Egyptian Journal of Anaesthesia 33 (2017) 113–117

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Contents lists available at ScienceDirect

Egyptian Journal of Anaesthesia

journal homepage: www.sciencedirect.com

Review article

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

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ARTICLE INFO

Article history:
Received 3 September 2016
Revised 26 October 2016
Accepted 19 November 2016
Available online 8 December 2016

Keywords:
Renal clearance
Enoxaparin
Critically ill
ICU

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

Peer review under responsibility of Egyptian Society of Anesthesiologists.

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http://dx.doi.org/10.1016/j.egja.2016.11.001
1110-1849/

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

Table 1
Demographic and laboratory data. Data are presented as mean ± SD, frequency (%).

	Augmented renal clearance group (n = 20)	Normal kidney function group (n = 30)	P value
Age (years)	37 ± 16	34 ± 14	0.48
Male gender	14(70%)	18(60%)	0.67
Weight(kg)	78 ± 10	77 ± 9	0.7
APACHE2	14 ± 7	17 ± 6	0.03
SAPS2	32 ± 15	33 ± 15	0.8
Sepsis	14(70%)	8(26%)	0.005
Inotropic support	2(10%)	2(6%)	0.98
Albumin	2 ± 0.5	2 ± 0.7	1
BUN (mg/dl)	16 ± 7	26 ± 8	0.0001
Na (mg/dl)	139 ± 10	140 ± 9	0.7
K (mg/dl)	4 ± 0.6	4 ± 0.6	1
INR	1 ± 0.2	1 ± 0.2	1
PLT (mcl)	288 ± 168	243 ± 117	0.26
Serum creatinine (mg/dl)	0.5 ± 0.4	0.9 ± 0.2	0.0001
Creatinine clearance (ml/min)	214 ± 46	112 ± 11	0.0001

APACHE2: Acute Physiology and Chronic Health Evaluation.
SAPS2: Simplified Acute Physiology Score.
BUN: Blood urea nitrogen.
INR: international normalized ratio.
PLT: platelet count.

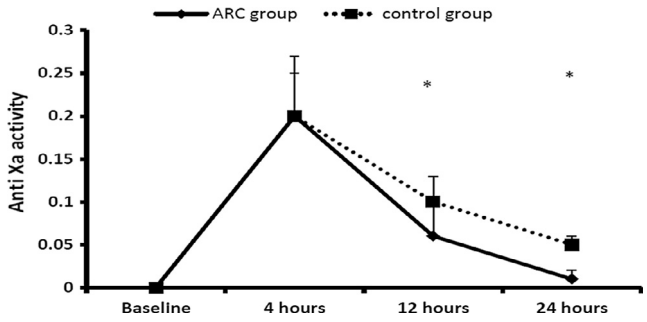

Figure 1. Anti Xa activity. Data are presented as mean, error bars are SD. ∗ denotes statistical significance between both groups.

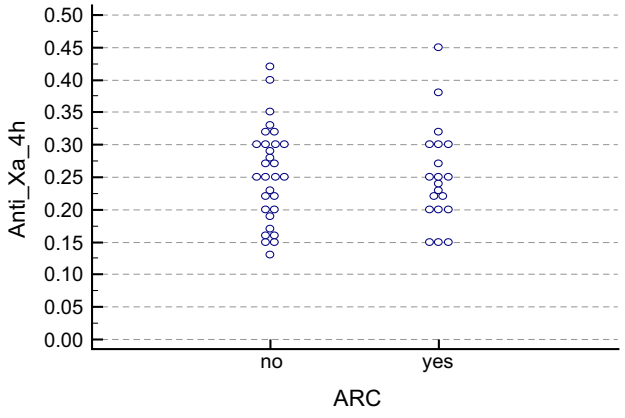

Figure 2. Anti Xa activity after four hours.

patients per group was required for a power of 80% with P 0.05. The sample size in each group was increased to 30 patients per group to compensate for possible dropout.

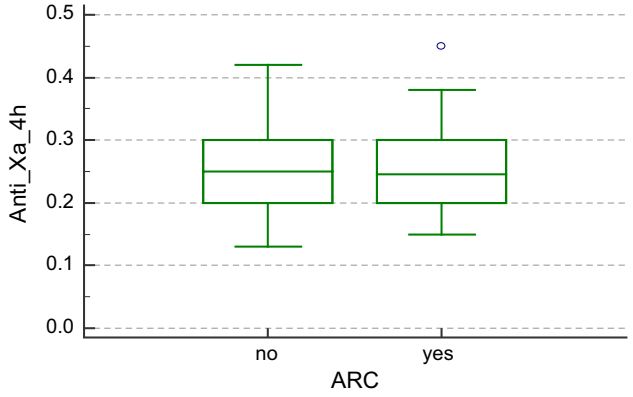

Figure 3. Anti Xa activity after four hours. Transverse lines are medians. Boxes are interquartile ranges, whiskers are ranges.

Table 2
Anti Xa activity. Data are presented as mean ± SD.

	Augmented renal clearance group (n = 20)	Normal kidney function group (n = 30)	P value
Anti Xa baseline	0	0	1
Anti Xa 4 h	0.2 ± 0.07	0.2 ± 0.05	1
Anti Xa 12 h	0.06 ± 0.03	0.1 ± 0.04	0.0004
Anti Xa 24 h	0.01 ± 0.01	0.05 ± 0.01	0.0001

Anti factor Xa activity was measured in units/ml.

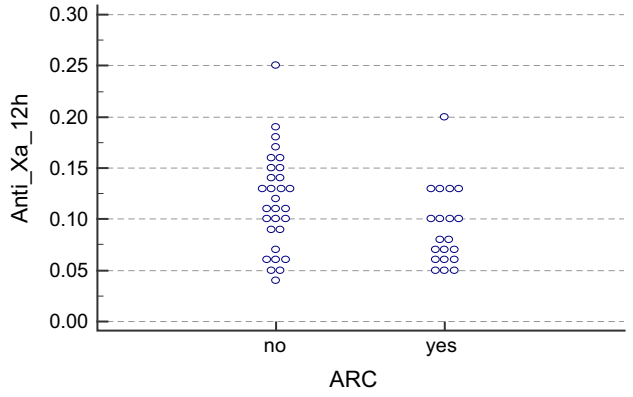

Figure 4. Anti Xa activity after 12 h.

Categorical Data was presented as number (frequency) and analyzed using pearson's Chi squared test. Continuous data was presented as mean (standard deviation) and analyzed using Mann-Whitney U-test for single measures and two-way Analysis of Variance (ANOVA) for repeated measures. Correlation between anti-factor Xa (aFXa) activity and CrCl in the ARC group was established using the Spearman's coefficient (Rs). Multivariate linear regression analysis was used to predict anti-factor Xa (aFXa) activity in patients with ARC.

3. Results

A cohort of 50 patients was included in this study. Twenty-two patients (44%) were septic shock patients, fifteen patients (30%) were neurosurgical patents, and 13 patients (26%) were medical patients. Augmented renal clearance (ARC) was higher in septic shock patients compared to control group {14(70%) vs. 8(26%), P

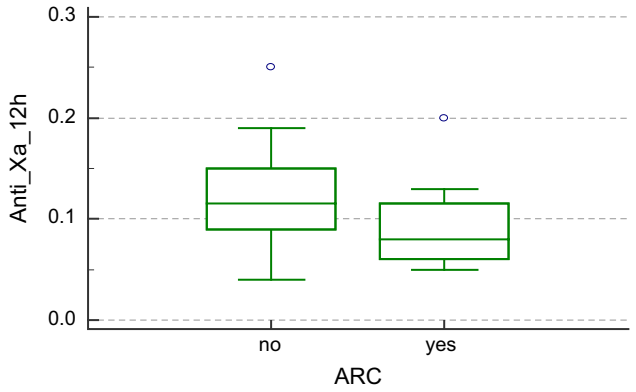

Figure 5. Anti Xa activity after 12 h. Transverse lines are medians. Boxes are interquartile ranges, whiskers are ranges.

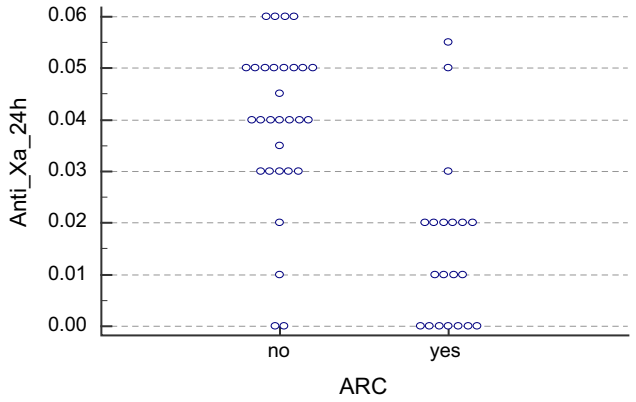

Figure 6. Anti Xa activity after 24 h.

value = 0.03}. No statistically significant difference between the two patient groups as regards demographic data (age, gender, weight), severity of illness (APACHE II and SAPS II scores), and laboratory investigations (NA, K, INR, albumin, platelets). Serum BUN and creatinine were significantly lower in ARC patients, while as creatinine clearance was higher in ARC patients (Table 1).

As regards Anti Xa activity; no statistically difference was reported between ARC group and control group at baseline measure and after four hours (0.2 ± 0.07 vs. 0.2 ± 0.05, P = 0.3) (Table 1), (Figs. 1–3). There was a significant decrease in Anti Xa activity in ARC group compared to control group after 12 h (0.06 ± 0.03 vs. 0.1 ± 0.04 P = 0.001) and after 24 h (0.01 ± 0.01 vs. 0.05 ± 0.01 P = 0.05) (Table 2) (Figs. 4–6).

4. Discussion

In this study the possible impact of ARC on therapeutic effect of enoxaparin in critically ill patients was evaluated. The main finding was the decreased duration of action of enoxaparin in patients with ARC. Although the aFXa activity levels was the same in the two groups of patients (ARC patients and patients with normal kidney function) after 4 h of subcutaneous administration, its level was significantly lower after 12 h (0.06 ± 0.03 vs. 0.1 ± 0.04, P = 0.001) and 24 h (0.01 ± 0.01 vs. 0.05 ± 0.01, P = 0.001) in ARC group compared to patients with normal kidney function.

Augmented renal clearance (ARC) refers to the enhanced renal elimination of circulating solute, such as nitrogenous waste products, or pharmaceuticals [8]. ARC was reported in a large observational multicenter study conducted on 932 critically ill patients where 65.1% manifested ARC on at least one occasion during the first seven study days. This finding suggests a possible impact on drug pharmacokinetics for a variety of drugs especially renally eliminated ones (such as low molecular weight heparins, aminoglycosides, glycopeptides, and β-lactams) [9], leading to subtherapeutic concentrations. Another study reported an incidence of ARC in critically ill patients to be 52%, it also reported an association between ARC and worse outcomes [10].

The prevalence of ARC in the population of critically ill patients might be due their unique physiology that is infrequently seen in a ward or out-patient setting. Many features in critically ill patients contribute to the high prevalence of ARC in this population; a common feature of critical illness is the systemic inflammatory response syndrome (SIRS), an innate humoral based response to cellular inflammation and trauma [11] which is characterized by hyperdynamic circulation [12] with a high cardiac output and a low systemic vascular resistance leading to augmented blood flow to major organs including Renal blood flow [13].

Other possible explanation for the prevalence of ARC in critically ill patients especially sepsis patients is the current guideline that stresses aggressive fluid resuscitation and early use of vasoactive medications to achieve specific haemodynamic targets restoring hemostasis [14]. Such interventions themselves can have important effects on renal function, promoting ARC. Inotropic administration has been correlated with an increase in cardiac output (CO), renal blood flow (RBF) and creatinine clearance (CLCR) [15]. Large volume fluid resuscitation to restore an adequate plasma volume (especially crystalloid) is also associated with an increase in CLCR and is considered to enhance ARC [16].

The effect of ARC on the therapeutic effect of different drugs was reported in many drugs especially antimicrobials [17]. Studies that reported subtherapeutic concentrations of β lactam antimicrobials [18], vancomycin [19], and meropenem [20] in critically ill patients with ARC have brought the attention to the importance of therapeutic drug monitoring in critically ill patients.

To the best of our knowledge this is the first study to report the impact of ARC on the therapeutic action of enoxaparin. Many studies in literature reported the efficacy and the optimum dose of enoxaparin in critically ill patients however none of them related the efficacy of the drug to ARC.

The therapeutic of enoxaparin effect was usually measured by aFXa activity. AFXa activity levels between 0.1 and 0.3 IU/ml is considered of effective antitherapeutic activity [21,22]. The peak concentration of AFXa is usually at 3–4 h after subcutaneous dose [23,24]. This was the cause of measuring AFXa activity at four hour interval in our patients. We measured AFXa activity also at 12 and 24 h to determine the possible effect of ARC on the duration of action of enoxaparin.

Although many authors reported low effectiveness of the 40 mg SC enoxaparin, once daily dose in achieving the recommended anticoagulant aFXa levels, this dose is still the European standard dose of used as VTE prophylaxis [25].

Another study compared different doses of enoxaparin using the AFXa activity as an index of effective anticoagulation reported a dose of 60 mg SC every 24 h to be superior to other doses, however the finding of this study didn't change the guidelines yet [26]. None of the previous studies criticizing the 40 mg SC dose suggested ARC to be the explanation of the insufficiency of this dose.

This study had some limitations; first limitation is the lack of clinical follow up of patients using Doppler ultrasound to screen for DVT, no available data about venous thromboembolism in our cohort of patients. Second limitation is the absence of follow up for patients to detect the impact of ARC on their final outcome, however this may be justified by the fact that this study was not designed for this outcome and the sample size might be not large enough to detect clinical significance as regards final outcome.

5. Conclusion

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

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