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Original investigation

Assesment of Analytical Performance of HbA1C Test by Six Sigma Methodology

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ABSTRACT

Background and Objective: The HbA1 c test is a biomarker used to evaluate the long-term outcomes of diabetes, and therefore its role in diabetes management is important Analytical reliability of clinical laboratories may be obtained by Internal Quality Control (IQC), External Quality Control (EQC) etc. by analyzing the data with statistical methods. In six sigma methodology, which is one of these methods, the analytical performance can be evaluated with a single number named "process sigma value". This study aimed to compare the six sigma levels in line with the results of IQC and EQC of HbA1 c tests which is one of the most commonly used tests in our laboratory.

Material and Methods: IQC and EQC data between May 2015-August 2015 were collected. Monthly process sigma levels were calculated by using formula "(TEa% - Bias%)/CV%. For Bias; values that the firm provided from IQC results and the standard deviation index (SDI) values in EQC reports were used. 6% were basis for the allowed total error values (NGSP).

Results: Process sigma level were determined according to IQC1, IQC2 and EQC results by month as May (3.4–8.4–9.6), June (3.9–5.2–4.5), July (5.9–8.4–4.7), August (8.7–8.4–8.2), respectively in 2015.

Conclusions: In our study it was observed that HbA1C test is in conformity with the process sigma levels according to IQC and EQC data. HbA1 c test was found to be compatible with internal quality control and external quality control results in accordance with process sigma levels and it was also evaluated as favorable considering our laboratory performance.

Key words: Quality assessment, six sigma, analytical reliability

INTRODUCTION

Hemoglobin is a protein that exists in red blood cells and helps carry the oxygen. After the synthesis of hemoglobin, modified hemoglobin is formed by post translational modifications and hemoglobin A1 c (HbA1 c) is the most frequently seen hemoglobin type among these (1, 2). Hemoglobin A1 c (HbA1 c) measurements give information about the glucose level in the last 3 months (3, 4). ADA (American Diabetes Association) recommended HbA1 c to be used for diabetes follow up (5, 2). The HbA1 c test is a biomarker used to evaluate the long-term outcomes of diabetes, and therefore its role in diabetes management is important. It is known that over 70 methods are available for the analysis of HbA1 c around the world (6).

Since each of these methods measure different fractions of glycated hemoglobin in different ways, different results may be yielded. In order to provide a standardization among the methods of HbA1 c measurement, NGSP (National Glycohemoglobin Standardization Program) was founded by AACC (American Association for Clinical Chemistry) in 1993 (7). In 1995, IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) initiated the standardization project for HbA1 c. In 2001, reference method created by IFCC for HbA1 c was approved and started to be used (8).

HbA1 c is a very frequent test in our laboratory. In HbA1 c assay principle are based on reverse-phase cation exchange "High Performance Liquid Chromatography HPLC (HPLC).

The analytical quality of laboratories is evaluated by statistical analysis of data such as internal quality control (IQC), external quality control (EQC), patient results. The internal quality control checks the precision of the method and the external quality control checks the accuracy of the analytical method. The metrics of internal and external quality control are based on statistical science (e.g. SDI, CV, Z-score) and they are graphically represented by statistical charts.

Six sigma methodology is a quality control means which is based on statistical calculations, focused on process variables and provides information about process performance (9). In our country, six sigma practices are very common in industry, however clinical laboratory practices are very rare (10).

Six sigma methodology is composed of five steps; define, measure, analyse, improve, control (DMAIC). These steps are universal and can be applied in business, industry and medicine. The Six sigma method shows the degree of deviation of the process from perfection. The performance of the analytical process can be evaluated according to the Six Sigma methodology in clinical laboratories and is expressed in a single number defined as the "process sigma value". In the Six sigma methodology, variables are considered to be sources of error. Basic indicator is the process sigma level. High sigma level means that the analytical errors are low and that the test results are acceptable. Low sigma level is accepted as error (11).

In our study, it was aimed to compare the process sigma levels of HbA1 c (the frequently used test in our laboratory) in accordance with the internal and external quality control results.

MATERIALS and METHODS

Subjects: This study was conducted in the clinical biochemistry laboratory of Ahi Evran University Training and Research Hospital in Kırşehir.

Methods: We used Arkray HA-8160 for HbA1 c analysis, the assay principle is based on reverse phase cation exchange "High Performance Liquid Chromatography HPLC (HPLC). HbA1 c in the sample interacts ionically with the column material and is separated from other hemoglobin fractions. Ion exchange chromatography allows the separation of Hb species according to their charge. The separated hemoglobin species are monitored on the principle of light absorption and the resulting chromatogram is recorded by the computer. The concentration of HbA1 c is expressed as a percentage of the ratio of the hemoglobin peak area to the total hemoglobin peak area.

IQC data were collected from laboratory information system and EQC data were collected from Randox International Quality Assessment Scheme (RIQAS) program in May 2015–August 2015. Internal quality results which are outside the acceptable range because of random errors (staff using the wrong quality control material, exchange of normal and pathological materials, using materials which are kept waiting too long etc.) were not included to our study.

Statistical analysis

Data were evaluated using Microsoft Excel 2010. Means, standard deviations and CV's were calculated. CV (%) was calculated from the internal QC data over the four month period using the formula: CV (%)=(standard deviation × 100)/laboratory mean (IQC). In addition CV% value, which is provide from IQC material and close to the EQC material concentration, was used.

Sigma levels were calculated using the formula as follows: Process sigma=(TEA% - bias%/CV%)

The% TEa (the allowed total error values) is the amount a test result may deviate from the "true value" and still be acceptable. In this study% TEa value of% 6 for HbA1 c was taken from NGSP (National Glycohemoglobin Standardization Program).

Process sigma metrics were calculated separately according to IQC and EQC bias results. Bias was calculated from the IQC results using the following equality Bias (%)=(Our mean – target mean)/(target mean) × 100.

Bias was calculated from the EQC data using the following equality: Bias (%)=(mean of all laboratories – our mean)/(mean of all laboratories) × 100.

RESULTS

Two different concentrations of internal quality control samples were analyzed (QC1 and QC2).

Laboratory target means were 5.9% for QC1 and 11.4% for QC2 respectively. Our internal quality control study mean results were found as; 5.8%, 5.9%, 5.9%, 5.8% for QC1, 11.3%, 11.3%, 11.3%, 11.2% for QC2 respectively in May, June, July and August.

Our external quality assessment mean results were found as; 12.8%, 6.8%, 4.7%, 8.2% in May, June, July and August (Table 1). According to external quality reports, Bias values are 4.1, 1.3, 0.3, 3.5 respectively (Table 1).

Process sigma level were determined according to IQC1, IQC2 and EQC results by month as May (3.4–8.4–9.6), June (3.9–5.2–4.5), July (5.9–8.4–4.7), August (8.7–8.4–8.2), respectively (Table 2).

Table 1. Internal and External quality control data

HbA1 c (%)	Target mean	Laboratory mean	SD	% CV	% Bias
May IQC 1–2	5.90	5.80	0.10	1.72	1.69
	11.40	11.30	0.08	0.71	0.88
May EQC	12.30	12.80	0.08	0.63	4.07
June IQC 1–2	5.90	5.96	0.09	1.51	1.02
	11.40	11.30	0.13	1.15	0.88
June EQC	6.71	6.80	0.09	1.32	1.30
July IQC 1–2	5.90	5.90	0.06	1.02	0.00
	11.40	11.30	0.08	0.71	0.88
July EQC	4.72	4.70	0.06	1.28	0.34
August IQC 1–2	5.90	5.80	0.04	0.69	1.69
	11.40	11.20	0.08	0.71	1.75
August EQC	7.92	8.20	0.06	0.73	3.51

IQC, internal quality control; EQC, external quality control

Table 2. Sigma values calculated for Internal and External quality control data

HbA1 c (%)	% Tea	% Bias	% CV	Sigma value
May IQC 1–2	% 6	1.69	1.72	3.48
		0.88	0.71	8.48
May EQC	% 6	4.07	0.63	9.60
June IQC 1–2	% 6	1.02	1.51	3.97
		0.88	1.15	5.22
June EQC	% 6	1.30	1.32	4.53
July IQC 1–2	% 6	0.00	1.02	5.90
		0.88	0.71	8.48
July EQC	% 6	0.34	1.28	4.70
August IQC1–2	% 6	1.69	0.69	8.70
		1.75	0.71	8.40
August EQC	% 6	1.69	0.73	8.20

IQC, internal quality control; EQC, external quality control

DISCUSSION

In analytical process; test methods, analysers, internal and external quality control, calibration rise to prominence and in this process the control of the variables is possible (12). In order to prove the performances, six sigma methodology is an effective tool (13). To provide a holistic perspective, pre-analytical and post-analytical processes must be evaluated with the analytical process. HbA1 c is a globally accepted analyte in its utility for monitoring the complications of diabetes (14)

In the USA HbA1 c is analyzed using the reference method of BioRex 70 iyon-exchange HPLC by National Standardization Program (National Glyhemoglobin Standardization Program/ Diabetes Control and Complications Trial-NGSP/DCCT) (15). In our laboratory HbAc1 is analyzed in the same way.

The HbAc1 unit established by international scientific circles is mmol/mol. However there is a continuing discussion on units. In the USA percentage (%), HbA1 c (recommended by NGSP) unit is accepted, however IFCC accepts both units, but IFCC recommends using mmol HbA1 c/mol (15–17). In our laboratory, % HbA1 c unit which is recommended by NGSP is used and this unit was also used during the evaluation with six sigma methodology.

In our evaluation, we made use of accuracy and repeatability of the analytical process performance criteria. In this evaluation we used bias values obtained from IQC and EQE results. This is a questionable debate. As is known, bias is obtained from comparison experiments during method validation studies. It is monitored with everyday IQC results. Laboratory also monitors itself for accuracy in accordance with external quality evaluation programs. Some researchers recommend using the bias value obtained from EQ evaluation results (10).

Huysal et al., conducted a study using six sigma methodology to evaluate the analytical performance of HbA1 c analyzer test results. In their study, bias values and process isgma levels obtained from external quality reports were evaluated (18).

TEa is chosen in accordance with total error criteria which is decided to be monitored. TEa selection may vary in accordance with biological variability, Clinical Laboratory Implementation Amendments 1988 (CLIA 88) and ecole such as Rilibak and NGSP. TEa may be taken as follows; 10% for CLIA 88, 3% for biological variability, 6% for NGSP (19). In the study of Huysal et al., TEa was taken 10% (18).

In our study we determined TEa value as 6% (NGSP), six sigma values may vary up to this value.

In the study Weykamp et al. conducted on HbA1 c quality assessment, they demonstrated that biological variation and sigma metrics models are suitable for setting and evaluating quality targets within and between laboratories. Weykamp et al. suggested that a target of 2 Sigma is sufficient for routine laboratories in evaluating quality targets using Sigma-Metrics (20).

Maine et al. conducted a study using six sigma methodology and evaluated the analytical quality of HbA1 c test. In this study, they found sigma value as; Abbott Architect, range 3.5–30 Sigma; Bio-Rad Variant range 0.4–21 Sigma; Roche Tina-quant, range 0–7.2 Sigma; and TOSOH G8, range 0–4.2 Sigma. TEa value determined in this study was 6% (21).

EQAS data from 137 laboratories in Netherlands revealed that 70.1% of the laboratories met the criteria for sigma greater than 2 with a TEa of 6% (22)

Bozkaya et conducted a study evaluated the analytical quality of HbA1 c analyzer according to sigma metrics. The mean sigma levels for low and high quality control materials were found to be 3.0 and 4.1, respectively (23).

Wang and colleagues in their study; by applying biological variability and Six Sigma model, they evaluated the analysis performance of 6 different HbA1 c analyzers. Generally the analytical performance of 6 HbA1 c analyzers in their laboratory were good, However, 50% (3/6) and 67% (4/6) of the HbA1 c analyzers reached the acceptable level in the biological variation and six Sigma model, respectively (24).

In our study, process sigma levels were determined according to IQC1, IQC2 and EQC results by month as May (3.4–8.4–9.6), June (3.9–5.2–4.5), July (5.9–8.4–4.7), August (8.7–8.4–8.2), respectively (Table 2). Although process sigma levels are in the ideal range in our laboratory, diversity is observed according to bias values of IQC and EQC. Although six sigma methodology can be used effectively in evaluating analytical performance and arranging IQC-EQC practices, two factors should be taken into account while calculating the sigma value. Firstly, different sigma values can be obtained in accordance with the chosen TEa reference. Secondly, different sigma values and different bias values can be obtained depending on the IQC sample level and analyte concentration level of the external quality material.

Sigma measurements helps to evaluate analytical methods and improve laboratory performance. This works as a guideline for quality conrtol strategy. It may serve as a self assessment tool for clinical function. Six sigma methodology may provide a detailed evaluation for measurement processes of problematic tests and it may also help take the variable under control. Six sigma methodology is the key to solve analytical and managerial problems in laboratory and it helps decrease errors to a minimum level.

Consequently, it was observed that using six sigma values as a quality indicator in order to evaluate the analytical phase is quite useful for providing the integration of both IQC and EQC data. Six sigma practices enables performance comparison among the clinics around the world by providing universal criterion for laboratory performance.

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