Validity of {12.34+ (0.69xBMI)} formula for total weekly warfarin dose calculation in antiphospholipid syndrome Jordanian patients

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Abstract: To evaluate the effect of different patient demographic factors on total weekly warfarin maintenance dose formula {12.34+ (0.69xBMI)} in antiphospholipid syndrome Jordanian patients.
Methods: Our prospective observational study included 112 patients, of both sexes, aged 29-64years, classed II-III physical status by the American society of anesthesiologists and presented to the rheumatology clinic as antiphospholipid syndrome labeled subjects during the year 2013 at King Hussein hospital, King Hussein medical city, Amman, Jordan, after obtaining approval from our local ethical board review committee of the royal medical Jordanian military services. Patients were divided into warfarin dose group I (n= 56, ≥70mg) and warfarin dose group II (n=56, ≤50mg). Patients with target INR ranges of 2.5 to 3.5 only were included. Demographic patients data were related to target INR and with the warfarin weekly maintenance dose {12.34+ (0.69xBMI)} .
Results: The mean age was 31.5 years(range of 29-34 years) in group I and 46 years(range of 32-60 years) in group II($P<0.05$) The female preponderance was 43(76.8%) in group I and 21(37.5%) in group II.$P<0.05$. The mean BMI was 38.3kg/m^2 (range of 32.2-39.1) in group I and 28.4kg/m^2 (range of 25.6-29.5) in group II. Patients presented with target INR were 49 patients (87.5%) in group I and 52 patients (92.9%) in group II. The mean total weekly warfarin dose in group II was 38.1 mg and the mean dose in group I was 62.5 mg.
Conclusions: Female young Jordanian antiphospholipid syndrome labeled patients need less total weekly warfarin maintenance dose to achieve INR target of 2.5-3.5 and that the formula cannot be applied on this group.
Keywords anticoagulation; antiphospholipid; demographics; formula; warfarin

1. Introduction

Tacrolimus is widely used as a primary Warfarin is the most frequently administered anticoagulant for the prophylaxis of thromboembolism and other hypercoagulable conditions for patients with or at risk of thrombosis. Warfarin is given as a racemic combination of two enantiomers,(R)warfarin and (S) warfarin that requires active monitoring to enhance results of oral anticoagulation management.The warfarin dosing is difficult due to many known and unknown causes that affect persons reaction.Many various causes are incriminatedin the different influence of warfarin including VKORC1-1639G>A polymorphism,body weight,age and serum albumin start warfarin management, the majority of physicians choose to start with traditional doses of 5 mg per day, and calibrate as required to attain a therapeutic international normalized ratio (INR)(1). Experience demonstrated that patients may need from changes,diet,drug and herbal influences,co-morbidity and social habits as smoking or alcohol use.Warfarin metabolism is determined by factors including diet, drugs and personal patient demographics. As both warfarin underuse and overuse may increase hazards to patients, some investigations have tried to formulate dosing regimens. Some have studied effect of patient body mass index (BMI) on warfarin dosing. Warfarin is commonly administered for the management of thromboembolic situations for a diverse of medical events such as antiphospholipid syndrome. The dosing of warfarin is patient related. Although there are multiple protocols to

0.5 mg up to 20 mg or more of daily warfarin to achieve a predetermined INR. This large discrepancy in warfarin dose can be attributed to simultaneous drugs, sex, nutritional condition, liver disease,

alcohol consumption, diarrhea, hyperthyroidism, fever and chronic heart failure.

In the past, it was believed that old aged patients need smaller total weekly warfarin maintenance doses in comparison to younger patients (2).Other investigations showed that females need lower warfarin doses than males (3). Little proof is available regarding the effect of body mass index (BMI) on total warfarin weekly dose. Defined impacts of patient related factors on warfarin dose can enhance attaining therapeutic INRs after starting of warfarin protocol. The aim of our study was to assess the effect of patient body mass index on the total weekly warfarin dose in antiphospholipid syndrome patients using the formula of 12.34+ (0.69xBMI).

2.Methods

This prospective observational investigation enrolled 112 patients, of both genders, aged 29-64years, classed II-III physical status by the American society of
anesthesiologists and presented to the rheumatology clinic as antiphospholipid syndrome subjects during the period of the year 2013 at King Hussein hospital, King Hussein medical city, Amman, Jordan, after obtaining approval from our local ethical board review committee of the royal medical Jordanian military servic All patients were using warfarin and were followed up for pharmaceutical care of anticoagulation management. Patients were divided into warfarin dose group I (n= 56, ≥70mg) and warfarin dose group II (n=56, ≤50mg). Only patients with stable total weekly warfarin dose for three consecutive months were enrolled. Patients with target INR ranges of 2.5 to 3.5 only were included.

General demographics included: age, sex, body mass index, date of warfarin therapy start, indication, target INR range (2.5 to 3.5) and total weekly warfarin maintenance dose. Body mass index (BMI) was calculated via weight/ (height)^2.

Statistical analysis

Descriptive variables were evaluated using Chi-square and Students t tests where probability <0.05 was considered statistically significant.

3.Results

There were no significant differences between the two groups in terms of sex, ASA and indication for warfarin management. The overall mean age was 46.5 years(range of 29-64 years).The mean age was 31.5 years(range of 29-34 years) in group I and 46 years(range of 32-60 years) in group II(P<0.05).The overall female incidence was 57.1%(64) and male incidence was 42.9%(48).P<0.05 .The female preponderance was 43(76.8%) in group I and 21(37.5%) in group II.P<0.05.The male preponderance was 13(23.2%) in group I and 35(62.5%) in group II.P>0.05.ASA II was present in 5 patients(8.9%) in group I and in 6 patients(10.7%) in group II(P>0.05),while ASA III was present in 51(91.1%)patients and in 50 patients(89.3%),in groups I and II, respectively. P>0.05. Table I.

The mean BMI was 38.3kg/m^2 (range of 32.2-39.1) in group I and 28.4kg/m^2 (range of 25.6-29.5) in group II.P>0.05.The indication for warfarin therapy was antiphospholipid syndrome .Most of our patients experienced INR target ranges of 2.5 to 3.5 (n = 101, 90.2%).Of these, 49 patients (87.5%) were in group I and 52 patients (92.9%) were in group II.P>0.05.Table II.

Table I. Demographic data (no).

	GI	GII	P
N	56	56	
Total weekly warfarin dose(mg)	≥70mg	≤50mg	
Age(yr)range	29-34 y	32-60y	<0.05
Sex F	43	21	<0.05
M	13	35	
BMI(kg/m^2)range	32.2-39.1	25.6-29.5	<0.05
ASA II	5	6	>0.05
III	51	50	

Table II. Comparison of the two warfarin dose patient populations.

	G I	G II	P
INR within 2.5-3.5	49	52	>0.05
INR outside 2.5-3.5	7	4	>0.05
Age(yr) mean	31.5	46	<0.05
Sex F	41	20	<0.05
M	8	32	
BMI(mean)	38.3	28.4	<0.05
ASA II	4	5	>0.05
III	45	47	
Actual weekly warfarin dose(mg-mean)	62.5	38.1	<0.05
Predictive weekly warfarin dose(mg-mean)	38.77	31.94	

Patients in group I were found to be significantly younger (31.5 years) than in group II (46 years).P<0.05.Female preponderance was

significantly different between the two groups and it was significantly more than males in both groups.
The mean total weekly warfarin dose in group II was 38.1 mg and the mean dose in group I was 62.5 mg ($P<0.05$).Table II. Applying the total weekly warfarin maintenance dose formula: 12.34+0.69xBMI, the dose would be 38.77mg in group I and 31.94mg in group II.

4.Discussion

This study enrolled patients with target INR of 2.5-3.5.The target INR had a reduced effect on total warfarin dose in our patients. Some researchers found that one of the potent patient related factors that affect total warfarin dose is the simultaneous administration of CYP-inducing drugs (4). The predominately active warfarin isomer (S) is metabolized via CYP450 2C9, while the less active isomer (R) is a substrate of the 1A2, 2C19 and 3A4 isoenzymes. Adding drugs that stimulate the metabolism of these enzymes would increase plasma warfarin concentrations and reduce the total warfarin dose requirement. The discrepancy in mean total warfarin dose between patients groups that were and were not administered CYP-inducing drugs were showed to be statistically significant (4).
Age was a statistically significant prognostic of total warfarin dose. It was demonstrated that a total warfarin dose of 2.4 milligrams are used for each additional decade of patient age, controlling all other parameters.Garcia et al (5) demonstrated that the total warfarin dose decreased by 0.4 mg per year of life(decrease by 6% per decade). Age was shown to be significantly different between the high and low warfarin dose groups, with high dose patients tending to be younger. Patients in the low and high groups of warfarin administration averaged 46 and 31.5 years of age, respectively. Total weekly maintenance warfarin dose is inversely proportional to age (6).The volume of warfarin needed to attain a predetermined international normalized ratio depends on age with older subjects needing less warfarin.Age is a major determinant of the dose of warfarin needed to maintain the INR.

Regarding correlation between sex and total warfarin dose, and although not statistically significant, women patients needed a 2.55 mg lower total warfarin dose in comparison with men (4). Other investigations found that females need 4.5 mg less of warfarin per week (5). Sex is an important factor in prognosis of warfarin dose (7).

In terms of correlation between BMI and total warfarin dose, and with controlling all other parameters, it was demonstrated that there is positive correlation. Other investigations showed weak association between BMI and warfarin dose (4). Height has more prognostic value of total warfarin dose than does body weight or BMI(8). BMI affects total warfarin dose equally to sex (2). There is a correlation between BMI and the total weekly warfarin maintenance dose. This may have dosing consequences for both patients and physicians, as patients with a high BMI will be predicted to need more doses of warfarin to attain a therapeutic INR.
There have been multiple studies of the affect of tobacco (9) and aspirin use (10) on warfarin metabolism and INR. Sconce et al (8) proposed that genetics, specifically CYP 2C9 and VKORC1 genetic polymorphisms, may cause up to 55% of total warfare dose differences.The formula we used in our investigation was used in other previous studies(11). They demonstrated that for each 1-point increase in BMI, the weekly warfarin dose increased by 0.69 mg and that the mean warfarin weekly dose in this group can be calculated using the formula: $12.34 + 0.69 \times$ BMI.
Our study has limitations. It included small number of patients and other patient related factors were not quantified to assess significance. The study included only patients with antiphospholipid syndrome. Our investigation was performed only in Jordanian subjects of Middle East of Asia.Afro-caribbeans need more warfarin than Asians.The cause for this discrepancy in warfarin requirement includes genetic and cultural (diet) differences. Asians are more likely to be vegetarian with high vitamin K intake. Whites need intermediate doses and blacks need increased doses.

We assume that factors having the most effect on total warfarin dose to include age,sex and BMI. Positive correlations between total warfarin dose and the following factors exist: younger age, female patients and high BMI. Our assumption can help reduce results of supratherapetuic INRs while enhancing the attaining of therapeutic levels. This can lead to reduced duration of simultaneous injectable anticoagulant administration and decreased hospital stay which may finally reduce healthcare costs.

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