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Review article

Impact of augmented renal clearance on enoxaparin therapy in critically ill patients

Hala Ezzat Mohamed Abdel El Naeem, Mona Hossam Eldin Abdelhamid *, Dina Atteya Mohamed Atteya

Department of Anesthesia, ICU, and Pain Management, Faculty of Medicine, Cairo University, Egypt

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ABSTRACT

Background and aim of the work: Augmented renal clearance (ARC) was reported in critically ill patients. ARC was associated with poor patient outcome due to decreased effectiveness of drugs leading to treatment failure. The aim of this study is to find the possible impact of ARC on therapeutic action of enoxaparin measured by anti-factor Xa activity.

Patients and methods: Fifty critically ill patients receiving enoxaparin prophylactic dose (40 mg/day) were included in the study. Creatinine clearance was measured and patients were divided into two groups: normal kidney function group (group C) and augmented renal clearance group (group A). serum anti-factor Xa was measured at baseline, four hours, 12 h, and 24 h. Both groups were compared regarding demographic data, severity scores, kidney function, and anti-factor Xa activity.

Results: Twenty patients (40%) showed ARC and thirty patients (60%) showed normal kidney function. Creatinine clearance was 214 ± 6 in group A versus 112 ± 11 in group C (P = 0.001). Serum anti-factor Xa levels was similar in the two groups after four hours (0.2 ± 0.07 vs. 0.2 ± 0.05, P = 1). Serum anti-Xa levels were significantly lower in group A compared to group C at 12 and 24 h (0.06 ± 0.03 vs. 0.1 ± 0.04, P = 0.004), (0.01 ± 0.01 vs. 0.05 ± 0.01, P = 0.001) respectively.

Conclusion: ARC patients showed short activity of enoxaparin. This finding draws the attention towards dose adjustment in this type of patients.

Contents

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* Corresponding author.
E-mail address: Monahossam29@yahoo.com (M.H.E. Abdelhamid).

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1. Introduction

Augmented renal clearance (ARC) has been defined by increased CrCl (above 130 mL/min). ARC has been previously reported in a number of pathological and physiological variables, including intervention procedures, vasopressor infusions. Critically ill patients are characterized by disturbed physiology with higher prevalence of ARC compared to non-critical patients [1].

ARC has been reported to affect patients' outcome. ARC impairs the effectiveness of many drugs especially for drugs eliminated via kidneys, as this might lead to treatment failures unless the dose is adjusted [2,3].

LMWH is an essential drug used for anticoagulation in critically ill patients [4]. Inadequate dosage is considered as one of the possible mechanisms for failure enoxaparin in ICU patients [5]. Because it is difficult to measure LMWH concentrations directly, pharmacokinetic studies generally use surrogate biological effect markers such as anti-Xa activity, which has been shown to be correlated with the administrated dose as well as the clinical effect [6]. The impact of ARC on the therapeutic effect of many drugs was previously reported [7]; however, it was not studied on Enoxaparin till now. We aim to find the possible effect of ARC on the therapeutic effect of Enoxaparin in critically ill patients that might need re-evaluation of its dose.

2. Patients and methods

Fifty critically ill adult patients of either sex were selected from those patients who were admitted in a Ten bedded ICU in Cairo university hospitals, during the period between November 2013 and November 2014 after approval of the Hospital Medical Ethical Committee.

Patient is initially considered to be a candidate for this study when a prophylactic anticoagulation with LMWH (enoxaparin 40 mg/day) was initiated. History of medical and surgical disorders, physical examination and complete investigation were obtained upon enrolment into the study.

2.1. Inclusion criteria

Patients were eligible for the study if they fulfilled the following criteria:

- Critically ill adult patients who were $\geqslant$ 18 years of age, with a minimum stay of > 48 h.
- Patients were on prophylactic anticoagulation with LMWH (enoxaparin 40 mg/day).

2.2. Exclusion criteria

The patients were excluded primarily for any of the following criteria:

- Renal replacement therapy.
- Serum creatinine concentration (SCr) > 1.3 mg/dL on the first day of the study.
- Coagulation disorders.
- Massive blood transfusion.
- Pregnant women.
- Patients in need for operation.
- Patients weighing <50 kg or >90 kg.

2.3. Drug administration

All patients received fixed dose of Enoxaparin (*Clexane* ®, *Sanofi-aventis France*) of 40 mg/day as subcutaneous injection.

The duration of enoxaparin treatment was determined by attending physician on the basis of clinical status and laboratory results.

2.4. Data collection

The following data were retrieved from each patient's medical record on admission:

1. Age in years.
2. Gender.
3. Weight (wt) in kg.
4. History of medical and surgical disorders.
5. Diagnosis on admission.
6. Serum albumin concentration (gm/dl).
7. Serum creatinine (S.cr).
8. Blood urea nitrogen (BUN).
9. Sodium and potassium blood levels.

The patients were classified according to standard ICU severity-of-illness scoring systems, Acute Physiology and Chronic Health Evaluation (APACHE II), and Simplified Acute Physiology Score (SAPS II) on the day of entry into the study.

The following patient data obtained on the day of sampling:

1. Diuretics and inotropes intake.
2. Prothrombin time (PT).
3. Platelets count.
4. INR.

2.5. Blood sampling and enoxaparin measurement

For enoxaparin serum determination four blood samples were drawn from indwelling catheters immediately before enoxaparin adminstration, then at 4, 12, 24 h after the administration to determine anti-factor Xa (aFXa) activity. Blood samples were centrifuged at 3000 rpm for 10 min, the separated serum was stored frozen at – 20 °C till analysis.

For creatinine clearance (CrCL) measurement 24 h urine were collected for all patients at the same day of enoxaparin adminstration and accordingly patients were categorized into one of two groups:

Group C (control group) with CrCL $\leqslant$ 130 ml/min/1.73 m^2.
Group A (ARC group) with CrCL > 130 ml/min/1.73 m^2.

The plasma samples were assayed to determine levels of aFXa activity using a chromogenic factor Xa inhibition assay. Both study groups were compared as regards demographic data and levels a aFXa activity.

2.6. Statistical analysis

The primary outcome measure of this study was activity of antifactor Xa in the serum after 12 h from enoxaparine administration. No previous studies were done to determine the impact of ARC on enoxaparine administration so we've done a pilot study that reported activity of antifactor Xa to be 0.16(0.05) units in the control group and 0.12(0.05) units in the ARC group. Based on the findings in the aforementioned study a sample size of 26

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