

Original Research Article

RELATIONSHIP BETWEEN PT/INR AND APTT IN PATIENTS ON WARFARIN: A STUDY AT A TERTIARY CARE TEACHING HOSPITAL.

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 relationship between INR and APTT in a cohort of patients on long term warfarin.

Material 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 sample during their regular clinic visit using semi-automated 4 channel CA-104 analyzer. Data were analyzed statistically by using SPSS.

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

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 the 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 & 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 by only 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 relationship between PT/INR and APTT in a cohort of patients on long term warfarin.

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.

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.

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.

Routine blood sample of 2 CC (1.8 ml blood, 0.2 ml citrate in 9:1 ratio) from the selected patients were collected into 3.2% tri sodium citrate tubes to assess the PT/INR and APTT after their informed written consent.

Both PT/INR and APTT values were evaluated using semi-automated 4 channel CA-104 analyzer which operates according to the turbodensitometric measuring principle. “Actin FS” and “Thomboral S” reagents were used to measure APTT and PT respectively. The ISI value specific for the “Thomboral 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.

RESULTS

From eighty nine (89) participants fourteen (14) were excluded according to the exclusion criteria and an outlier was identified with the disproportionately prolonged APTT. 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).

In our patient cohort, atrial fibrillation (52.70%), deep vein thrombosis (22.97%) and pulmonary embolism (8.11%) were 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).

In our 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, Figure 1). All the patients had prolonged PT value above 12.5 s (Table 4) and majority of patients showed an INR value between 2.00-2.99 which is the therapeutic range (Table 5). Majority of the study population showed an APTT value between 31.0 s- 40.9 s (mean= 39.18 s) (Table 6).

There was a significant relationship between INR and APTT (Figure 2) since the level of significance was $p < 0.05$. Pearson correlation between INR and APTT was 0.799. It is closed 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.

DISCUSSION

This analytical cross-sectional study had been carried out to find out whether there is a correlation between APTT and INR in patients on long term warfarin. For this study, according to our inclusion and exclusion criteria 75 subjects were recruited. In total one outlier was identified as it was outside of 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 our study, the highest number of participants (44.6%) had PT value within the range of 21.0 s - 30.9 s. All the participants showed PT values above the upper reference limit. We observed that the majority of subjects (51.35%) were in the therapeutic range of INR which is 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.

Majority of patients (43.24%, n=32) had APTT values within the 31.0 s – 40.9 s. There were 12.16% (n=9) subjects within the normal reference range. Rest of the population (87.84%, n=65) was above the upper reference limit.

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 is assessed by the APTT or by the PT [10].

When the distribution patterns of APTT, PT and INR were considered, we 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. We further analyzed data to find out a specific reason for above deviation. Then we 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 for prolongation of phospholipid dependent coagulation tests in-vitro [6].

When the distribution patterns of APTT and INR were examined, we observed that the 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) were within the 31.0 s - 40.9 s range of APTT (1.2-1.6 times mean reference value).

Patients with INR above the therapeutic range (n=16) showed APTT values higher than the upper reference limit (>28.7). The majority of above patients had APTT higher than the mean

APTT of the study population (mean = 39.18 s). More than half of the subjects who had INR below the therapeutic range, showed APTT 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 linear correlation exists between the degree of elevation of the PT and APTT ($r= 0.821$) [10].

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.

LIMITATIONS

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

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Tables

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

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

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

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

Figures

Figure 1: Distribution of APTT among the study population.

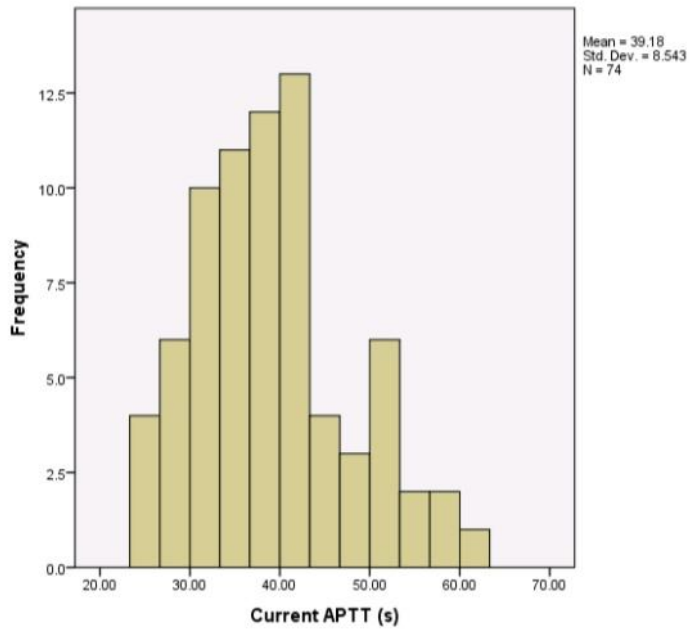


Figure 2: Correlation between INR and APTT.

