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Original Article
Effects of Analytical Goals on Evaluating Performance of HbA1c Measuring Method

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ABSTRACT

HbA1c measuring plays a critical role in the monitoring and diagnosis of diabetes. So, analytical performance of its measuring method must be acceptable. It is the responsibility of clinical laboratories to continuously monitor the performance of commercial methods in use, both by the implementation of a proper internal quality control (IQC) and participation in appropriately organized external quality assessment schemes (EQAS). Efficieny of both of IQC and EQA is strongly affected by selected analytical goals.During eighteenth and nineteenth runs of external quality assessment program (EQAP), in Jully 2014 and November 2014, two freshly prepared commutable patient QC samples were sended to 650 and 858 laboratories which used five common HbA1c kits. Target values for total group and also for peergroups were calculated. Performance of each laboratory was determined according to two different allowable total errors (TEa), including ±6% and ±20%, which are suggested by National Glycohemoglobin Standardization Program (NGSP) and Reference Health Laboratory of Iran, respectively. when we used TEa of ±20% for evaluating HbA1c method performance, about 11% and 9% of participant laboratories had unacceptable performance during EQAP-18 and EQAP-19. respectively. But when this evalution was performed according to TEa of ±6%, unacceptable results increased significantly to 50%and 55%, respectively. Using improper analytical goals leads to misinterpretation of IQC and EQA results. Analytical goals must be defined in a such way that the test could save its clinical usefulness. In order to maintain clinical usfulness of HbA1c results we need to reduce TEa of ±20% to ±6% and improve HbA1c measuring method performance.

1. Introduction

HbA1c test plays a critical role in the monitoring and diagnosis of diabetes[1].So, it is essential that its clinical use be supported by standardized results, i.e., accurate and equivalent among different commercial methods and clinical laboratories using them. The diagnostic manufacturers should implement analytical systems that produce results traceable to the higher-order references and able to fulfil the analytical goals of measurement uncertainity, established on the basis of clinical application of test. Finally, it is the responsibilty of clinical laboratories to continuously monitor the performance of commercial methods in use, both by the implementation of a proper internal quality control (IQC) and participation in appropriately organized external quality accessment schemes (EQAS)[2].

In order to siginificanly reduce differences among results obtained by various commercial methods, it is necessary to standardize methods of HbA1c measurement. This has been achieved by International Federation of Clinical Chemistry (IFCC)and National Glycohemoglobin Standardization Program (NGSP)[3].Although, there are differences from metrological point of view between IFCC and NGSP measurement systems, by using IFCC-NGSP master equation [NGSP(%)=0.09148*IFCC (mmol/mol)+2.152] we can convert results of these systems to each other[3, 4].The American Diabetes Association (ADA) recommends that laboratories use only HbA1c methods that have been NGSP certified and report results as "%HbA1c" or "%HbA1c equivalents"[5, 6]. The ADA also recommends that all laboratories performing HbA1c testing participate in the CAP fresh sample proficiency testing survey[5].

Using NGSP certified methods is not the only step in reaching to precise and accurate analytical measuring HbA1c method. It needs coninuously monitoring the performance of the method. In this regard, defining analytical goals with which method performance must be evaluated, has profound effects on detection of anlytical errors. In this study we evaluate the effects of to different analytical goals, defined as total allowable error (TEa), on interpretation of

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EQAS HbA1c results. TEa encompasses the imprecision and bias of a single test measurement and is used to evaluate laboratory tests performance in EQAS[7].

2. MATERIAL AND METHODS

During eighteenth and nineteenth runs of external quality assessment program (EQAP), in Jully 2014 and November 2014, two freshly prepared commutable patient QC samples in EDTA-containing vials were sended to 731 and 1011 participant laboratories, respectively. These kits included Pars Azmon, Pishtaz Teb, Biosystem, Roche, and NycoCard. Before sending to participant laboratories, homogeneity of control material vials was assessed and confirmed. After sending. stability of these control material were assessed and confirmed. These assessments and confirmation were done according to WHO requirements[8].

There is more than ten HbA1c kits in Iran. But in this study we focused on common kits for which the number of using laboratories was at least ten, so their statistical analysis could be valid. These included Biosystem, Nycocard, Pars Azmon. Pishtaz Teb, and Roche kits which their assay priniples were immunoturbidimetry, enzymatic, cation-exchange chromatography, immunoturbidimetry, and boronate-affinty chromatography, respectively.

Each participant laboratory should examined sended control material as a routine patient sample according to instructions of measuring kit provider and should calibrated and controlled its measuring method by calibrator and control material, as internal quality control, provided by kit producer.

After measuring HbA1c, results were sended to EQAP and statistical analyses were done. According to used kit, results were grouped in five peer groups. Then mean, standard deviation (SD), and coefficient variation (CV) of each peer group and also total results were calculated. In EQA, mean of each peer group is used as target value to evaluate each laboratory perfomance. For this, it is neccessary to delet outliers which are out of Mean ± 2SD or 3SD[9]. In EQAP, we used Mean ± 2.5SD. After deleting outliers, calculation of mean and SD was repeated until there was no outliers. The last calculated mean, termed as weighted mean, was used as target value. Statistical analysis were done by SPSS 20 software.

Target values for total group and also for peergroups were calculated. In Iran, laboratory performance is evaluated according to standard deviation interval (SDI). SDI is calculated by following formula[6, 10]:

$$SDI = \frac{\text{Laboratory result} - \text{Peer group target value}}{\text{Peer group SD}} \times 100$$

In this formula, we use adjusted SD which is calculated following formula:

$$\text{Adjusted SD} = \frac{CCV\% \times \text{Peer group target value}}{100}$$

In which, CCV (Chosen Coefficient Variation) is defined by Reference Health Laboratory of Iran and equals 10% for HbA1c mehods. SDI ≤ 2 is considered as acceptable result. This CCV and acceptability criteria represent TEa of 20%; i.e. SDI = 2 shows that result is 2 SD far from mean target value and SD equals 10% of mean target value, so TEa = 2 SD = 2 * 10% = 20%.

In this study, we compared unacceptable results during EQAP-18 and EQAP-19 with TEa of ±20% and also TEa of ±6% suggested by NGSP and CAP[5].

3. RESULTS

In eighteen run of EQAP (EQAP-18), 650 participated laboratories used desired kits, grouped in five peer group, including Pars Azmon, Pishtaz Teb, Biosystem, Roche, and NycoCard, with 98, 104, 245, 17, and 186 participated laboratories, respectively. Table 1 shows target value, SD, and CV% each peer group and also total.

In nineteen run of EQAP (EQAP-19), 858 participated laboratories used desired kits, grouped in five peer group, including Pars Azmon, Pishtaz Teb, Biosystem, Roche, and NycoCard, with 130, 150, 291, 19, and 268 participated laboratories, respectively. Table 2 shows target value, SD, and CV% each peer group and also total.

As shown in tables 3 and 4, when SDI was used to evaluate HbA1c method performance, about 11% and 9% of participant laboratories had unacceptable performance during EQAP-18 and EQAP-19. respectively. But when this evalution was performed according to TEa of ±6%, unacceptable results increased significantly to 50% and 55%, respectively.

Table 1. Weighted mean (target value), standard deviation (SD), coefficient variation (CV) of HbA1c measurement kits in EQAP-18

Kits	No.	Mean	SD	CV(%)
Pars Azmon	98	7.18	0.66	9.2%
Pishtaz Teb	104	7.32	0.40	5.5%
Biosystem	245	7.76	0.92	11.9%
Roche	17	7.83	0.36	5.0%
NycoCard	186	7.22	0.60	8.3%
Total	650	7.45	0.77	10.33%

Table 2. Weighted mean (target value), standard deviation (SD), coefficient variation (CV) of HbA1c measurement kits in EQAP-19

Kits	No.	Mean	SD	CV (%)
Pars Azmon	130	7.58	0,67	8.8%
Pishtaz Teb	150	7.86	0.47	6.0%
Biosystem	291	7.72	0.90	11.7%
Roche	19	8.33	0.44	5.3%
NycoCard	268	8.18	0.65	7.9%
Total	858	7.89	0.68	8.6%

Table 3. Unacceptable results of HbA1c in EQAP-18 with target mean value of 7.45 and different allowable total error (TEa)

Kit	No.	Reported Range	Unacceptable Results according to different TEa			
			TEa = %6		TEa = 20%	
			No.	Percent	No.	Percent
Pars Azmon	98	4.16 - 9.60	56	57%	3	13%
Pishtaz Teb	104	3.40 - 9.80	41	39%	14	13%
Biosystem	245	3.70 - 13.90	137	56%	36	15%
Roche	17	7.30 - 8.40	8	47%	0	0%
NycoCard	186	5.30 - 14.00	82	44%	17	9%
Total	650	3.40 - 14.00	324	50%	70	11%

Table 4. Unacceptable results of HbA1c in EQAP-19 with target mean value of 7.89 and different allowable total error (TEa)

Kit	No.	Reported Range	Unacceptable Results according to different TEa			
			TEa = %6		TEa = 20%	
			No.	Percent	No.	Percent
Pars Azmon	130	4.60 - 10.30	78	60%	11	8%
Pishtaz Teb	150	5.20 - 14.90	63	42%	11	7%
Biosystem	291	4.48 - 13.30	176	60%	39	13%
Roche	19	7.32 - 9.16	11	58%	0	0%
NycoCard	268	4.40 - 15.00	144	54%	14	5%
Total	858	4.40 - 15.00	472	55%	75	9%

4. DISSCUSSION AND CONCLUSION

Allowable total error (TEa) is a simple comparative quality concept used to define acceptable analytical performance. TEa is determined for each test and is the amount of error that can be tolerated without invalidating the medical usefulness of the analytical result. If total analytical error (sum of random and systematic error) is less than TEa, then the performance of the test is considered acceptable. However. if the error is larger than the TEa, corrections must be made to reduce the error or the method rejected. This process ensures that laboratory tests give accurate, clinically relevant information to physicians to manage their patients effectively[11].

According to Diabetes Control and Complications Trial (DCCT), HbA1c results <7.0% show good glycemic control and results >8.0% show poor glycemic control. In order to properly classify a patient with an HbA1c value of 7.5%, the measurement error should not exceed ±0.5% (as absolute value of HbA1c), which equals relative total error of ±6.7%. Indeed, if the measurement error is greater, a patient of 7.5% would be indifferently classified in both good and poor glycemic control categories and this obviously would not be acceptable[2].

Results of our study show that using CCV% = 10% and SDI > 2 for evaluting HbA1c method performance (equals to TEa of 20%), according to clinical needs, is not proper and leads to misclassifying of about 40% of laboratories as acceptable. So, if we want the HbA1c results to be usefull for management diabetic patiens, it is necessary to use TEa = 6% which is now suggested by NGSP and used in CAP surveys for evaluating laboratory performance in measuring HbA1c[5].

In 2007, the CAP used wide acceptance limits of ±15% for evaluating performance of laboratories measurng HbA1c. In 2008, the CAP narrowed this limit to ±12%, and then in 2009 to ±10%, in 2010 to ±8%, in 2011 to ±7%, and finally in 2013 to ±6% [5]. As in United States where CAP plan to gradually tightenning the acceptance limits from ±15% in 2007 to ±6% in 2013, in Iran gradually thightenning of TEa from improper ±20% to proper ±6% is necessary. In this regards, Iranian clinical laboratories that have unacceptable results, must do corrective action to reduce their analytical errors or use another HbA1c measuring methods that has acceptable performance.

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