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Research Article

Assessment of the Accuracy of Blood Uric Acid Measurements Made by an Electrochemical Biosensor

Yih-Shiou Hwang[1,2,3*], Szu-Tah Chen[1,2], Yao-Fan Fang[1,2], Shu-Fu Lin[1,2,4], Wei-Chi Wu[1,2], Chi-Chun Lai[2,5], Eugene Yu-Chuan Kang[1,2]

[1]Department of Opthalmology, Chang Gung Memorial Hospital, Linkou branch, Taoyuan City, Taiwan;[2]Department of Opthalmology, Chang Gung University, Taoyuan City, Taiwan;[3]Department of Opthalmology, Chang Gung Memorial Hospital, Xiamen branch, Xiamen, China;[4]Department of Opthalmology, Chang Gung Memorial Hospital, Tucheng branch, New Taipei City, Taiwan;[5]Department of Opthalmology, Chang Gung Memorial Hospital, Keelung branch, Keelung, Taiwan

ABSTRACT

Uric acid (UA) measurements are important for individuals with a wide range of conditions, including gout, pregnancy, diabetes, and cardiomyopathy. Many patients therefore use portable electrochemical biosensors to perform self-monitoring and maintenance of their UA concentration levels, while such biosensors are also used in various clinical settings. However, performance evaluations of the accuracy of such devices for UA measurement are lacking.

Using self-imposed accuracy criteria and testing blood samples from 100 subjects, the present study compared the accuracy of a commercially available UA measurement biosensor chemically modified to reduce interference, namely, the BX-M000 device (General Life Biotechnology, Taiwan), with those of the Sysmex XE-5000 automatic whole blood analyzer and the Hitachi LABOSPECT 008 chemistry analyzer.

The BX-M000 UA biosensor yielded ≥ 95% of measurements within ± 0.75 mg/dl at UA concentrations <5 mg/dl and ≥ 95% of measurements within ± 15% at UA concentrations ≥ 5 mg/dl, successfully exceeding the accuracy requirements. Furthermore, hematocrit sensitivity results showed that there was no significant interference from a variety of common medications at their high therapeutic levels.

The BX-M000 UA monitoring device exhibits sufficient accuracy for the screening and monitoring of blood UA concentration levels for both self-monitoring and clinical contexts.

Keywords: Accuracy assessment; Electrochemical biosensor; Hematocrit sensitivity; Uric acid biosensor; Uric acid measurement

ABBREVIATIONS

CI: Confidence Interval; OR: Odds Ratio; TB: Tuberculosis; WHO: World Health Organization; SNNP: South Nations Nationalities and Peoples

INTRODUCTION

Uric acid (UA) measurements are important for individuals with a wide range of conditions, including gout, pregnancy, diabetes, and cardiomyopathy, among others [1-5]. For example, gout results from blood UA concentrations above 390 μmol/L (6.5 mg/dL) and is associated with a variety of other metabolic syndromes [6]. Many patients therefore use portable electrochemical biosensors to perform self-monitoring and maintenance of their UA concentration levels, which can be controlled both by drugs, such as allopurinol and rasburicase, and dietary measures, while such devices are also used in a variety of clinical settings [7,8].

At the same time, many patients for whom UA measurements are of value can also benefit from measurements of other health indicators, such as total cholesterol and blood glucose levels. For example, various studies have shown the benefits of careful blood glucose control for diabetes patients, including improved HbA1c values and reduced rates of related complications [9,10]. Therefore, a number of multi-function UA monitoring devices that can be used to simultaneously monitor UA and other health indicators, such as blood glucose and total cholesterol levels, have been

Correspondence to: Hwang YS, Department of Opthalmology, Chang Gung Memorial Hospital, Linkou branch, Taoyuan City, Taiwan, Tel: 886221945179; E-mail: sub183280@gmail.com

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introduced [11,12]. By providing UA and other health indicator measurements, these multi-function UA devices can ease the self-testing and self-management of patients with various conditions and comorbidities; however, the accuracy of the UA measurements that they provide remains a cause for concern due to a lack of comprehensive testing thus far.

Relatedly, a non-enzymatic method of UA detection made possible by the use of chemically modified electrodes provides a number of advantages over older spectrophotometric methods (including, for example, no costs associated with the purchase and storage of enzymes), and is thus the method utilized by the majority of portable UA biosensors currently available on the market [12,13]. However, biosensors using non-enzymatic technology for UA detection have commonly encountered the problem of interference from a variety of common medications (e.g., acetaminophen) and biological substances (e.g., ascorbic acid), due to UA having similar chemical characteristics as those other substances [14]. As such, the possibility of such interference poses another potential issue for the accuracy of multi-function UA devices that must be further investigated [15].

In the present study, therefore, we compared the UA measurement accuracy of a multi-function UA devices, the BX-M000 (General Life Biotechnology, Taiwan), with the measurement accuracy of the Sysmex XE-5000 automatic whole blood analyzer and the Hitachi LABOSPECT 008 chemistry analyzer in order ascertain whether the multi-function UA device provides sufficient UA measurement accuracy for home and clinical healthcare contexts.

MATERIALS AND METHODS

This study was conducted at Linkou Chang Gung Memorial Hospital in Taoyuan, Taiwan, from April 1, 2018, through December 31, 2019. The hospital's institutional review board approved of the study protocol, and written informed consent was obtained from all of the study participants.

Study participants

The study participants were chosen due to pre-existing metabolic syndromes such as diabetes, dyslipidemia, high uric acid levels, high blood pressure, obesity, abnormalities with coagulation factors, and more. The primary reasons for exclusion were: (1) being under 20 years of age, (2) mental instability or unconsciousness, (3) incapacitation, (4) pregnancy, and (5) being at-risk of certain conditions or otherwise in need of extra protection. If at any point during the study, the selected participants felt any discomfort, they were able to immediately suspend their participation and seek the necessary assistance from the hospital staff. Furthermore, if a subject's test results were found to be abnormal at any time, the subject was then referred to the hospital's metabolism department for follow-up diagnosis and treatment. The study utilized blood samples drawn from capillaries in the fingertips and veins in the antecubital area of the arm. Samples from a total of 150 participants were collected for use in the study, although data from only 100 of those participants was ultimately used for the accuracy comparisons.

Monitoring systems

This study was designed to test the accuracy of the BX-M000 device when measuring uric acid (UA) concentration levels in the blood, hematocrit values, and the effects of potential interference caused by different substances. The BX-M000 UA measuring system consists of BK-SU1 Uric Acid Test Strips and displays results for UA concentration in mg/dL.

Reference measurements

The results of the BX-M000 were referenced against results provided by the Hitachi LABOSPECT 008 chemistry analyzer.

Testing procedure and protocol

The UA measurement accuracy of the BX-M000 system was tested through the use of three different test strip lots. A total of 150 participants were enrolled in the study in order to provide a sufficient number of blood samples for each test strip lot, though data from only 100 of the participants was ultimately used for the accuracy comparisons.

The measurement procedure steps for each participant were as follows: First, a sample of capillary blood was taken from the participant's fingertip. Next, that sample was subjected to measurement by the BX-M000 UA monitoring system (using two test strips from the first test strip lot). Second, duplicate UA measurements were also made with two test strips from each of the other two BX-M000 system test strip lots. Next, each participant had their blood withdrawn and used in determining the hematocrit sensitivity of the BX-M000 system UA measurements.

The UA concentrations of the blood samples were distributed as follows: 30% of the samples had UA concentrations between 3.0 and 5.0 mg/dl, 40% of the samples had UA concentrations ≥ 5.1 and up to 7.0 mg/dl, 15% of the samples had UA concentrations ≥ 7.1 and up to 9.0 mg/dl, 10% of the samples had UA concentrations ≥ 9.1 and up to 11.0 mg/dl, and 5% of the samples had UA concentrations ≥ 11.1 mg/dl. Samples with UA concentrations ≥ 9.1 mg/dl were obtained through UA supplementation with urate.

Statistical analysis

Our self-imposed accuracy requirements stated that 95% of the measurement values per test strip lot should either fall within ± 0.75 mg/dl at UA concentrations <5 mg/dl or within ± 15% at UA concentrations ≥ 5 mg/dl. For the data analysis, differences were then calculated between each of the 200 UA measurement results for each test strip lot. A difference plot was then generated to visualize the accuracy results, shown in Figure 1.

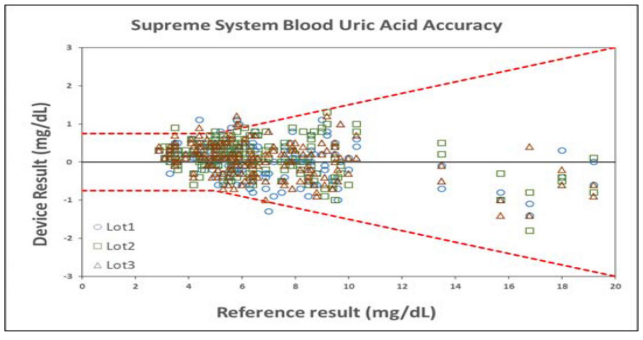

Figure 1: Difference plot for the investigated BX-M000 uric acid monitoring system. The dotted lines indicate the system accuracy limits, and the results for the three investigated test strip lots are displayed in different colors and icons.

The method proposed by Bland and Altman was used to determine

the relative bias of the UA measurement results for each test strip lot [16]. The hematocrit sensitivity of the BX-M000 system was then shown by illustrating the relative bias, in terms of hematocrit, of the measurement results for each lot, shown in Figure 2.

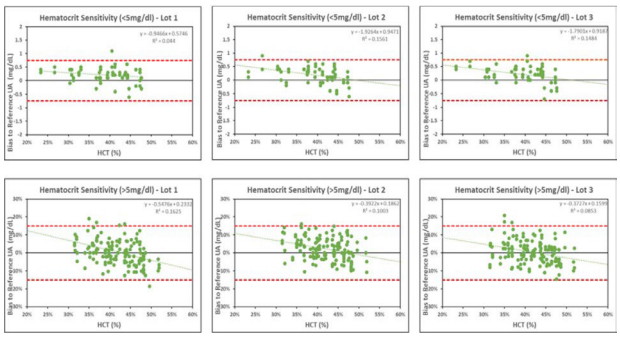

Figure 2: Bias to reference method at different hematocrit levels for the BX-M000 uric acid measurement results. The dotted lines indicate the system accuracy limits.

RESULTS

The accuracy of the BX-M000 system UA measurements was evaluated by assessing the biosensor's UA measurements according to the aforementioned accuracy requirements. Table 1 shows the UA accuracy results and measurement bias for the BX-M000 system. The system provided 98.3% of measurements at UA concentrations <5 mg/dl and 97.6% of measurements within ± 15% at UA concentrations ≥ 5 mg/dl, successfully exceeding the accuracy requirements.

For data analysis, differences were calculated between each of the 200 UA measurement results per test strip lot and the corresponding comparison device measurement results, and the associated accuracy results are visualized in the difference plot shown in Figure 1. In the figure, the dotted lines indicate the system accuracy limits, and the three investigated test strip lots are displayed in different colors and icons.

Meanwhile, Figure 2 shows the relative bias of the BX-M000 system UA measurement results in terms of hematocrit in order to illustrate the hematocrit sensitivity of the system, while Table 2 lists the hematocrit sensitivity results for the system for the three different reagent lots in simple numerical terms. In light of the fact that the UA measurement accuracy of a biosensor can be impacted by abnormal hematocrit levels, it was critical to determine the extent to which any variations in hematocrit variations affected the UA measurements of the BX-M000 system [17]. Taken together, the results showed that the hematocrit interference levels for the system were low enough that the accuracy of the system's UA measurements would not be adversely affected in a meaningful way.

Table 1: Characteristics of 10 included studies to estimate the pooled prevalence of tuberculosis and its association with cigarette smoking in Ethiopia.

	System accuracy				
System	Uric acid concentration	Within ± 0.75 mg/dl or ± 15%	Within ± 0.5 mg/dl or ± 10%	Within ± 0.25 mg/dl or ± 5%	Bias
BX-M000	<5 mg/dl	98.3% (177/180)	90.6% (163/180)	43.9% (79/180)	0.20 mg/dl
	≥ 5 mg/dl	97.6% (410/420)	86.4% (363/420)	52.4% (220/420)	0.88%
	Combined	97.8% (587/600)	87.7% (526/600)	49.8% (299/600)	

Table 2: Meta regression to identify source of heterogeneity for the prevalence of tuberculosis in Ethiopia.

		Differences between average bias of measurements with HCT <40% & HCT ≥ 40%		
System	Uric acid concentration	Lot 1	Lot 2	Lot 3
BX-M000	<5 mg/dl	0.03 mg/dl	0.26 mg/dl	0.16 mg/dl
	≥ 5 mg/dl	3.05%	1.50%	2.00%

DISCUSSION

The self-testing and self-management of patients with various conditions and comorbidities can be aided considerably by multi-function UA monitoring devices that can be used to simultaneously monitor UA levels and other health indicators, such as blood glucose and total cholesterol levels [11,12]. More specifically, the use of such monitors allows patients with a range of different conditions to self-monitor and maintain their UA concentration levels, which can be controlled both by drugs, such as allopurinol and rasburicase, and dietary measures [7,8]. However, in order for such efforts aimed at the self-management of UA levels to be effective, the biosensors that patients use to make UA measurement musts be sufficiently accurate and reliable. At the same time, biosensors using non-enzymatic technology for UA detection, the approach used by the majority of portable UA biosensors currently available on the market, have commonly encountered the problem of interference from a variety of common medications (e.g., acetaminophen) and biological substances (e.g., ascorbic acid), due to UA having similar chemical characteristics as those other substances [12-14]. As such, it is important to test the biosensors used by patients for the self-monitoring of UA levels in order to confirm that such interference is not too strongly affecting the accuracy of the UA measurements made by those sensors [15].

The present study was thus conducted in order to test the UA measurement accuracy and interference levels of one such sensor, the multi-function BX-M000 device. The results indicated that the UA measurements of the system met the accuracy requirements of ▯95% of measurements within ± 0.75 mg/dl at UA concentrations <5 mg/dl and ▯95% of measurements within ± 15% at UA concentrations ≥ 5 mg/dl. Furthermore, the hematocrit sensitivity results showed that there was no significant interference from a

variety of common medications at their high therapeutic levels.

In summary, then, the findings of the present study indicate that the investigated multi-function BX-M000 system is sufficiently accurate in terms of its UA measurements, while also providing valuable blood glucose and total cholesterol measurements. As such, the sensor can serve as a reliable and valuable tool for patients seeking to self-monitor their UA, blood glucose, and total cholesterol levels through the use of drugs or dietary measures.

CONCLUSION

In Ethiopia, around one fifth of individuals were infected with tuberculosis. Individuals who smoke cigarette were more exposed to TB infection than non smokers in Ethiopia. Therefore, the government and health institutions should focus on awareness creation about risk of cigarette smoking to reduce TB infection.

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