Asian Hematology Research Journal

Volume 7, Issue 3, Page 1-7, 2023; Article no.AHRJ.97608

Correlation between PT/INR and APTT in Patients on Warfarin: A Study at a Tertiary Care Teaching Hospital

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/97608

Original Research Article

Received: 14/01/2023
Accepted: 17/03/2023
Published: 23/03/2023

ABSTRACT

Background: Warfarin prolongs coagulation by inhibiting the synthesis of biologically active forms of coagulation factors and regulatory factors, which are dependent on vitamin K. The Prothrombin Time (PT) and International Normalized Ratio (INR) are routinely used to monitor warfarin therapy in clinical settings. In addition to PT, APTT is also prolonged by warfarin therapy due to the effect of warfarin on intrinsic pathway. In this study we aimed to evaluate the distribution of PT/INR, distribution of APTT and correlation between INR and APTT in a cohort of patients on long term warfarin.

Materials and Methods: Seventy four (74) patients on long term warfarin therapy were recruited from University Haematology clinic of Colombo South Teaching Hospital. PT and APTT were performed in the routine citrated blood samples during their regular clinic visits using semi-automated 4 channel CA-104 analyzer. Data were analyzed statistically by using SPSS.

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Results: Among the recruited 74 patients, 36 were females and 38 were males. In this cohort, PT was normally distributed. The distribution pattern of APTT deviated from the normal standard pattern due to some exceptional cases of females. There was no significant correlation between INR and warfarin dose. The statistical results of the study established that there was a good (strongly positive) linear correlation between the APTT and INR since Pearson correlation coefficient equals to 0.799 (p=0.000).
Conclusion: Our study concluded that in addition to the elevation of PT/INR and APTT by warfarin, there is a good linear correlation between elevation of INR and APTT.

Keywords: Activated Partial Thromboplastin Time (APTT); Prothrombin Time (PT); International Normalized Ratio (INR); warfarin.

1. INTRODUCTION

Activated Partial Thromboplastin Time (APTT) and Prothrombin Time (PT) are specific types of coagulation tests which are used to assess the haemostatic process in the blood and to determine the efficacy of coagulation.

APTT is used to assess the activity of intrinsic pathway and common pathway of the coagulation cascade [1,2]. The efficiency of the intrinsic pathway depends on the overall level and function of contact factors, factor XI, factor VIII, factor IX, factors of the common pathway and fibrinogen [3,4]. In addition, APTT is also sensitive to circulating inhibitors to clotting factors.

PT is used to assess the activity of the extrinsic and common pathways of the coagulation. The tissue factor, factor VII, factor II, factor I, factor V, X levels, and their functions can be monitored by using PT. Therefore it can be used to measure the effect of coumarin drugs like warfarin, on coagulation cascade as coumarin drugs inhibit the synthesis of some of the above factors (factor II, VII, IX and X). The PT is usually expressed as International Normalized Ratio (INR) in patients on warfarin treatment.

For more than five decades, warfarin, a vitamin K antagonist (VKA), was the sole oral anticoagulant available in clinical practice [5]. Warfarin inhibits the synthesis of biologically active forms of coagulation factors II, VII, IX, X, and regulatory factors like protein C and S, which are dependent on vitamin K. It has an inhibitory effect on vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K into its reduced form after the carboxylation of the above clotting factors [6]. Due to under-carboxylation, the coagulation factors produced in the absence of vitamin K have a reduced function. Warfarin has a very narrow therapeutic index and reacts with certain drugs and foods. Therefore, the dosing of warfarin is always monitored with the help of PT, INR in clinical settings [7,8].

Even though warfarin depletes the activated factor IX, the PT which is used to monitor warfarin, is not affected by factor IX. Therefore, the effect of warfarin on factor IX cannot be measured by using PT [9]. This can be detected only by APTT. As APTT measures the efficacy of both intrinsic and common pathways which are influenced by vitamin K dependent clotting factors (IX, X, II), patients treated with warfarin have prolonged APTT.

Mulliez SMN, Bogaert JV and Devreese KMJ., (2015) conducted a study to evaluate the impact of vitamin K antagonist (VKA) on APTT using 700 samples from patients who were treated with VKA in the Ghent University hospital. They stated that APTT can be prolonged due to the VKA treatment [6].

A research done by Hauser VM and Rozek SL., (1986) to study the effect of warfarin on Activated Partial Thromboplastin Time concluded that the degree of elevation of the PT and the degree of elevation of the APTT for the study group had a good linear association [10].

As there is no published data on the relationship between PT/INR and APTT in patients on warfarin in Sri Lankan setup, our aim is to evaluate the correlation between PT/INR and APTT in a cohort of patients on long term warfarin.

2. MATERIALS AND METHODS

For this analytical cross-sectional study seventy four (74) patients on long term warfarin were recruited from University Haematology clinic, Colombo South Teaching Hospital (CSTH), Sri

Lanka, after considering inclusion and exclusion criteria.

2.1 Inclusion Criteria

1. Patients on long-term warfarin for various indications and monitored by PT/INR in routine clinic visits.
2. INR similar to or more than 1.5.

2.2 Exclusion Criteria

Patients with concurrent conditions known to affect PT and APTT were excluded from the study.

1. Patients with acute or chronic alcohol abuse.
2. Patients with uncontrolled congestive heart failure (CHF).
3. Patients with chronic liver cell disease.
4. Patients with known clotting factor deficiencies.
5. Patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome.
6. Patients on concurrent heparin.

A routine blood sample of 2 CC (1.8 ml blood, 0.2 ml citrate in 9:1 ratio) was collected into a 3.2% tri sodium citrate tube from each selected patient to assess the PT/INR and APTT after his or her informed written consent.

Both PT/INR and APTT values were evaluated using semi-automated 4 channel CA-104 analyzer which uses turbo-densitometric measuring principle for testing. “Actin FS” and “Thromborel S” reagents were used to measure APTT and PT respectively. The ISI value specific for the “Thromborel S” reagent and the CA- 104 analyzer was 1.03. The analyzer was calibrated according to the international standards and quality control samples were run daily prior to the analysis.

A simple linear regression analysis with 95% and 90% prediction limits between APTT and PT/INR was done. All the statistical analysis was done using the SPSS database.

3. RESULTS

From eighty-nine (89) participants, a total of fourteen (14) patients were excluded according to the exclusion criteria of the study. An outlier was identified with a disproportionately prolonged APTT leaving only 74 patients for further analysis. Out of 74 recruited patients, 48.6% (n=36) were females and 51.4% (n=38) were males. Majority of patients (n=56) were between 46 and 75 years (Table 1).

Table 1. Distribution of patients on warfarin according to the age

Age Group	Frequency	Percentage (%)
26-35	03	4.1
36-45	03	4.1
46-55	16	21.6
56-65	23	31.0
66-75	17	23.0
76-85	10	13.5
86-95	02	2.7
Total	74	100

In this patient cohort, atrial fibrillation (52.70%), deep vein thrombosis (22.97%) and pulmonary embolism (8.11%) were identified as the most common indications for warfarinization (Table 2). The warfarin dose administered for various indications among the population was normally distributed with the mean dose of 5.5208 mg (Table 3).

Table 2. Indications for warfarin among the study population

Indication	Frequency	Percentage (%)
Atrial Fibrillation (AF)	39	52.70
Deep Vein Thrombosis (DVT)	17	22.97
Pulmonary embolism	06	8.11
Atrial Flutter	05	6.75
Apical thrombosis	03	4.05
Tachy Brady Syndrome	01	1.35
STEMI	01	1.35
Aortic valve replacement	01	1.35
Cerebral venous sinus thrombosis	01	1.35

In the study group, PT and INR were normally distributed (Table 4, Table 5) but the distribution pattern of APTT was deviated from the normal standard pattern (Table 6, Fig. 1). All the patients had prolonged PT values above 12.5 s with a majority of patients showing INR values between 2.00-2.99 which was the therapeutic range. Majority of the study population showed an APTT value between 31.0 s- 40.9 s (mean= 39.18 s).

Table 3. Distribution of patients according to the dose of warfarin

Warfarin Dose (mg)	Frequency	Percentage (%)
1.0 – 1.9	01	1.35
2.0 – 2.9	02	2.70
3.0 – 3.9	08	10.81
4.0 – 4.9	14	18.91
5.0 – 5.9	21	28.37
6.0 – 6.9	11	14.86
7.0 – 7.9	10	13.51
8.0 – 8.9	04	5.40
9.0 – 9.9	03	4.05

Table 4. Distribution of PT among the study population

Range of PT (S)	Frequency
11.0 – 20.9	18
21.0 – 30.9	33
31.0 – 40.9	18
41.0 – 50.9	05

Table 5. Distribution of INR among the study population

Range of INR	Frequency
1.00 – 1.99	20
2.00 – 2.99	38
3.00 – 3.99	15
4.00 – 4.99	01

Table 6. Distribution of APTT among the study population

Range of APTT (s)	Frequency
21.0 - 30.9	14
31.0 – 40.9	32
41.0 – 50.9	17
51.0 – 60.9	10
61.0 – 70.9	01

There was a significant correlation between INR and APTT (Fig. 2) since the level of significance was $p < 0.05$. Pearson correlation between INR and APTT was 0.799 which was close to 1.0 (Table 7). Therefore, there was a good linear (Strong positive) correlation between the APTT and INR in patients on long term warfarin.

There was no significant correlation between INR and warfarin doses (> 0.05) (Table 8).

4. DISCUSSION

This analytical cross-sectional study was carried out to find out whether there was a correlation between APTT and INR in patients on long term warfarin. For this study, according to the inclusion and exclusion criteria 75 subjects were recruited. One outlier was identified as it was outside the 95% prediction limit with disproportionately prolonged APTT (80.2 s), PT (90.35s) and high INR (8.43). Finally, data from 74 subjects were used for further analysis. Even though the minimum sample size calculated for the study was 52, the higher number in sample size (74) improved the statistical validity of the study.

The specific reference ranges for APTT and PT which were used in this study were 22.4 s - 28.7 s (mean-25.5 s) and 10.3 s - 12.5 s (mean-11.4 s) respectively. The INR/ISI system was introduced to standardize PT variation with the use of different thromboplastin reagents to monitor the patients under warfarin therapy. The Thromboplastin reagent used for this study had high sensitivity since ISI was close to 1.00. Therefore, the accuracy of INR was high.

According to the results of the study, the highest number of participants (44.6%) had PT values within the range of 21.0 s - 30.9 s. All the participants showed PT values above the upper reference limit. It was observed that the majority of subjects (51.35%) were in the therapeutic range of INR which was 2-3. There were 27.03% (n=20) subjects who had sub therapeutic INR and 21.62% (n=16) showed values above the therapeutic range.

There were 12.16% (n=9) subjects who had APTT values within the normal reference range. Rest of the population (87.84%, n=65) showed values above the upper reference limit with a majority of patients (43.24%, n=32) having values between 31.0 s – 40.9 s and 28 patients (37.83%) showing values above 41 s.

The findings of this study indicated that warfarin significantly prolonged both APTT and PT in patients anticoagulated with warfarin alone. A study conducted by Hauser VM and Rozek SL., (1986) had reported that the time required to occur coagulation was increased by warfarin whether it was assessed by the APTT or by the PT [10].

When the distribution patterns of APTT, PT and INR were considered, it was observed that there was a normal distribution of PT and INR among the study population but the distribution pattern of APTT was deviated from the normal standard pattern. When data was further analyzed to find

out a specific reason for above deviation, it was observed that all the males in the study population had normally distributed APTT and two exceptional cases of females attributed for that deviated pattern of APTT. One of the two females had high CRP and she did not have any other suspected conditions such as antiphospholipid syndrome to account for high APTT. A study by Mulliez SMN, Bogaert JV and Devreese KMJ., (2015) had revealed that the interaction of CRP on the phospholipids caused prolongation of phospholipid dependent coagulation tests in-vitro [6].

Table 7. Correlation between INR and APTT of the study population

		Current APTT (s)	Current INR
Current APTT (s)	Pearson correlation	1	.799**
	Sig. (2-tailed)		.000
	N	74	74
Current INR	Pearson correlation	.799**	1
	Sig. (2-tailed)	.000	
	N	74	74

Table 8. Correlation between INR and warfarin dose

		INR	Warfarin dose (mg)
INR	Pearson correlation	1	-.179
	Sig. (2-tailed)		.135
	N	74	71
Warfarin dose (mg)	Pearson correlation	-.179	1
	Sig. (2-tailed)	.135	
	N	71	72

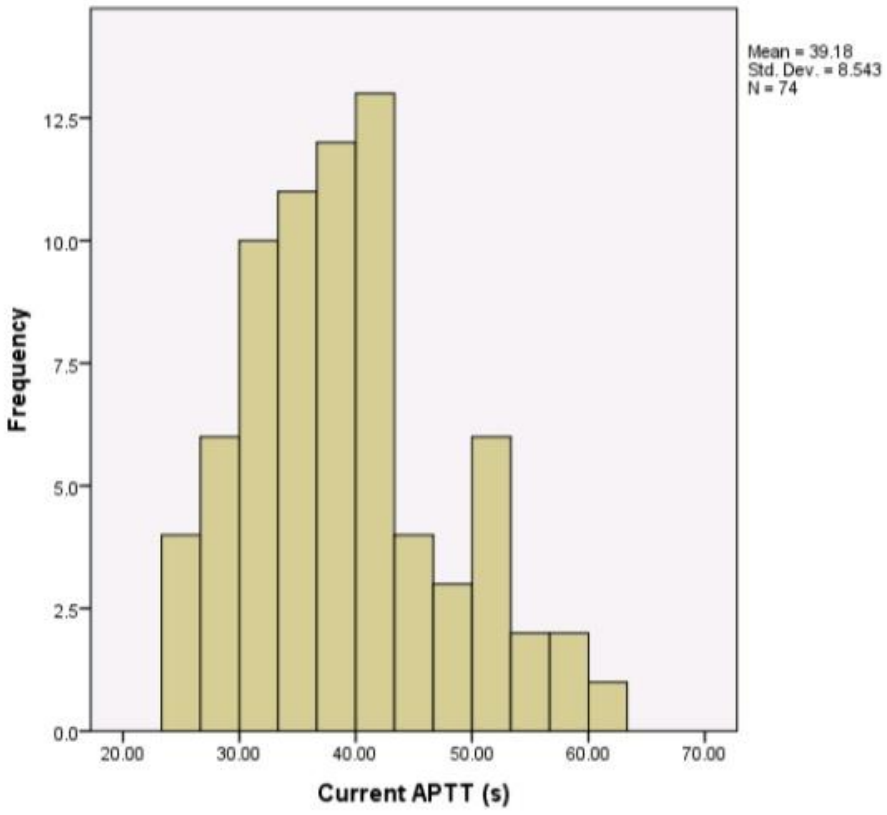

Fig. 1. Distrribution of APTT among the study population

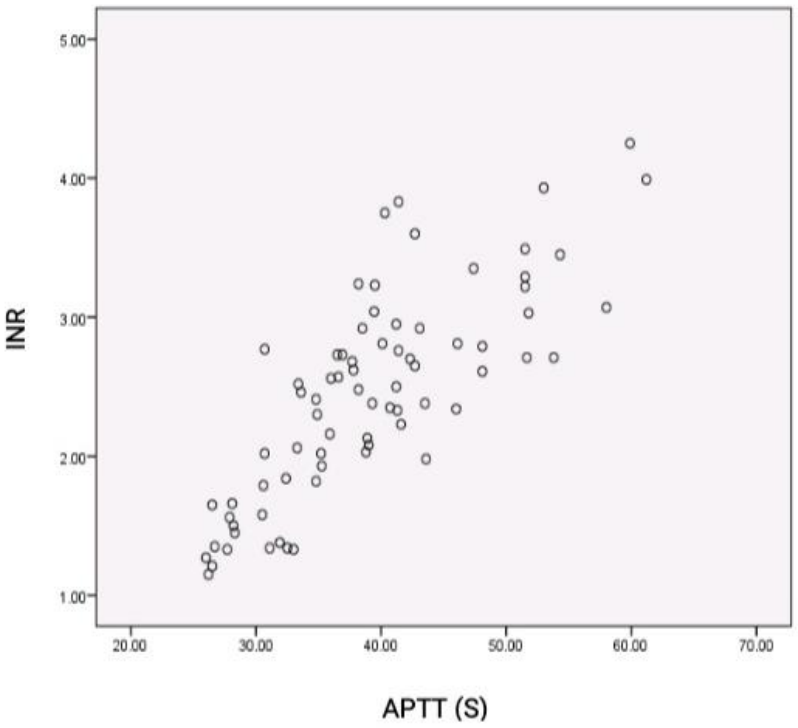

Fig. 2. Correlation between INR and APTT

When the distribution patterns of APTT and INR were examined, it was observed that most of the patients (n=38) were within the therapeutic range of INR (2.0-3.0). APTT distribution pattern showed that these patients had APTT higher than the upper reference limit of APTT (28.7 s). More than half of the patients among them (21 of 38 patients) had values within 31.0 s - 40.9 s (1.2-1.6 times mean reference value) but 15/38 patients had values above 41s.

Majority of the patients with INR above therapeutic range (n=15/16) showed APTT values higher than the mean APTT of the study population (mean = 39.18 s). Most of the values varied between 41-61s. More than half of the subjects who had INR below the therapeutic range, showed APTT values less than the mean APTT of the study population.

The statistical results of the study established a good (strongly positive) linear correlation between the APTT and INR, as reflected by Pearson correlation of 0.799 for the total group. The study by Hauser VM and Rozek SL., showed that a good liner correlation exists between the degree of elevation of the PT and APTT (r= 0.821) [10].

5. CONCLUSION

This study concluded that in addition to the elevation of PT/INR and APTT by warfarin, there is a good linear correlation between elevation of INR and APTT.

6. LIMITATIONS

As patients who were already on warfarin were recruited for the study, a baseline APTT and the degree of elevation of baseline APTT due to warfarin could not be evaluated.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical clearance was obtained from the Ethics Review Committees of Faculty of Medical Sciences, University of Sri Jayewardenepura and Colombo South Teaching Hospital.

ACKNOWLEDGEMENT

The authors would like to thank all the Consultant Haematologists at University Haematology clinic, CSTH for their enormous support for this study. Also, authors wish to extend their gratitude to Mr. W.M.L. Dananjaya, technical officer, University Haematology clinic, CSTH.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/97608