Author’s response to reviews

Title: Evaluation of Prophylactic Dosages of Enoxaparin in Non-Surgical Elderly Patients with Renal Impairment

Authors:

Nibal Chamoun (nibal.chamoun@lau.edu.lb)

Hady Ghanem (hady.ghanem@laumcrh.com)

Ahmad Hachem (ah220@aub.edu.lb)

Essa Hariri (Essa.Hariri@umassmed.edu)

Christelle Lteif (christelle.lteif@lau.edu)

Hanine Mansour (hanine.mansour@lau.edu.lb)

Hani Dimassi (hani.dimassi@lau.edu.lb)

Richard Zalloum (richard.zalloum@laumcrh.com)

Georges Ghanem (georges.ghanem@laumcrh.com)

Version: 1 Date: 12 Apr 2019

Author’s response to reviews:

April 11, 2019

Response Letter: BMC Pharmacology and Toxicology

Manuscript: PHAT-D-19-00040

Dear Dr. Al-Sallami,

Thank you for the opportunity to revise our submission. I would like to take this opportunity to thank the reviewers for their comments. Please find below a point by point response to all of the comments. Thank you again and looking forward to hearing from you soon.
Author’s Reply to the Reviewer Comments:

Reviewer reports:

Haider F. Alsaedi, Ph.D. candidate (Reviewer 1): (Evaluation of Non-Surgical VTE Prophylaxis: Enoxaparin 20 mg versus 30 mg Subcutaneously Once Daily in Elderly Patients with Impaired Renal Function)

Title of study

Comment 1: the title of study should be comprehensive and not determining the selected doses used in the study.

Comment 2: the subcutaneous route is only known route for administration of enoxaparin in prophylaxis cases, therefore no need to mention it in the title of the study.

Comment 3: it is a comprehensive title and well expressed on contents of the study.

Suggestion the title of study to be: Evaluation of prophylactic dosages of enoxaparin in non-surgical elderly patients with renal impairment

• Thank you for this suggestion. We have changed the title to: “Evaluation of prophylactic dosages of enoxaparin in non-surgical elderly patients with renal impairment”

Methodology

Comment 4: the selection of 20 mg or 30 mg/daily as dosing regimen instead of specific unit per kilogram/day (dose/kg) is considered less accurate dosing regimen especially in patients with impaired renal diseases because the non-obese patients that included in this study also still widely variable in weights.

Suggestion: considered the patient weighing a 70 kg given 20 mg daily regimen so he must receive nearly 0.3 gm/kg and 0.4/kg in case of 30 mg daily.

• Thank you for your comment. I agree that weight based dosing might have been more accurate however we chose to study the standard doses of 20 versus 30 mg as recommended by the package inserts for dvt prophylaxis in patients with renal impairment.

• Since the study was randomized and prospective, if we calculate the weight based dosing per arm retrospectively, we wouldn’t have the same weight based dosing per arm.
Note 5: the study not excludes patients with heart failure that reducing absorption of drugs that given subcutaneously and the effect of antithrombotic activity of drug.

Suggestion: given same calculated dose with another route e.g. i.v. for heart failure patients or excluded them.

- Thank you for your comment.
- We analyzed the anti-xa excluding the CHF patients and achieved similar findings as the overall study results. This has been added to the last paragraph of the discussion (p.14, line 273-278)

Comment 6: the measurement of anti-Xa at zero time the after treatment in order to estimate the effect of drug only on patient with different diseases and on different treatment.

- Since the study was prospective, we unfortunately cannot measure anti-Xa at zero time the after treatment.

Results

Comment 7: line no.175. The mean length of follow up was 7.18 days in the 20 mg group and 7.27 days in the 30 mg group, (p=0.826).

Suggestion: The mean length of follow up was nearly 7 days for both groups. This time of follow up not needed to studied statistically because it depend on previous clinical trials that recommended the continued period of treatment range from (6 or 7) to (10 or 11) days.

Suggestion: omit the (p=0.826) in line 176.

- Thank you, I removed the p-value from line 176.
- The sentence is now: The mean length of follow up was 7 days in both groups.

Discussion

Comment 8: a weak point of including the heart failure patient into one arm, this reflect a potent interfere of others factors such as past medical history and medications.

- If we remove the CHF patients completely from the study, we will be left with 7 patients in the 20mg arm and 10 patients in the 30mg arm. Instead of doing this, to respond to this
valuable comment, we analyzed the anti-\textit{x}a after removing the patients with CHF and included it in the discussion. (p.14, lines 273-278)

- We removed the following standalone sentence from paragraph 1 in the discussion section:
  - It is important to note that although congestive heart failure was more common in the 20mg arm, which may have led to decreased subcutaneous absorption.

- We added the following to the last paragraph of the discussion:
  - It is important to note that although congestive heart failure was more common in the 20mg arm, which may have led to decreased subcutaneous absorption, a sensitivity analysis excluding all patients with CHF from both arms showed consistent findings with the overall study results. The enoxaparin 20mg peak anti-\textit{X}a levels were 0.11\pm0.10 vs enoxaparin 30mg 0.26\pm0.11 , p=0.010 and enoxaparin 20mg trough anti-\textit{X}a levels were 0.02 \pm0.02 vs enoxaparin 30mg 0.06\pm 0.03, p=0.012. (p.14, lines 273-278)

Conclusions

Comment 9 : line 272-273 : omit this phrase because it same in both doses ( with no evidence of increased bleeding)

- Okay, well noted. It has been removed.

Comment 10 : line 276 delete this phrase (or UFH 5000 units SC BID or TID) because this effect out of article work.

- Okay, well noted. It has been removed.

Finally : this article could be accepted after revision the language and general notes mentioned above. It is important due to it included clinical trial of unfilled space with consideration of ethical criteria .

- Thank you. We reviewed the English and hopefully addressed all of your notes. Thank you.

With best regard

Haider F. Shamikh Al -Saedi
PhD Pharmacology & Toxicology

Saeed Alqahtani (Reviewer 2): Introduction:

The argument about the significance of this study is not comprehensive enough. The authors need to strengthen this point.

• Thank you for your comment. We added two references to the introduction.(references 22 & 26)

• On p5, line 87-88, we added: Although heparin is preferred in patients with renal impairment, its use has been attributed to a higher risk of bleeding in comparison to LMWH. (Alikhan R, Forster R, Cohen AT. Heparin for the prevention of venous thromboembolism in acutely ill medical patients(excluding stroke and myocardial infarction). Cochrane Database of Systematic Reviews. 2014;(5):CD003747.) Moreover physicians and nurses may also prefer LMWH over heparin because of the less frequent administration. Although enoxaparin is commonly prescribed, manufactures of enoxaparin do not have a unified recommendation for dose adjustment in renal impairment. Doses of 20mg or 30mg subcutaneously (SC) once daily are both used, depending on the country it’s being used in.[23-25]

• On p.5, lines 94-96 we added:

• In Lebanon, 20mg of enoxaparin is available as a prefilled syringe and hence many providers select this dosing strategy. A recent retrospective study showed that enoxaparin 20mg as thromboprophylaxis in renal impairment resulted in acceptable rates of thromboembolism and bleeding. Karaoui LR, Tawil S, Salameh P, Chamoun N. Enoxaparin 20 mg for thromboprophylaxis in severe renal impairment. J Int Med Res. 2019 Jan;47(1):225-234. doi: 10.1177/0300060518799896

• On p11, lines 224-225.We also added one statement related to the study published by Karaoui etal in the discussion section on page 11, second paragraph.

Page 2, paragraph 1, line 89:

What is this word "opt" means?

• The word “opt” has been changed to “select”.

Page 2, paragraph 2, line 96:

Is the CrCl <35? All the arguments before were about 30!
This is true, dosing adjustment in renal impairment is recommended when the creatinine clearance is less than 30ml/min. Our institution specific practice is to recommend renal dose adjustment in elderly patients when the crcl is 35ml/min because elderly patients with renal impairment may have fluctuating renal function on a day to day basis. We made sure to highlight that this research was conducted on patients with a crcl<35ml/min to make sure the readers are aware of the design.

The authors need to elaborate more on the use of heparin in some of the patients in both groups and if this would affect on the findings

The last paragraph of the discussion includes the following section:

- We evaluated the results excluding the patients who received heparin and obtained the same results. This was mentioned in the discussion to reassure the reader that this was taken into consideration. “After excluding these patients from the analysis, the anti-Xa levels were still consistent with the results, enoxaparin 20mg peak anti-Xa levels 0.13±0.10 vs enoxaparin 30mg 0.27±0.11, p=0.004 and enoxaparin 20mg trough anti-xa levels were 0.03 ±0.03 vs enoxaparin 30mg 0.06± 0.03, p=0.038.”

Table 1:

There are some differences in the basic characteristics of the patients, although, it is not statistically significant, but these differences may affect on the final results of the study.

- We followed a randomized design in order to reduce bias and the differences. Unfortunately, due to the small sample size, it was not possible to eliminate the differences.