Majalah Farmaseutik
ISSN-e: 2614-0064 | ISSN-p: 1410-590x
Volume 20(4), 588-596

Discordance between Activated Partial Thromboplastin Time and Anti-factor Xa in Unfractionated Heparin Monitoring: Literature Review

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Submitted: 29-07-2024 *Revised: 05-09-2024* *Accepted: 05-09-2024*

ABSTRACT

Anticoagulants are prescribed very frequently, but their use is often associated with adverse drug reactions. The optimal monitoring of heparin is unknown, either by aPTT or anti-Xa levels. This paper compares which anti-Xa or aPTT most closely correlates with patients on intravenous heparin. This review also compares the achievement of target goals of unfractionated heparin (UFH) using aPTT and anti-Xa tests. Literature searching was started in June 2024 and ended in July 2024 through some online scientific databases: Scopus, PubMed, Google Scholar, Science Direct, and Willey Online Library. This review includes fifteen studies, at least involving 2,938 patients or 94,038 sets of measurements. The review demonstrates that anti-Xa outperforms aPTT in achieving the therapeutic range of unfractionated heparin, time to therapeutic goal, and dose modification.
Keywords: anti-xa; apt; UFH; monitoring; discordance

INTRODUCTION

Anticoagulants are prescribed very frequently. Among parenteral anticoagulants, only unfractionated heparin (UFH) has a short half-life, is safe for kidney disease, and is fully reversible. It, therefore, remains an anticoagulant that finds wide application in modern cardiovascular procedures and critically ill patients (Tan et al., 2022).

Despite its common use, UFH carries risks, including the possibility of bleeding rates and other adverse effects. Major bleeding and hemorrhage rates for acute massive pulmonary thromboembolism (PTE) were reported in a cohort study by Ucar et al. (2015). Thus, in clinical practice, close monitoring of UFH is required to guarantee patient safety (Smythe et al., 2016).

The optimal monitoring of heparin is unknown, either using aPTT or anti-Xa level test (Smythe et al., 2016). Experience still drives many uses of UFH (Tan et al., 2022). Comparison review of aPTT and anti-Xa is limited. Thus, this paper compares which anti-Xa or aPTT most closely correlates with patients on intravenous heparin. Again, this review also compares unfractionated heparin's achievement of therapeutic target using aPTT and anti-Xa tests.

METHODS

This review, which includes observational or randomized trials, examines the relationship between anti-Xa and activated partial thromboplastin time (aPTT) in patients receiving intravenous heparin. Literature searching was started in June 2024 and ended in July 2024 through some online scientific databases: Scopus, PubMed, Google Scholar, Science Direct, and Willey Online Library.

Retrospective and prospective observational studies were included. The studies enrolled patients receiving intravenous heparin for any conditions monitored by at least aPPT and anti-Xa tests with or without mentioning clinical outcomes. Keywords in this review are filtered in the title of the article: ("heparin" OR "UFH" OR "'unfractionated heparin'") AND ("APTT" OR "'activated partial thromboplastin time'") AND "Xa".

The inclusion criteria are: 1) the subject is adult human; 2) got intravenous unfractionated heparin; 3) monitored by APPT and anti-Xa; 4) original research articles published within the last ten years (2014-2024); and 5) written in English. Excluded articles comprised: 1) duplication studies, 2) similar studies, and 3) insufficient data.

RESULT AND DISCUSSION

After an extensive search through three databases, 75 studies were found. Furthermore, 60 studies were excluded for various reasons: duplications, review studies, irrelevant, children, similar study, and others. Consequently, fifteen studies were included in this review, at least involving 2,938 patients or 94,038 sets of measurements. The detailed selection process will be shown in Figure 1.

Tables I and Table II represent the results of the included studies providing a summary of the author, year, type of study, patients, number of patients, set of measurements or paired observations, and summary of results. Table I focuses on the agreement between aPTT and anti-Xa tests for monitoring UFH. Furthermore, Table II demonstrates a comparison of monitoring UFH using aPTT and anti-Xa tests.

Key Finding 1: The Concordance Rate and Correlation between aPTT and anti-Xa Tests for Monitoring Unfractionated Heparin

This review study provides the agreement between the aPTT and anti-Xa tests. The results of various conditions in patients are inconsistent between studies, ranging from concordance to discordance of aPTT and anti-Xa. Furthermore, a study claimed that both groups were in equilibrium.

Key Finding 2: A Comparison of Monitoring Unfractionated Heparin Using aPTT and Anti-Xa Tests

The monitoring of UFH includes its association with dose adjustment, percentage of therapeutic target, time to therapeutic goal, and total dose modification. Compared to anti-Xa values, the aPTT has a weak correlation to heparin doses. In contrast, the target goals in the anti-Xa cohort were higher than in the aPTT cohort. Moreover, the anti-Xa cohort reached a faster therapeutic range and required fewer dose modifications than the aPTT group.

Unfractionated Heparin (UFH)

Heparin is still be the option globally in the treatment and prevention of thrombosis in the inpatient population for some conditions as prophylaxis of venous thromboembolism (VTE), acute coronary syndromes (ACS), cardiac surgeries including cardioversion, and in the perioperative and critical care settings (Lever et al., 2012; McRae et al., 2021). It is indicated for patients with body mass index (BMI) greater than 40 kg/m^2 or weight less than 50 kg. It is also advised for patients with creatinine clearance less than 30 mL/min. Additionally, UFH is entirely reversible (Streiff et al., 2016). Furthermore, UFH can be administered to all populations since it is considered safe. They are including pregnant women, neonates, and children (McRae et al., 2021). The recommended initial dose for UFH in VTE treatment is 5,000 units or 80 units/kg as bolus, followed by 18 units/kg/hour (Smythe *et al*., 2016).

Heparin exhibits an affinity for cellular and plasma proteins beyond antithrombin. As a result, there are varied pharmacokinetic and pharmacodynamic characteristics (Garcia et al., 2012). Due to its poor oral bioavailability, heparin necessitates parenteral administration. Thus, continuous intravenous (IV) infusion and subcutaneous injection are preferable (Garcia et al., 2012). When UFH was given as a continuous intravenous infusion (IV), its half-life was 30 minutes. However, when it is supplied subcutaneously by parenteral injection, its half-life is 90 minutes (McRae et al., 2021).

Laboratory Monitoring of Unfractionated Heparin (UFH)

Optimal therapy outcomes necessitate the adjustment of UFH, in conjunction with the implementation of laboratory monitoring. An optimal laboratory monitoring test should possess precise and uniformly defined reference ranges across all laboratories and reagents. In addition, it is expected to be affordable, user-friendly, and thoroughly evaluated in terms of clinical results, including adverse effects like bleeding. Regrettably, there is currently no available test for this purpose, which poses difficulties in monitoring UFH in a laboratory setting (Derbalah et al., 2019).

The most effective method for monitoring heparin is currently uncertain. Either activated partial thromboplastin time (aPTT) or monitoring of heparin anti-Xa levels can be utilized. Smythe et al. (2016) propose the utilization of anti-Xa level monitoring in individuals who exhibit heparin resistance, a prolonged baseline aPTT or changed heparin response. Although both anti-Xa tests and

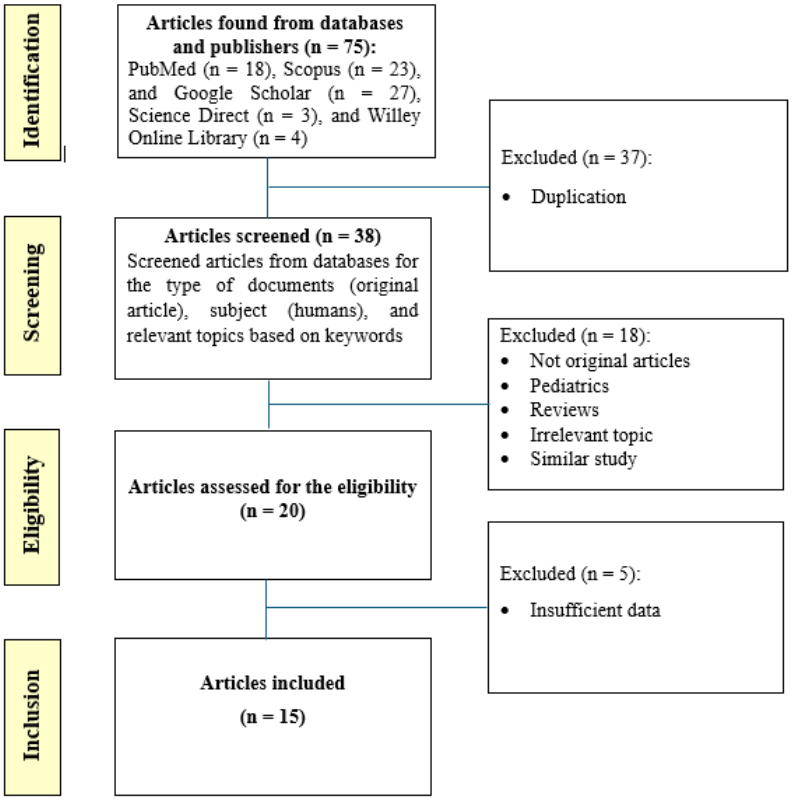

Figure 1. Study selection flowchart

aPTT tests are conducted on the same automated coagulation analyzers, anti-Xa tests exhibit worse reliability and provide greater challenges in terms of standardization. Moreover, the expensive cost and specialized requirements of anti-Xa tests result in a lack of availability of this test in many smaller hospitals and research organizations (McRae et al., 2021).

aPTT vs Anti-Xa Monitoring

Discordance Rate

Overall, the results of the discordance rate are inconsistent among studies. Thalappil et al. (2023) demonstrated an overall concordance rate of 73.3% in 90 samples, with the correlation coefficient of 0.74 ($p < 0.001$). Despite the strong agreement and correlation between the assays, significant discrepancies were evident in the interpretive values, particularly when comparing therapeutic anti-Xa levels with aPTT levels that were outside the therapeutic range (Thalappil et al., 2023).

In contrast, Gombar et al. (2019), who conducted a study with a large sample of more than nine thousand, showed a different result. The study revealed a high discordance between the aPTT and anti-Xa, with only 6.8% of the values within therapeutic target for both anti-Xa (0.3–0.7 u/mL) and PTT (50–100 s).

On the other hand, Mahmoud et al., (2016) had a different result: the agreement between aPTT and anti-Xa was 50% in 26 hospitalized patients. It indicates that there is an equal proportion between concordance and discordance.

The results are heterogeneous. It is likely due to the difference in subject conditions. Additionally, Aubron et al. (2023) and Vo et al., (2023) showed the same result in ECMO (Extracorporeal Membrane Oxygenation) patients. They claimed that there was a weak correlation between aPTT and anti-Xa tests. Coagulopathy and heparin resistance could perhaps contribute to discrepancy (Aubron et al., 2023).

e I. Concordance Rate and Correlation between aPTT and anti-Xa tests for Monitoring UFH

hor, Year	Study design	Patients	Number of patients	Set of measurements (aPTT/anti-Xa pairs)	Summary of agreement between aPTT and an Xa tests
tya et al., 2015	prospective study	patients with CF-LVADs	38	340	Patients undergoing bridging therapy with warfa Discordance rate: 63.8% (104 samples) Patients with device obstruction and/or hemolys Discordance rate: 84.2% (149 samples) *p < 0.001
ron et al., 3	pilot randomized unblinded, parallel-group controlled trial	critically ill patients who underwent ECMO	32	581	Patient with at least one discordant (n=32 patien Discordance rate: 75% (24 patients) Overall (n=581 samples) Discordance rate: 202 samples
nbar et al., 9	a follow-up study of a pilot retrospective analysis cohort	adult inpatients	9,467	56,775	The PTT and anti-Xa were highly discordant (r^2 = 0.356) Concordance rate: 6.8%
mmoud et al., 6	retrospective cohort study	hospitalized patients	26	-	The overall concordance rate: 50%.
aughlin et al., 9	single-center, quality improvement study	patients being treated with UFH therapy for at least 24 hours	80	84	The correlation coefficient: 45.71%
ano et al., 2019	retrospective study	critical care patients	2,283 patient admissions (2,085 patients)	35,595	The overall concordance rate: 59.6%
o et al., 2023	retrospective observational study	critically ill patients	99	271	The overall concordance rate: 45%

Activated Partial Thromboplastin Time; CF-LVAD: Continuous Flow Left Ventricular Assist Device; ECMO: Extracorporeal; Membrane Oxygenation; INR: International Norma
PTT: Partial Thromboplastin Time; UFH: Unfractionated Heparin

e I. (Continued)

hor, Year	**Study design**	**Patients**	**Number of patients**	**Set of measurements (aPTT/anti-Xa pairs)**	**Summary of agreement between aPTT and an Xa tests**
uel et al., 6	single-centre prospective cohort pilot study	adult patients	anti-Xa: 37 aPTT: 48 Total: 85	234 paired values from 37 patients	Discordance rate: 57%
appil et al., 3	prospective non-randomized study	patients who received UFH during the study period	-	90	The overall concordance rate: 73.3% The estimated kappa value: 0.483 (0.396–0.57) The correlation: 0.74 (p<0.001)
t al., 2023	retrospective cohort study	adult patients managed on ECMO for at least 24 hours	27	227	Spearman's correlation coefficient: 0.4
tman-Purves ., 2018	prospective cohort, nonrandomized study with historical control	patients in the cardiology units	201	-	The overall discordance rate: 49%
mohammadi et 014	prospective observational study	patients with CF-LVAD	38	-	Patients getting treated for sub-therapeutic INR Concordance rate: 41.9% Patients getting treated for hemolysis/de thrombosis Concordance rate:18.8%

Activated Partial Thromboplastin Time; CF-LVAD: Continuous Flow Left Ventricular Assist Device; ECMO: Extracorporeal; Membrane Oxygenation; INR: International Norma
PTT: Partial Thromboplastin Time; UFH: Unfractionated Heparin

e II. Comparison of Monitoring UFH Using aPTT and anti-Xa tests

hor, Year	Patients	Number of patients	Monitoring	APTT Group	Anti-Xa Group	p-va
ouk et al., 0	adult ECMO patients	34	The correlation coefficient of heparin dose-to-assay	0.106	0.414	< 0.
elin et 021	patients with anti-Xa monitoring compared with a historical control with aPTT	anti-Xa: 100 aPTT: 103	Time to therapeutic	21.9 ± 15.9	18.1 ± 16.4	0.0
			Therapeutic anticoagulation achieved	83 (80.6)	91 (91.0)	
			Dose adjustment	2.4 ± 2.0	1.8 ± 1.7	0.0
			Dose adjustments per 24 hours of UFH	1.2 ± 1.3	0.7 ± 0.7	0.0
g et al., 1	adult venoarterial ECMO patients in the cardiology units	anti-Xa:12 aPTT: 29 201	Mean time to first goal (hours)	20.22	12.05	0.1
			Achievement of target goal (%)	35.0	47.7	0.1
tman- es et al., 3			Time to therapeutic range (hours)	24 (2.5-118.8)	16 (0.8-69.3)	< 0
			Number of adjustments required	4 (0-24)	3 (0-16)	0.0

Activated Partial Thromboplastin Time; ECMO: Extracorporeal Membrane Oxygenation; UFH: Unfractionated Heparin

Similarly, Adatya et al. (2015) and Yarmohammadi et al. (2014) researched on patients with CF-LVADs. Both results show that more than half of the population had discordance values for aPTT and anti-Xa.

Therapeutic Target and Dose Adjustment

The conventional approach for monitoring UFH has been using serial aPTT measurements, which are usually taken at regular intervals (within two hours after initiating continuous intravenous infusion, and every 6 hours thereafter). The dose of UFH can be modified based on the aPTT and the frequency of monitoring may decrease as the desired range is reached and maintained. Although physicians routinely know and use this therapeutic aPTT range, there is minimal empirical data supporting this advice (McRae et al., 2021).

Table II represents the anti-Xa has a higher positive correlation with heparin dose the heparin compared to the aPTT (Arnouk et al., 2020). Furthermore, the aPTT group reached therapeutic time significantly longer than the anti-Xa group (Kindelin et al., 2021). Whitman-Purves et al. (2018) showed the same result as Kindelin et al. (2021). Otherwise, Kulig et al. (2021) showed that in adult venoarterial ECMO patients, both aPTT and anti-Xa groups had no difference in the time to therapeutic.

Similarly, anti-Xa achieved therapeutic goals better than aPTT group, yet there was no significant difference between them (Kindelin et al., 2021; Kulig et al., 2021). In addition, the aPTT group required dose adjustment more than the anti-Xa (Kindelin et al., 2021; Whitman-Purves et al., 2018). Patients in the aPTT cohort experienced a higher number of infusion interruptions because of supratherapeutic values (P = 0.007) and required boluses due to subtherapeutic values (P = 0.044) (Kindelin et al., 2021).

CONCLUSION

In conclusion, the results of the discordance rate of aPTT and anti-Xa tests are inconsistent among studies. The heparin dose-to-assay correlation coefficient and therapeutic targets were higher for the anti-Xa than aPTT. The anti-Xa cohort achieved a faster time to therapeutic range and required fewer dose adjustments compared to the aPTT control. The review demonstrates that anti-Xa outperforms aPTT in achieving the target therapeutic range of UFH, time to therapeutic, and dose modification.

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