The Success of Self-Testing for Anticoagulation Therapy

Antikoagulasyon Tedavisinde Kişisel Ölçüm Cihazlarının Başarısı

INR Ölçümünde Kişisel Ölçüm Cihazları / Self Testing Devices for INR Measurement

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Özet

Amaç: Varfarin tedavisinin optimum olabilmesi için gerekli olan terapötik INR (International normalized ratio) aralığı oldukça dardır. Sık kontrol gerektiren doz ayarının yapılabilmesi için çok çeşitli yöntemler mevcuttur. Bu çalışmanın amacı; kişisel ölçüm cihazlarının doz ayarlanmasının yapılmasında ne kadar güvenli olduğunun tespit edilmesidir. Gereç ve Yöntem: Herhangi bir sebeple varfarin tedavisi alan 46 hasta çalışmaya dahil edildi. Hastaların yaşları 24-84 aralığında değişmekte idi. 26 hasta erkek, 20 hasta ise kadındı. Hastalar laboratuvar INR sonuçlarına göre 3 gruba ayrıldılar. Grup 1: INR değeri 2,0'ın altında olan, grup 2: INR değeri 2,0–3,5 , grup 3: INR değeri 3,5 ve üzerinde olan hastalardan oluşturuldu. Her üç grupta sırasıyla 15, 16, 15 hasta vardı. Hastalara parmak ucu kanından kişisel ölçüm cihazı ile INR kontrolü yapıldı. INR sonuçlarının etkileneceği etmenler göz önünde bulundurularak, üç grupta ortalama yaş, cinsiyet, hematokrit değeri, trombosit sayısı, kullanılan ilaçlar açısından istatistiksel anlamlı bir farklılık yoktu. Bulgular: Birinci grubun laboratuvar ölçümlerinde INR ortalaması 1.26 iken kişisel ölçüm cihazında ölçülen ortalama INR değeri 1.45 olarak tespit edildi ve her iki grup arasında istatistiksel anlamlı bir fark bulunamadı (p=0.15). İkinci grubun laboratuvar ölçümlerinde tespit edilen INR ortalama INR değeri 2.74 iken cihazda tespit edilen ortalama INR değeri 3.51 olarak tespit edildi (p=0.01). Üçüncü grubun laboratuvar cihazıyla tespit edilen ortalama INR değeri 4.27 iken cihazda tespit edilen ortalama değer 5.25 olarak tespit edildi (p=0.01). Tartışma: Varfarin tedavisinin sebep olacağı hemorajik ve tromboembolik komplikasyonların önlenmesi açısından, INR doz ayarlanmasının düzenli aralıklarla, uzman kişiler tarafından ve hastanelerde yapılmasının uygun olacağını savunuyoruz.

Anahtar Kelimeler

Uluslararası Normalleştirilmiş Oran; Antikoagülanlar; Varfarin

Abstract

Aim: The optimal therapeutic range for INR of the patient who were on warfarin therapy is narrow. There are various methods of INR monitoring to adjust the appropriate dosage of warfarin therapy. This study aims to test the reliability of POC (Point of care) devices used for INR(International normalized ratio) monitoring. Material and Method: Forty six patients who were on warfarin therapy for any reasons were enrolled for this study. Their INR were divided into 3 groups according to their laboratory INR results. Grup 1 had INR results lower than 2, group 2 had INR levels of 2 to 3.5, group 3 had INR levels of higher than 3.5 INR of the patients were remeasured with the POC device. Results: The ages of the patients were between 24 to 84. Twenty six patients were male and 20 were female. The mean INR level of laboratory measurements was 1.26 in group 1 whereas it was 1.45 for POC device measurements. There were not statistically significant difference between two devices for group 1 (p=0.15). In group 2 the mean INR levels were measured by laboratory instrument and POC device were 2.74 and 3.51 respectively (p=0,01). In group 3 mean INR levels were measured by laboratory instrument and POC device were 4.27 and 5.25 respectively (p=0.01). Discussion: We suppose it is rational to adjust warfarin dosage by specialists using laboratory results in order to prevent hemorrhagic and thromboembolic complications.

Keywords

International Normalized Ratio; Anticoagulants; Warfarin

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Introduction

Safe and impressive warfarin therapy is essential in long term care where atrial fibrillation, venous thromboembolism, mechanic valve prosthesis and other disorders requiring anticoagulation are endemic. Warfarin therapeutics have preventable adverse results such as bleeding from over anticoagulation and thrombotic issues resulting from insufficient treatment [1]. Routine monitoring of the prothrombin time is fundamental to minimize the risk of both bleeding and thromboembolic events. The proper warfarin dosing is adjustment based on monitoring of the International Normalized Ratio (INR) [2].

A recent trend in long-term anticoagulation treatment is the development of patient self-testing programs, in which patients are supplied with their own portable instruments so that frequent measurements can be procured easily at home [3]. Point-of-care (POC) anticoagulation tests have potential for increasing use of warfarin therapeutics in long-term care in some respects. Most importantly, they provide quick results. Despite these evident advantages, the accuracy of POC devices in long term care cannot be assumed. The success of self-testing depends on accuracy and reliability of POC systems.

Our goal is to analyze the accuracy of POC instruments by comparing the different INR results generating from whole blood with results created by a central laboratory instrument using citrated plasma.

Material and Method

Patient Sample

The study was conducted at the Turkiye Yuksek Ihtisas Research and Education Hospital in Ankara, Turkey. Forty-six consecutive patients on warfarin therapy for long-term anticoagulation of venous thromboembolism or mechanical prosthetic valves were included in this study. Written consents were obtained from all patients. The research protocol was approved by the educational committee of the Turkiye Yuksek Ihtisas Hospital. Patients with high hematocrit levels (55% or more), low hematocrit levels (30% or less), liver disease, congestive heart failure or other diseases effecting the action of oral anticoagulants and INR values were excluded.

INR Monitoring Devices

We used the INR Ratio 2 (HemoSense Inc, Alere Diagnostic USA) device as the portable measurement instrument. The INR Ratio 2 system uses a modified version of the one-stage PT test. After a drop of blood is applied to the test strip, it is drawn into the test area and mixed with reagents that initiate coagulation. When the blood clots, changes in impedance in the sample are detected by the meter. The meter calculates the PT and INR resulting from this impedance change and reports them on the display. Each test strip contains two channels. Reagent channel includes recombinant thromboplastin and buffer, control channels include human plasma extracted coagulation factors and buffers to yield predetermined clotting times for a low and high control. INR Ratio devices international sensitivity index (ISI) was 1.

INR results were generated from citrated plasma with a central laboratory instrument, the Sysmex Ca-7000 system which international sensitvity index was 0.96 was accepted as a gold standart device.

Study Plan

INR level of patients who were on warfarin therapy were measured using the Sysmex Ca-7000 system. All vein punctures were performed within 15-30 min. before the corresponding self-monitoring with a handheld device. Patients were separated into three groups according to their first INR levels. INR levels of all the patients were remeasured using INR Ratio 2 portable device to compare the two results. The same person held the second measurement using the portable device.

Group 1: INR level was lower than 2.0
Group 2: INR level was between 2.0-3.5
Group 3: INR level was higher than 3.5

There were 15 patients in group 1, 16 patients in group 2 and 15 patients in group 3. Although some patients were on beta blocker, digoxine, diuretics, acetylsalicylic acid that may affect INR measurement, there were not statistically significant differences between the groups in terms of drug usage.

POC device measurements were carried out by the same person, 15-30 minutes after the laboratory measurements. Test stripes were stored in the room temperature and the alcohol was totally removed the from fingers of the patients to have standartized and safe measurements. QC1 (Quality control) and QC2 values indicating the reliability of the measurements were between the acceptable ranges for all the tests held by the POC device.

Statistical Analyses

Statistical analysis was performed by using SPSS 16.0 statistical package program. P values less than 0.05 was considered statistically significant. After the examination of normallity and homogenity of variance assumptions, as a parametric test Independent Samples T Test was performed for group 1 and group 3, as a non-parametric test Mann-Whitney U Test was performed for group 2. Also, Pearson Correlation Coefficient was used for studying the relation between the samples. Continuous variables were expressed as mean ± standard deviation in parametric tests, as median in non-parametric test. . There were not differences between mean and median values for group 2 , we used mean values in our results for group 2. ANOVA test was used for comparison between three groups of age, hematocrit levels and thrombocyte counts. We used chi square test for categorical variables(sex,drug usage etc.)

Results

Forty-six patients, whose ages were between 24-84, were examined in this study. These patients were seperated into three groups according to their INR levels measured by the laboratory instrument. Mean age of the patients was 53.6 ± 15.8 in group 1, 53.1 ± 10.3 in group 2 and 51.3 ± 10.3 in group 3 ($p>0.05$). Twenty six were male and twenty were female. There were not statistical differences between the three groups in terms of gender and mean age (table 1).

Mean hematocrit levels were 41.2 ± 7.1 for group 1, 42.6 ± 5.1 for group 2 and 40.6 ± 5.4 for group 3. Trombocyte counts were 253000 for group 1, 225000 for group 2 and 274000 for group 3. There were not statistically significant differences among

Table 1. Baseline characteristics of the groups

	Group 1 Mean ± SD	Group 2 Mean ± SD	Group 3 Mean ± SD	p value
Age	53.6 ± 15.8	53.1 ± 10.3	51.3 ± 10.3	0.87
Thrombocyte count (/ mm3)	253,000	225,000	274,000	0.35
Hematocrit	41.2 ± 7.1	42.6 ± 5.1	40.6 ± 5.4	0.64
	n	n	n	
Sex				
Male	11	8	7	0.27
Female	4	8	8	0.14
Drug use				
Beta blocker	6	3	6	0.34
Digoxin	1	2	4	0.29
ACE inhibitors	3	6	1	0.11
Diuretics	2	5	7	0.13
Acetylsalicylic acid	7	6	1	0.04
Diabetes Mellitus	2	1	4	0.27
Hypertension	6	7	6	0.97
Hyperlipidemia	5	7	3	0.36
Smoking	5	1	1	0.05

ACE: Angiotensin-converting enzyme

groups in terms of hematocrit levels and trombocyte counts (table 1).

The mean INR level of laboratory measurements was 1.26 in group 1 whereas it was 1.45 for POC device measurements. There were not statistically significant differences between two devices for group 1 (p=0.15). In group 2, the mean INR levels were measured by laboratory instrument and POC device were 2.74 and 3.51 respectively (p=0,01). In group 3 mean INR levels were measured by laboratory instrument and POC device were 4.27 and 5.25 respectively (p=0.01) (figure 1). The differences

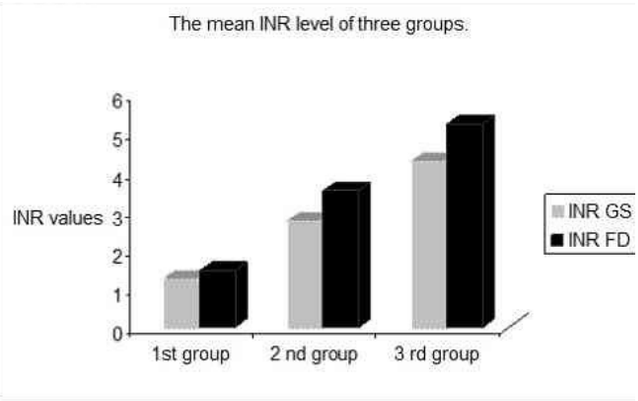

Figure 1. The mean INR level of three groups (INR GS; INR goldstandard, INR FD; INR fordevice).

between group 2 and 3 INR results were statistically significant. As a result of Pearson correlation coefficient (r=0.87) and p value (p=0) there was a strong positive correlation between the two INR measurements. But the difference between the two measurements seems to be increasing with ascending INR levels (figure 2).

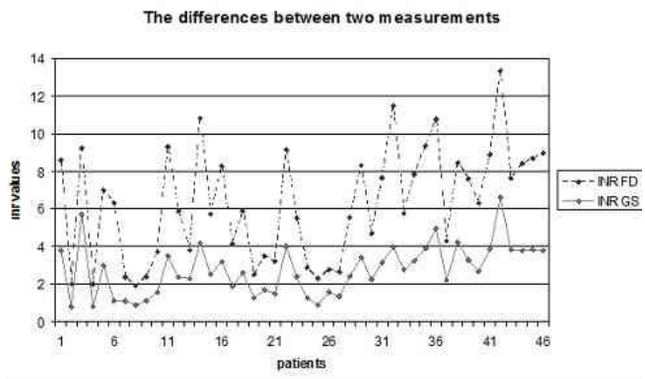

Figure 2. The differences between two measurements. (INR GS; INR goldstandard, INR FD; INR fordevice).

Discussion

Warfarin is a widely used antithrombotic agent for both primary and secondary thromboembolic prophylaxis. The narrow therapeutic range complicates the patient treatment using this drug and requires frequent INR monitoring. The development of point-of-care prothrombine time INR devices has promoted the care and treatment of patients receiving long-term warfarin. Optimal warfarin treatment requires correct measurement of the INR. The choice of a POC device for INR management depends on the reliability of INR data created by the device.

Our study reveals, POC measurements of INR show positive bias as INR values increase, despite overall good correlation with central laboratory instrumentation for the entire range of INR measurements. This observation has potentially profound clinical implications. The reason for this positive bias as INR values, decreases INR dosage and it would be at the potential expense of increased thromboembolic events.

Age, gender, some of the therapeutics and comordities may influence the INR levels. For this reason we paid special attention on group formation and similar distribution according to these factors. Reiss et al.[4], reported that the hemotocrite levels can effect the INR measurements [4]. So we excluded the patients whose hemotocrite levels were lower than 35% or higher than 55% and took care on group formation in order to have a similar hemotocrite level distribution among the groups.

Dorfman et al.[5], compared the INR measurements of the POC devices and the laboratory instruments and concluded that the POC measurements of INR were higher than laboratory instruments measurements. The ISI level of the laboratory instrument was 1.29 while the ISI level of POC device was 2.0 and 1.0 and this was the most important limiting factor of this study was [5]. The ISI values of the POC device and the laboratory instrument in our study is 1.0 and 0.96 respectively so, our false positive results were low. Perry et al.[6], adduced that antyphospholipid antibodies affect INR measurement of POC devices. An important limiting factor of our study is not to evaluate antyphospholipid antibodies of patients [6].

POC devices measure higher INR levels as shown in our study and many other studies [8;9]. We revealed that POC devices measure statistically significant higher levels of INR even in between 2-3.5 range of INR that is theurapeutic for many diseases. It is not rational to use the POC devices for routine INR monitoring because it may cause tromboembolic events result-

ing from lower doses of warfarin therapy according to false high levels of INR.

The ProTime monitor has been shown to correlate well with laboratory testing of INR with correlation coefficients on the order of 86-93% in some studies [7-10] whereas some studies explain the poor INR correlation between various POC systems and laboratory methods [8;9]. Similarly, the results of our study, do not correlate between POC devices and central laboratory results especially INR values greater than 2.0.

Kaatz et al [11], compared INR determinations using two POC monitors and four clinical laboratories against a criterion WHO standart. The authors reported that INR results from two laboratories using sensitive tromboplastine had good correlation with the criterion, whereas INR values determined from less sensitive reagents at the remaining two laboratories had poor correlation. The authors concluded that large interlaboratory variation could occur, indicating the need for cautious interpretation of INR tested with POC againts conventional laboratory methods [11].

As a result, still the best option is adjusting the warfarin therapy regularly by a specialist using standart laboratory instrument results in order to prevent thromboembolic and hemorrhagic complications.

Competing interests

The authors declare that they have no competing interests.

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