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RESEARCH ARTICLE

IDEAL WARFARIN DOSE ADJUSTMENT IN CARDIAC PATIENTS FOR SAFETY INR OUTCOME.

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Abstract

Background: warfarin is effective for the primary and secondary prevention of both arterial and venous thromboembolic disorders. Its variable dose response and narrow time therapeutic range (TTR) mandate periodic monitoring of the international normalized ratio (INR).

Aims: monitoring the dose change of warfarin therapy to adjust the INR in ideal values.

Patients and methods: this study included 200 patients (103 males and 97 females) on oral anticoagulant, their age ranged from 17 to 66 years' old, classified into group 1(69) patients suffering from rheumatic heart disease (RHD), group 2(115) patients suffering from valve replacement and group 3(16) patients suffering from other cardiac conditions. They were subjected to full clinical examination and laboratory investigations including prothrombin time (PT), prothrombin concentration (PC) and INR, recording and follow up to the dose of oral anticoagulants, the control group included 28 healthy subjects matched in age and sex.

Results: The target warfarin dose was 3-4 mg for RHD and 4-5mg for valve replacement; INR in the RHD versus valve replacement was 2/3 ($p = 0.001$). PT in the RHD versus valve replacement was 16/23 sec. ($p = <0.001$).

Conclusion: close monitoring of anticoagulant dose is required by blood testing (INR),during the initial stage of treatment, checking may be required daily.

Introduction:-

Warfarin is effective for the primary and secondary prevention of both arterial and venous thromboembolic disorders. Its variable dose response and narrow therapeutic index mandate periodic monitoring of (INR) . Less frequent INR monitoring may be feasible in stable patients (1).Patients who are well-established on a warfarin regimen there is need for routine monitoring of INR to improve safety outcome, and patient satisfaction, but more frequent INR assessment increase the (TTR)(2). TTR is a well-established surrogate outcome that indirectly correlates with the bleeding risk (3). The interpretation of the relationships between TTR and treatment efficacy is complex. More TTR would be associated with the safety outcome (4). INR values are influenced by various patient-related factors including age, sex, body weight, smoking, diabetes mellitus, liver failure, CHF, pulmonary disease, also concomitant use of other medications, particularly amiodarone (5). Also other patient-related factors, such as

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culture and education, socioeconomic status, healthcare and quality of medical service, all these factors have profound impact on the efficacy of warfarin TTR, and safety of drugs (6). So Hospital/clinic specific policies and protocols, alone can't justify coverage, all mentioned factors must be working in combination (7, 8). The maintenance dose of warfarin can fluctuate significantly depending on the amount of vitamin K in the diet. Keeping vitamin K intake at a stable level can prevent these fluctuations (9). VKORC1 polymorphisms explain 30% of the dose variation between patients (10). Particular mutations make VKORC1 less susceptible to suppression by warfarin (11). Lowdose haplotype group (A) and a high-dose haplotype group (B) (12). For warfarin-managed patients, there are variable wide variations in INR control between countries and sites. This has been answered the questions regarding the relevance of the overall data for individual patients, or different countries, with more refined management systems (13).

Important factors responsible suboptimal use of warfarin especially in patients with AF is due to difficult achieving therapeutic anticoagulation, dietary modifications and the necessity for INR assessment, also warfarin require bridging with parenteral anticoagulants at the start of therapy (14). Bleeding risk for patients taking warfarin who are found to have INR prolongation, reversal can be accomplished with fresh frozen plasma, prothrombin complex concentrate (PCC), and vitamin K (15,16). Moreover, clinical outcome data of bleeding patients on warfarin, suggests indirectly that warfarin reversal may not be clinically beneficial (17). Contraindications of warfarin are pregnancy, fetal warfarin syndrome (FWS), warfarin embryopathy(18).

Patients and Methods:-

Study design and populations: this study was conducted on 200 cardiac patients on warfarin therapy, at Internal Medicine Department, Sohag University Hospital, approved by the Ethical Committee of Sohag Faculty of Medicine; a written informed consent was obtained from all subjects. Their age was ranged from 17 to 66 years' old with median age 53 years, 103 males and 97 females. 28 healthy control subjects 17males and 11 females, their age ranged from 15 – 55 years' old with median age 46 year, were included.

Inclusion criteria:-

The study included 200 patients on warfarin therapy; they were classified into the following groups:

Group 1: Consisted of 69 patients suffering from RHD.

Group 2: Consisted of 115 patients with valve replacement.

Group 3: Consisted of 16 patients suffering from other cardiac conditions requiring oral anticoagulants.

Exclusion criteria:

Pregnancy, bleeding disorders.

Preparation of samples:-

4 ml of venous blood was drawn from each patient, 1. 8 ml of which was added to trisodium citrate tube provided by B.D, centrifuged at 2500 – 3000G unit for 15 min. at 20˚c to prepare platelet poor plasma (P.P.P), subjected to the prothrombin time. The remaining blood was subjected to the routine investigations.

Procedures:-

Prothrombin time (PT):-

Reagents: Thromborel®Sprovided by SIEMENS, Cat. No. 54690523, Siemens Health Care Diagnostic Products GmbH.

Reagent: lyophilized thromboplastin prepared from rabbit cerebral tissues, dissolved in 4ml purified D.W. per vial

Assay: The test was performed on fully automated SYSMEX-CA1500 (SYSMEX Corporation, Marburg/Germany),USA distributor.

Quality control:-

Two different levels of control were used, control N Cat. No. 50771820, and control P Cat. No. 50998227.

Recording the dose of oral anticoagulant:-

Close monitoring the dose change of oral anticoagulant and recording the corresponding change in the INR. The recording system starting from the initial dose then from (4-5 times)from the 3rd day to the 2nd week to reach the target INR.

Statistical analysis:-
Both excel program of Microsoft Office and Scientific Package of Social Statistics (SPSS) program version 19 were used for a comparative evaluation between tests. .

Results:-

Closed monitoring to INR wasperformed on 200 patients on warfarin therapy after a written consent, their age was ranged from 17to 66 years' old and the median age of 200 cases was 53years' old . The sex distribution in the study showed that 103 cases were males (51.5 %) and 97 (48.5%) were females. The control group consists of 28 subjects, 17 males and 11 females (60.3%, 39.7 respectively), their age was ranged from 15to 55 years' old; the median age was 46 years' old, they were clinically and laboratory healthy.Demographic data were present in table -1. **Diagnosis** of these patients were 69cases RHD (34.5%), 115 patients with valve replacement classified as follow; 28 cases aortic valve replacement (14%), another 36 with aortic and mitral valve replacement (18%), the last 48 cases withinthis group with mitral valve replacement (24%), and the rest of other diagnoses were dilated cardiomyopathy , congestive heart failure (CHF), atrial fibrillation (AF) and DVT; all constitutes (8%) referred as other cardiac condition, as in table - 2. The target **dose** of warfarin was 3.8 mg in RHD and 4.7mg in valve replacement patients; with($p = 0.01$) was significant; as in table -3. The dose within patients with RHD and patients with other cardiac diseases were nearly the same dose so the p- value was (0.77) non-significant as in Fig -1. As regard **INR** in the RHD patientsversus valve replacement patients; we noticed that the target INR of RHD patients was 2.45and in valve replacement patients was2.76, the p-value was(0.01)significant; onlynon-significant p-value (0.7) was noticed in the INR of the 1st week of therapy as in table- 4. When comparing INR in the valve replacement patientstothose with other cardiac condition; the mean of target INR was2.7 in both groups, ($p = 0.9$) was non-significant. The PC in the RHD patientsversus valve replacement patients was 52% and 68 %, respectively ($p= 0.001$) as in Fig-2.

Table 1:- Demographic data of the studied groups

Item	Rheumatic heart (n =69)	Valve replacement (n =115)	Other conditions (n =16)	p-values
Age in years Range (median) 40 (17 – 66)	41(17 47)	39(28 – 53)	45(38- 63)	0.042 (S)
Male/Female 103/97	34/35	59/56	10/16	0.633 (NS)

Table (2):- Clinical diagnosis of 200 patients on warfarin

Item	Frequency	Percent %
1-RHD	69	34.5
2-Valve replacement:		
Aortic Valve Replacement	28	14.0
Mitral Valve Replacement	48	24
Mitral and Aortic Valve Replacement	36	18
Mitral Valve Repair	3	1.5
3-Other Cardiac Condition		
AF	2	1.0
CHF AF	4	2.0
Dilated Cardiomyopathy	4	2.0
DVT	3	1.5
DVT LC	1	0.5
Tight Mitral Stenosis AF	2	1.0
Total	200	100.0

AF atrial fibrillation, CHF congestive heart failure, DVT deep venous thrombosis, LC local complications.

Table (3):- Dose in RHD group versus valvereplacement group

Item	Diagnosis	Mean	S.D	T test	P value
Initial Dose mg/day	RHD	2.45	1.13	5.04	<0.001**
	Valve replacement	3.03	0.38		
Frequency	RHD	4.49	1.82	4.59	<0.001 **
	Valve replacement	5.68	1.61		
Dose_3d	RHD	2.93	1.43	3.64	<0.001 **
	Valve replacement	3.60	1.03		
Dose_1W	RHD	3.56	2.35	2.06	0.040 *
	Valve replacement	4.30	2.10		
Dose_2W	RHD	3.80	2.49	2.63	0.009 **
	Valve replacement	4.75	2.29		
Target dose	RHD	3.80	2.46	2.58	0.010 *
	Valve replacement	4.73	2.30		

RHD rheumatic heart disease, 3d third day, 1W first week, 2W second week
* Significant p-value <0.5, ** highly significant p-value <0.01

Table (4):- INR in RHD group versus valve replacement group

	Diagnosis	Mean	S.D	T test	P value
First INR	RHD	2.11	1.35	3.418	0.001**
	Valve replacement	1.61	0.578		
Frequency	RHD	4.49	1.82	4.595	<0.001**
	Valve replacement	5.68	1.61		
INR_3d	RHD	2.36	1.56	3.268	0.001**
	Valve replacement	1.82	0.620		
INR_1W	RHD	3.05	0.924	0.084	0.933 N
	Valve replacement	3.16	0.39		
INR_2W	RHD	2.44	0.65	3.777	0.01*
	Valve replacement	2.76	0.49		
Target INR	RHD	2.45	0.63	3.722	0.01 *
	Valve replacement	2.76	0.49		

INR international normalized ratio, RHD rheumatic heart disease, 3d third day,
1W first week, 2W second week, * Significant p-value <0.5, **highly significant
P-value<0.01, N Non significant p-value >0.5

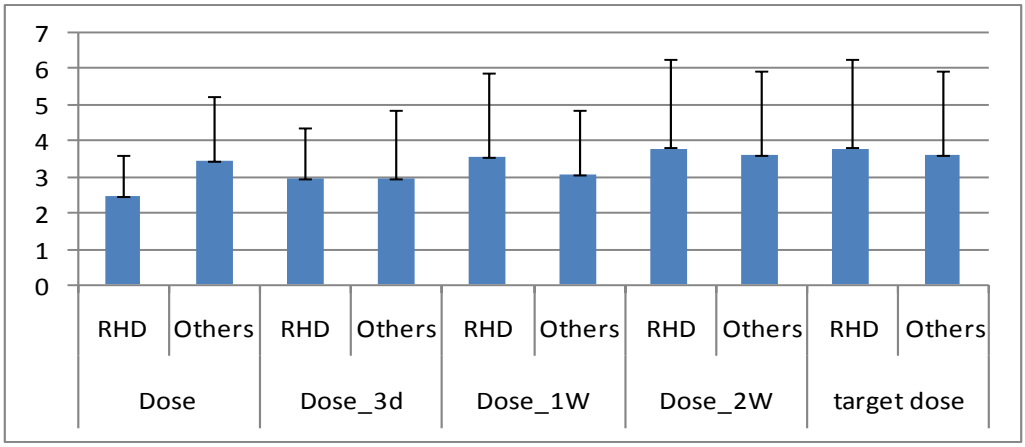

Fig. (1):- Dose in RHD group versus other cardiac conditions group

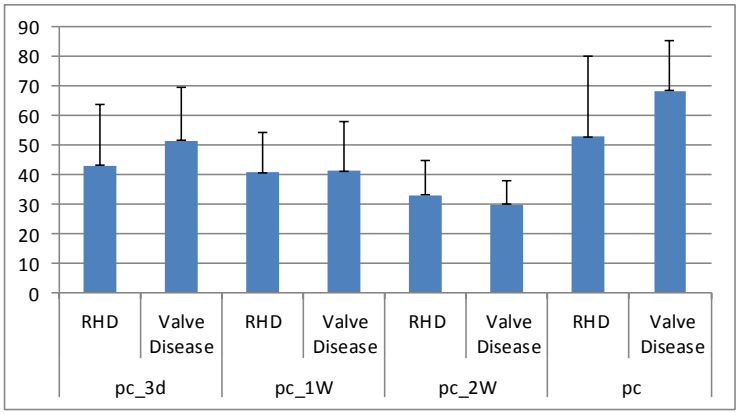

Fig. (2): PC in RHD group versus valve replacement group

Discussion:-

Warfarin is used to decrease the tendency for thrombosis or prophylaxis of further episodes in those individuals who have already had thrombus and help to reduce the risk of embolism (19). Dosing of warfarin is complicated by the fact that it is known to interact with many commonlyused medications and even with chemicals that may be present in certain foods (2, 3,20, 21, 22). These interactions may enhance or reduce its anticoagulation effect. In order to optimize the therapeutic effect without risk of bleeding, close monitoring of the degree of anticoagulation is mandated by measurement (INR) (4). In the present study PT, PC and INR were obtained from 200 patients with RHD, valve replacement and other cardiac conditions that required oral anticoagulants. The target dose of warfarin in RHD patients was about 3-4 mg but in patients with valve replacement; it was about 4-5mg and in those with other cardiac diseases it did not exceed 3mg, we followed up these patients daily from 4 to 6 times to get the target dose after two weeks , the dose in the RHD patients and in those with other cardiac conditions was nearly the same dose, this is in accordance withHirsh et al, (2007) andRatib etal, (2016)who hadreported that during the initial stage of treatment, checking may be required daily; intervals between tests can be lengthened if the patient manages stable therapeutic INR levels on an unchanged warfarin dose, In healthy people, the INR is about 1.0. For patients on anticoagulants, the INR typically should be between 2.0 and 3.0 for patients with atrial fibrillation, or between 3.0 and 4.0 for patients with mechanical heart valves. However, the ideal INR must be individualized for each patient (23, 13). Although multiple studies byStreiffet al, (2013) had addressed the optimal testing frequency, current guidelines suggest a time interval not exceeding 4 weeks between INR determinations (6). In the current study the target INR of both RHD and valve replacement patients were ranged from 2 to 3, INR in patients with other cardiac disease was ranged from 2-4. The INR in RHD patients versus patients with other cardiac condition was nearly the same 2-3. This is in agreement with study was performed by Schafer et al (2007) andAmerican Heart Association, (2014), who reported that; the target INR ranges of 2.0 to 3.0 or 2.5 to 3.5 have been recommended for most indications because INR values in these ranges are associated with the best combination of thrombosis reduction and bleeding avoidance(1, 5); it also agrees with Majeed etal, (2013) whostated thatfor patients on anticoagulants, the INR typically should be between 2.0 and 3.0 for patients with RHD; or between 3.0 and 4.0 for patients with AF;for patients on warfarin therapy, an INR recall interval not exceeding 4 weeks has traditionally been recommended; less frequent INR monitoring may be feasible in stable patients (14). In the current study, PC of patients with RHD was about 68% and in patients with valve replacement was about 52 %, so warfarin therapy is complicated by a narrow TTR and substantial interpatient variability in dose response as reported byPiccini etal, (2014); if the INR values were not within the target range, anticoagulation service asked and recorded the most appropriate reasons (4). Random variation of INR values may occur in a patient on stable oral anticoagulant dosage, as a result of both biological and analytic variation. These data has been used to evaluate whether a change in the INR represents clinically insignificant random variation, or a clinically relevant change requiring warfarin dose adjustment. It has been calculated that in a patient on fixed dose and steady state warfarin, a change in the INR is significant only if it isgreater than 0.28 times the previous INR value (3,13,and 24).

In conclusion careful monitoring the dose response to anticoagulant therapy is mandatory to reach the best value of INR and prevent serious complication of over dose.

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