	Clexan	Rolexan	p-value
<0.2 U/ml	6	11	0.16
0.2-0.5 U/ml	22	19	
>0.5 U/ml	2	0	

Also we measured platelet count, PTT, serum creatinine level for three days and did not find any significant change in these parameters (independent sample t-test, P>0.05). Also no other possible adverse effect related to the study medications was reported.

Discussion

Interchangeability of brand drugs with generic ones is a problematic controversial issue between physicians. In a survey on 1,152 primary care internists and specialists between August 2014 and January 2015, the physicians view was largely positive about the FDA's generic drug approval process (7). Better education about the generic drug approval process and standards may alleviate

concerns among the physician community and support the delivery of cost-effective health care (7).

Current randomized, single dose, cross-over study was performed in critically ill patients in order to compare Anti-X activity of enoxaparin sodium manufactured by Ronakpharm, to the reference medicinal product based on to the relevant EMA recommendation for LMWHs (5). Numerous generic forms of enoxaparin under the Abbreviated New Drug Application (ANDA) pathway has been approved by the FDA, which denotes that the brand and generic forms of enoxaparin could be used interchangeably in the USA (8). Conversely, EMA considers LMWHs as biological medicines and does not regulate interchangeability, switching, and substitution of a reference medicine by its biosimilar, leaving this decision at the national level (9).

So far, numerous national regulatory authorities, including the Dutch Medicines Evaluation Board, the Finnish Medicines Agency, Healthcare Improvement Scotland, the Irish Health Products Regulatory Authority, and Paul Ehrlich Institute in Germany, have already taken national positions to endorse the interchangeability of biosimilars under the supervision of the prescriber (10). Indeed, a recent questionnaire-based survey, conducted between November 2016 and January 2017 among experts from several Central and Eastern European countries, showed that substitution and interchangeability of original biologic drugs and their corresponding biosimilars were generally allowed, although in most countries that decision was taken at the discretion of the physician after a clinical assessment and the biosimilars were usually in the same homogeneous group, and internal reference pricing was usually employed (11).

In conclusion our study showed comparable efficacy of prophylactic doses between Clexan and Rolexan in critically ill patients. Further studies in different patient population are recommended.

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