Comparison of Point of Care INR Testing to Routine Coagulometric Method

INR Ölçümünde Hastabaşı Test Cihazının Rutin Koagülometrik Yöntemle Karşılaştırılması

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ABSTRACT

Aim: Point Of Care (POC) tests are quick tests that shorten the treatment period and are portable devices, which are easy to use for non-laboratory personnel. In this study we aimed to compare the results of INR (International Normalized Ratio) that were studied with POC testing using fingertip capillary blood and studied with coagulometric method using simultaneous venous blood in patients receiving anticoagulants.

Materials and methods: Two hundred and fifty outpatients (129 women and 121 men) using oral anticoagulant (OAC) drugs or monitoring for INR during preoperative preparation were included in this study. One hundred and three patients were using vitamin K antagonists (VKA) (%41,2). Approximately 10 µl of capillary blood collected from the fingertips of the patients were studied directly on the point of care test device (hemosense-inverness medical®), using electrochemical method. For the coagulometric method, approximately 2 ml blood samples were taken into a vacutainer tube containing sodium citrate. After centrifugation of the samples, tissue thromboplastin (TriniClot PT Excel S) was added, Prothrombin Time (PT) and INR analysis were performed with Coag A-MTX II-Trinity Biotech device. Daily controls of the device were performed before the study and samples were studied after obtaining the results in the expected range.

Results: INR measurements of venous and capillary blood samples of 250 patients were performed concurrently. The results were compared by linear regression analysis and a high correlation was found between the two methods (r=0.878). There were no significant difference between the genders. In the study, there was a good correlation in those with INR values below 2, and a high correlation in those with 2 and above.

Conlusion: The POC method is a promising inexpensive method to meet the needs of clinicians in terms of regulating the treatment of patients requiring immediate outcomes and rapidly assessing the risk of bleeding, when a quality control program is implemented in accordance with the manufacturer's recommendations.

Key words: point-of-care test; INR; oral anticoagulant

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ÖZET

Amaç: Hastabaşı testleri (HBT), tedavi süresini kısaltan, taşınması kolay olan ve laboratuvar dışı personel tarafından da kolayca uygulanabilen hızlı testlerdir. Bu çalışmada, antikoagülan kullanan hastaların parmak ucu kapiller kandan hastabaşı test cihazı (HBTC) ile çalışılan ve eşzamanlı venöz kandan koagülometrik yöntem ile çalışılan INR (Uluslararası Düzeltme Oranı) sonuçlarını karşılaştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya oral antikoagülan (OAK) ilaç kullanan veya preoperatif hazırlık için INR izlemi yapılan 129'u kadın toplam 250 ayaktan hasta dahil edildi. Hastaların 103'ü K vitamini antagonisti (VKA) kullanıyordu (% 41.2). Kan alma bölümünde, venöz kan alınmasının ardından parmak ucundan yaklaşık 10 µl kapiller kan alındı ve laboratuar personeli tarafından HBTC (hemosense-inverness medical®) kullanılarak elektrokimyasal metod ile INR ölçümü yapıldı. Koagülometrik yöntem için yaklaşık 2 ml kan örneği sodyum sitrat içeren bir kan tüpüne alındı. Numunelerin santrifüj edilmesinden sonra, doku tromboplastini (TriniClot PT Excel S) eklendi, PT (Protrombin Zamanı) ve INR analizi Coag A-MTX II-Trinity Biotech cihazı ile yapıldı. Cihazın günlük kontrolleri ölçümlerden önce yapılmış ve kontrol sonuçları beklenen aralıkta olduktan sonra örnekler çalışılmıştır.

Bulgular: Toplamda 250 hastanın venöz ve kılcal kan örneklerinin INR ölçümleri aynı anda yapıldı. Sonuçlar lineer regresyon analizi ile karşılaştırıldı ve iki yöntem arasında yüksek bir ilişki bulundu (r=0.878). Cinsiyetler arasında anlamlı bir fark yoktu. Çalışmada, INR değerleri 2'nin altında olanlarda iyi bir korelasyon, 2 ve üzerinde olanlarda yüksek bir korelasyon görüldü.

Sonuç: HBTC, üretici firmaların tavsiyelerine uygun olarak bir kalite kontrol programının uygulanması şartıyla, acil sonuç gerektiren hastaların tedavisini düzenlemek ve kanama riskini hızlı bir şekilde değerlendirmek isteyen klinisyenler için umut verici ve ucuz bir yöntemdir.

Anahtar kelimeler: hastabaşı test; INR; oral antikoagülan

INTRODUCTION

Atrial fibrillation (AF) or heart valve diseases are common diseases, which cause serious morbidity and mortality with thromboembolism. The incidence of thromboembolic events were significantly reduced with oral anticoagulant prophylaxis (1-4). More than half of thromboembolism cases are associated with atrial fibrillation and heart valve replacement. These events can be prevented and bleeding risk can be lowered, especially when anticoagulation is controlled under treatment with vitamin K antagonists (VKA) warfarin. However, due to insufficient or overdose of VKA, this protective effect cannot be observed at the desired rate (5). VKAs have narrow therapeutic range and prothrombin time measurement is used to adjust drug doses, whereas International Normalized Ratio (INR) is used to standardize the differences between laboratories (5).

Careful monitoring for INR is required to achieve an anticoagulation level, where thromboembolic events are reduced without excessive bleeding. It was recommended to measure INR values at least every 12 weeks (6).

Many diseases, including heart valve diseases and rhythm disorders, increase the risk of thrombosis and use oral anticoagulation reduce the risk of undesirable thrombosis (7). VKA has been used for oral anticoagulation for many years worldwide. VKAs have many advantages; they cost low (8) and they can be used in patients with severe renal insufficiency, as they are not excreted by the kidneys (9). They are used for a long time of period, physicians have more experience with this drug (8). However, the most important disadvantages are unpredictable pharmacokinetics, widespread interaction with drugs and foods, a narrow therapeutic window, and close monitoring for the drug dose (10). INR values lesser than 2 increase the risk of thromboembolism and values higher than 4 increases the risk of major bleeding (5). A major problem in drug dosage adjustment is not monitoring for INR as often as necessary, especially when patients are old, travel a lot or work hard (11).

Non-Vitamin K antagonist oral anticoagulants (NOAC) developed in recent years have improved efficacy / safety ratio. No routine monitoring for drug dose adjustment is needed and they have less food and drug interactions compared with VKAs (12,13). Despite these advantages, NOACs are more expensive than VKAs, and the experience of doctors in critically ill patients is insufficient for these new drugs. Also it is difficult to obtain antidotes. In addition, the guidelines did not approve NOACs in patients with mechanical valves and nonvalvular AF (14-17). Because these and many other reasons, VKAs are indispensable and they are the most widely used anticoagulants all over the world. Searching for a method to facilitate the monitoring for INR was initiated to see the desired efficacy in VKAs. Anticoagulation clinics have been established and INR self-monitoring devices have been developed for patients using VKA, inspired by the self-monitoring for glucose and glycated hemoglobin, which are currently used in diabetes requiring strict monitoring (18). These devices, called POC coagulometers, were originally designed for use by non-healthcare professionals. However, their robustness and accuracy, and their ability to produce rapid results, using capillary blood instead of venous blood, have made these devices preferable in anticoagulation and inpatient clinics and also for emergency surgery preparations (11).

In emergency cases, coagulation tests are prioritized in the routine laboratory, but time is delayed until arrival of sample to the laboratory and centrifugation for obtaining plasma. In such cases, POC coagulometers can be life-saving.

POC measurement of INR and PT levels started in the1970s and significant improvements have been witnessed in this field recently. The INR test has also been used with bedside devices for more than a decade all over the world. Frequency of use of these devices is increasing (19). Unfortunately, the use of these devices has not yet become as widespread in our country as well as in the world.

An increasingly popular option to facilitate more frequent testing of anticoagulation levels is the development of point of care (POC) testing or patient self-test (PST) programs. POC testing enable patients to test their INR at home using a fingertip blood sample. These devices are easy to use and can produce results instantly (19). In particular, rapid response with POC test has led to the preference of these devices, when time is very important such as during emergency surgery preparations in hospitals. Many commercially available POC devices including hemosense-inverness medical® are for healthcare professional use only (19). In line with the increasing demand for these devices, the accuracy of the results of the devices has been the subject of research. We aimed to compare the results of INR tests with POC testing devices and coagulometric methods from capillary blood and concurrent venous blood in a population of 250 patients in this study.

MATERIALS AND METHODS

In the study, 250 patients who admitted to outpatient clinic who used oral anticoagulant (OAC) drugs or who had monitoring for INR during preoperative preparation were included. The study was started after approval from the local ethics committee (2019/323). Patients were informed about concurrent capillary blood and venous blood sampling for INR measurement and informed consent was obtained. Patients under 18 years of age, patients incapable of giving written or verbal consent and pregnant women were excluded from the study. Approximately 10 µl of capillary blood collected from the fingertips of the patients were studied directly on the POC test device (hemosense-inverness medical®) using electrochemical method. For the coagulometric method, approximately 2 ml blood samples were taken into a vacutainer tube containing sodium citrate. After centrifugation of the samples, tissue thromboplastin (TriniClot PT Excel S) was added, Prothrombin Time (PT) and INR analysis were performed with Coag A-MTX II-Trinity Biotech device. Daily controls of the

device were performed before the study and samples were studied after obtaining the results in the expected range. In representative studies using photo-optical instruments and TriniClot PT Excel S, the interassay coefficient of variation (CV) was less than 2.0%. For hemosense-inverness medical CV was less than 6%.

Pearson's correlation coefficient (r) was used to measure the agreement between INR values. The comparison was made between venous INR and hemosense-inverness medical® result, then between venous INR and reference INR, and also between hemosense-inverness medical® result and reference INR. ($p<0.05$ was significant). Bland-Altman 95% limits of agreement were calculated as the mean difference between measurements. R value for correlation was defined as high correlation between 0.7-1 and good correlation between 0.5-0.7. Higher correlation is stronger. For data processing and analysis, NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program was used.

RESULTS

Concurrent venous and capillary blood samples were obtained from 250 patients for INR measurement. 41.2% (n=103) of the patients were admitted to the hospital for INR monitoring and received VKA treatment. According to the linear regression analysis of all patient results, a high correlation was found between the two methods (r=0.878) (Figure 1).

Patients were divided into 2 groups according to the results of the automatic coagulation device used in our hospital. 1st group of INR under 2, 2nd group consisted of INR 2 and above. Bland Altman analysis was performed by comparing each group statistically (Figure 2).

A good correlation was found in INR values below 2 (r=0.6836), and high correlation was obtained in INR 2 and above (r=0.8813).

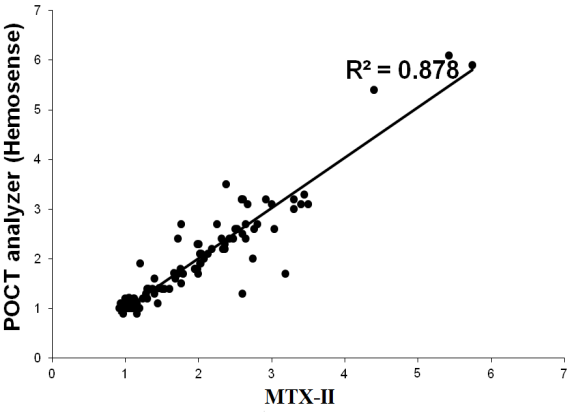

Figure 1. Linear regression of INR between MTX-II and POCT analyzer

Şekil 1. MTX-II ve POCT analizörü arasında INR' nin lineer regresyonu

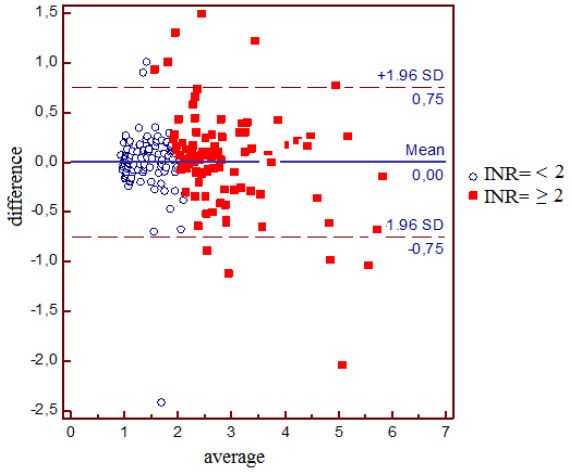

Figure 2. Bland-Altman analysis results according to INR values

Şekil 2. Bland-Altman analiz sonuçlarına göre INR değerleri

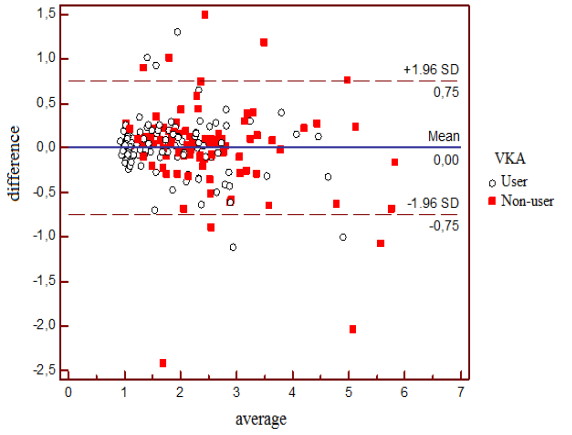

Figure 3. Bland-Altman analysis of VKA users and non-VKA users

Şekil 3. VKA kullanıcısı olan ve olmayanların Bland-Altman analizi

Bland Altman analysis of INR results of VKA user patients and not users is shown in 3rd Figure. Very high correlation was observed in non-VKA users with correlation cofficients ratio was 0.941, whereas high correlation was observed in VKA users with correlation cofficients ratio was 0.896.

DISCUSSION

Many studies have been reported the reliability of POC test devices in various patient groups and the results have been compared with fully automatic coagulation devices, a good fit has been achieved (20). In our study, a good correlation was found in INR values lower than 2 and a high correlation was obtained in values higher than 2. Our results support previous studies (21,22,23). In our study, the patient group was selected from the patients hospitalized for operation with cardiovascular problems or who received VKA treatment and admitted to our hospital for monitoring INR.

Both methods were correlated with each other only when VKA was used or when patients at the target INR level or non-target INR level were evaluated among themselves. The target INR varies according to VKA indication, it is between 2-3 in some diseases and 2.5-3.5 in others. For these groups, quick tests can be used safely because they give accurate results. However, it is certain that quick tests can not replace coagulation devices in clinical laboratories working with reference methods (12).

The POC method is a promising inexpensive method, which provides clinicians regulation for treatment of patients requiring immediate outcomes and rapidly assess risk of bleeding. In addition, it is very easy to measure INR with these devices at home for elderly patients, non-mobile patients and home care patients who are incapable of visiting healthcare facilities. (5,8,24-26).

Patients using VKA may become reluctant to give venous blood samples for monitoring, which can last many years. This situation reduces the effectiveness of anticoagulant therapy and may cause undesirable consequences such as bleeding or thromboembolism.

POC devices reduces the boredom of patients and help patients to self-monitor their treatment with high motivation using capillary blood (19,27). In many studies on patients using VKA, the success of adjusting the drug dose by monitoring for INR with POC test device without any special training was satisfactory and the quality of treatment was further improved by self-monitoring. (21-23,28-29) Patients who monitor for their INR levels and maintain their own treatment, have fewer thromboembolic events and lower mortality. This indicate that managing their own treatment positively affect patient motivation (30-32).

POC tests are more expensive than laboratory tests, but these tests are still cost effective, when turnaround time and labor saving are considered. (33). Current guidelines from the United Kingdom's National Institute of Health and Care Excellence (NICE) support self-monitoring for anticoagulation of patients with atrial fibrillation or heart valve disease with POC devices after appropriate training (34). However, self-monitoring or self-management is not recommended by NICE for patients with venous thromboembolism (35).

Although POC test devices are increasingly used all over the world, clinical laboratory analysers are used mainly in the diagnosis of diseases (36-38). We do not expect POC INR testing to replace routine lab measurements but it can be used as a reliable method in selected patients (patients who need close INR monitoring, patients away from the health center, non-mobile patients etc.). And this may provide convenience for patients who have to use VKA. It seems to be an effective method of preventing possible complications caused by insufficient dose use or overdose use. Efficient use of POC test devices depends on standardization, validation and comparison studies to ensure

accurate results. The decrease in prices of these devices and INR measuring strips, and their reimbursement by health insurances will lower the expenses and increase the use of POC test devices. Improvement in analytical sensitivity of these devices will also increase their use and reduce costs.

Testing, maintenance, quality controls and stock processes in hospitals are under control of users, whereas clinical laboratories are primary responsible for training and comparison studies. Calibrations with strips according to manufacturer instructions are important but not sufficient. A quality control program should be implemented in accordance with the manufacturer's recommendations. All health professionals inside and outside laboratories should work in cooperation with each other for accurate results.

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