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Short communication

Therapeutic inefficacy of protocol driven intravenous unfractionated heparin infusion in the current era

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ABSTRACT

Unfractionated heparin (UFH) is commonly used for several life-threatening conditions requiring anticoagulant therapy but failure to reach therapeutic levels in 24 h can be associated with adverse outcomes. Use of low molecular weight heparin (LMWH) may provide an alternative while providing superior outcomes as compared to UFH. We studied 100 patients who underwent UFH therapy for >24 h and found that theoretically 80 % were eligible for LMWH therapy. Only 29 % and 40 % of the total aPTT draws were in the therapeutic window within the first 24 h and at 25–48 h respectively. This study reports that a vast majority of patients remain outside of therapeutic aPTT within first 24–48 h when anticoagulated with UFH. With high eligibility for LMWH therapy, its substitution can potentially lead to better patient outcomes, higher levels of therapeutic efficacy, and decrease in hospital resources.

1. Introduction

Anticoagulation with or without use of antiplatelets is the recommended treatment for several life-threatening conditions including but not limited to patients presenting with acute coronary syndrome (ACS), deep venous thrombosis, pulmonary embolism, bridging for mechanical valves or atrial fibrillation, and unfractionated heparin (UFH) is the most commonly used anticoagulant. Low cost, short half-life and easy reversibility with protamine makes UFH as one of the most favorably used drugs for ACS [1] but despite years of refining algorithms its narrow therapeutic window requires frequent activated partial thromboplastin time (aPTT) monitoring which leads to overutilization of hospital resources [2]. Low-molecular-weight heparin (LMWH) has shown equivalence to UFH in the treatment of acute venous thromboembolic disease (VTE) and demonstrated superiority in acute coronary syndromes [3–5]. Despite superior efficacy, less pharmacokinetic variability, a longer plasma half-life, and its association with fewer complications [3–5], we noticed a lower trend of LMWH utilization and therefore through this study we seek to describe the eligibility of use of LMWH instead of UFH, for managing patients requiring anticoagulant therapies.

2. Methods

In this retrospective analysis, we reviewed 100 patients who underwent IV UFH therapy for >24 h, from May 1st, 2021, to September 30th, 2021. We excluded patients who were on heparin drip for <24 h. As per the algorithmic protocol, blood draws to check aPTT levels are done 6 hourly until therapeutic levels are reached at two occasions. Our main outcome was to measure the percentage of patients who were able to reach therapeutic levels at 1) 24 h and 2) 25–48 h of continuous IV UFH therapy. We also looked at the eligibility for LMWH among these patients and patients on hemodialysis (HD), had non-HD renal dysfunction with Creatinine Clearance <30 mL/min, or had an invasive procedure within 24 h were deemed ineligible for LMWH. The study was approved by the institutional ethics committee. Descriptive statistics were used to describe variables such as mean with Standard deviation for categorical variables. Analysis was completed using Microsoft Excel,

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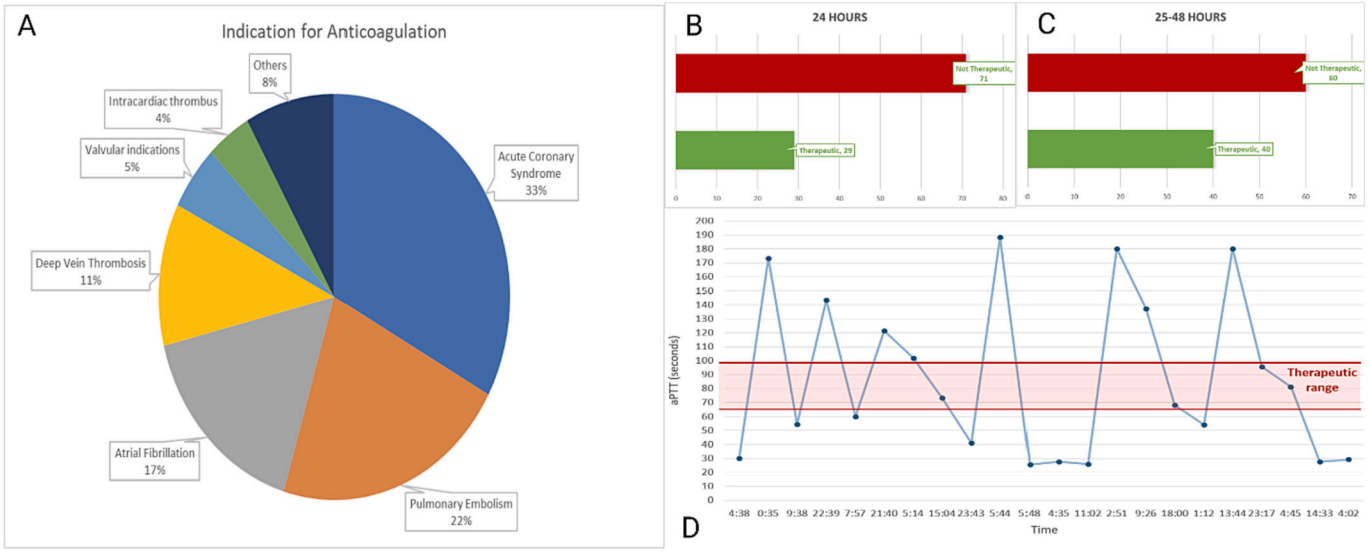

Fig. 1. A: Distribution of patients according to the indication for anticoagulation. B & C: Percentage of patients according in the therapeutic range as compared to not being in therapeutic range in 24 h (B) and 25–48 h (C). D: Pictorial representation of the variability of PTT range in a single patient on heparin drip. Abbreviations: PTT: Partial Thromboplastin Time.
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Version 2304 (Microsoft Office 365).

3. Results

Out of 100 patients, Acute Coronary Syndrome (33 %) and Pulmonary Embolism (22 %) were the most common indications for anticoagulant therapy (Fig. 1). The median age of our patients was 62 years with 46 % being male. 80 % of the patients were theoretically eligible for LMWH. Out of the total 263 aPTT draws within the first 24 h, only 77 (29 %) were within therapeutic range. At hour 6, 29 % of the patients had therapeutic aPTT, at hour 12 the rate was at 27 % and at hour 18 it was mere 13 %. Only 88 (40 %) of the 223 aPTT draws at 25–48 h reached the goal therapeutic range (Fig. 1). 38 % and 22 % of the aPTT draws at 25–48 h were in the subtherapeutic and supratherapeutic range respectively.

4. Discussion

While 71 % of patients did not reach therapeutic levels in 24 h, 60 % of the patients were still not in therapeutic range of aPTT at the end of 48 h. Expectedly, 80 % of the patients who received UFH therapy were eligible for LMWH therapy. This study highlights the current trends of therapeutic efficacy achieved with UFH and need to switch to LMWH as failure to reach the therapeutic range within the first 24 h of IV UFH therapy has been shown to have adverse outcomes [6]. Our findings are similar to other studies that have studied these trends with Ting et al. [7] reporting only 40 % of patients spending their time in therapeutic range whereas Alsulaiman et al. [8] reported only 25 % of their patient reaching therapeutic aPTT in 24 h. Several randomized controlled trials have shown the superiority of LMWH over UFH in decreasing death, myocardial infarction, angina or urgent revascularization without significantly increasing the risk of major bleeding episodes [3,4] With 80 % of the patients eligible for LMWH therapy, this clinical benefit along with having an ease of administration and more predictable pharmacokinetics, can potentially lead to better patient outcomes, higher levels of therapeutic efficacy, and decrease in hospital resources.

The major limitation of our study is the small cohort size, however demonstration of low therapeutic levels at 24 h and 48 h will help to develop protocols to prevent this and potentially change the trend from intravenous UFH therapy to LMWH in eligible patients. Secondly, the eligibility of LMWH has been calculated based on pharmacological contraindications of LMWH administration during chart review, thus does not represent the clinical acumen used at the time of ordering anticoagulation.

In conclusion, our study demonstrates that despite current hospital-based algorithms and electronic order sets to minimize variability, achieving a therapeutic aPTT, as mandated by current guidelines for at least ACS and DVT/PE, remained elusive. Despite this fact the use of UFH remains widely prevalent while most patients receiving intravenous UFH can be eligible for substitution with LMWH. Patients who qualify should be placed on the simpler and more reliable antithrombotic LMWH regimen.

Ethical statement

The study was approved by the institutional ethics committee at Newark Beth Israel Medical Center.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] J. Silvain, F. Beygui, O. Barthélémy, et al., Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis, BMJ 344 (2012), e553, https://doi.org/10.1136/bmj.e553.
[2] S.S. Anand, S. Yusuf, J. Pogue, J.S. Ginsberg, J. Hirsh, Relationship of activated partial thromboplastin time to coronary events and bleeding in patients with acute coronary syndromes who receive heparin, Circulation 107 (23) (2003) 2884–2888, https://doi.org/10.1161/01.CIR.0000077530.53367.E9.
[3] M. Cohen, C. Demers, E.P. Gurfinkel, et al., A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group, N. Engl. J. Med. 337 (7) (1997) 447–452, https://doi.org/10.1056/NEJM199708143370702.
[4] E.M. Antman, C.H. McCabe, E.P. Gurfinkel, et al., Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial, Circulation 100 (15) (1999) 1593–1601, https://doi.org/10.1161/01.cir.100.15.1593.
[5] J.J. Ferguson, R.M. Califf, E.M. Antman, et al., Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes

managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial, JAMA 292 (1) (2004) 45–54, https://doi.org/10.1001/jama.292.1.45.

[6] R.D. Hull, G.E. Raskob, R.F. Brant, G.F. Pineo, K.A. Valentine, Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis, Arch. Intern. Med. 157 (22) (1997) 2562–2568.

[7] C. Ting, K.W. Sylvester, J.W. Schurr, Time in the therapeutic range for assessing anticoagulation quality in patients receiving continuous unfractionated heparin, Clin. Appl. Thromb. Off. J. Int. Acad. Clin. Appl. Thromb. 24 (9_suppl) (2018) 178S–181S, https://doi.org/10.1177/1076029618798944.

[8] D. Alsulaiman, K. Sylvester, C. Stevens, D. Carter, Comparison of time to therapeutic aPTT in patients who received continuous unfractionated heparin after implementation of pharmacy-wide intervention alerts, Hosp. Pharm. 51 (8) (2016) 656–661, https://doi.org/10.1310/hpj5108-656.