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Improvement of the Quality of Work in a Biochemistry Laboratory *via* Measurement System Analysis

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Abstract

An adequate and continuous monitoring of operational variations can effectively reduce the uncertainty and enhance the quality of laboratory reports. This study applied the evaluation rule of the measurement system analysis (MSA) method to estimate the quality of work conducted in a biochemistry laboratory. Using the gauge repeatability and reproducibility (GR&R) approach, variations in quality control (QC) data among medical technicians in conducting measurements of five biochemical items, namely, serum glucose (GLU), aspartate aminotransferase (AST), uric acid (UA), sodium (Na) and chloride (Cl), were evaluated. The measurements of the five biochemical items showed different levels of variance among the different technicians, with the variances in GLU measurements being higher than those for the other four items. The ratios of precision-to-tolerance (P/T) for Na, Cl and GLU were all above 0.5, implying inadequate gauge capability. The product variation contribution of Na was large (75.45% and 31.24% in normal and abnormal QC levels, respectively), which showed that the impact of insufficient usage of reagents could not be excluded. With regard to reproducibility, high contributions (of more than 30%) of variation for the selected items were found. These high operator variation levels implied that the possibility of inadequate gauge capacity could not be excluded. The analysis of variance (ANOVA) of GR&R showed that the operator variations in GLU measurements were significant ($F = 5.296$, $P = 0.001$ in the normal level and $F = 3.399$, $P = 0.015$ in the abnormal level, respectively). In addition to operator variations, product variations of Na were also significant for both QC levels. The heterogeneity of variance for the five technicians showed significant differences for the Na and Cl measurements in the normal QC level. The accuracy of QC for five technicians was identified for further operational improvement. This study revealed that MSA can be used to evaluate product and personnel errors and to improve the quality of work in a biochemical laboratory through proper corrective actions.

Key Words: clinical biochemistry, measurement system analysis, quality control, repeatability, reproducibility

Introduction

The quality of healthcare services has been a subject of much debate in recent years. As the healthcare sector has long been regarded as a special type of service sector, hospital administrators should make use of both medical and administrative innovations to ensure the effective improvement of service pro-

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cesses (25). Clinical laboratory reports constitute an important resource for clinicians in making and refining their diagnoses and prescribing treatments. Thus, the provision of prompt and precise medical examination reports is a key objective of all clinical laboratories. In a clinical laboratory, analytical errors may occur as a result of systemic issues such as malfunctioning of probes and photometric lamps, blockages in tubing, non-conformity with internal quality control (QC) measures, random errors stemming from pipetting difficulties or problems with the analyzer, or problems resulting from fibrin clots, short samples, calibration drift, or contamination of reagents (8). QC and quality-assurance procedures in most hospitals are based on the Westgard multi-rules (22-24) supplemented by the ISO15189 international standards for better laboratory quality. The intent of total analytical error prevention is to ensure that laboratory measurements fulfill the ISO definition of accuracy as measurement precision impacted by only a limited combination of random and systematic errors. Acceptable accuracy implies that the combined precision and bias of most measurements should be small compared to the degree of measurement error that would make a given measurement unacceptably imprecise for medical use (24). In the U.S., the Clinical Laboratory Improvement Amendments (CLIA) sets quality requirements and emphasizes increased quality assessments for pre-analytic and post-analytic processes[1]. Nonetheless, using performance data evaluated on the σ scale, two investigators concluded that analytic quality continues to be a problem in clinical laboratories (23). The CLIA criteria for acceptability may not be objective or sufficiently indicative of the quality needed for medical care. To achieve the QC objectives of biochemistry laboratories, it would be better if the focus of relevant evaluations include measurements of three relevant variables: instruments, reagents, and operators. Although the use of high-quality instruments and reagents can help to improve overall examination quality, there is typically less evaluation of variations in measurement contributed by operators. Szecsi and Ødum reported that the majority (82.6%) of bias events was due to human errors, while relatively few were the result of technical errors in a standard clinical laboratory (19). Recently, using a national retrospective survey, Kang *et al.* reported that although most of the laboratories (93%) in China had established laboratory information system (LIS), only 10% were accredited by ISO 15189. Of those, only 11% of the laboratories explicitly specified that only staff with senior or higher grades were qualified to review and release reports (9). Relatedly, Simundic *et al.* argued that, even in ISO 15189-accredited laboratories, personnel should be reeducated in order to take actions to reduce the error rate in the preanalytical phase of the laboratory testing process (18). An adequate and continuous monitoring of such operational variations, however, can effectively reduce the uncertainty and enhance the quality of laboratory reports.

Two components of measurement error are investigated in determining the measurement capability of a given system, namely, the gauge repeatability and reproducibility (GR&R). Reproducibility is defined as the variability due to different operators using the gauge, while repeatability is seen as a reflection of the inherent precision of the gauge itself (11, 12). If the accuracy of the measurement system of a laboratory requiring a certain level of quality is unacceptable, measurement tracking should usually be carried out to determine whether there is a problem of repeatability or reproducibility. If there is a repeatability problem, it would be necessary to adjust the measurement instrument or change the reagent. If there is a reproducibility problem, it may be caused by the actions or errors of the system operators, such that further training may be required. Most institutions utilize a QS 9000 or D1-9000 quality system in conjunction with evaluations of GR&R (4, 15). The measurement variation can be applied to a QC program for a clinical biochemistry laboratory. A contemporary clinical LIS can be used to generate reports for the whole analytic process and to reduce measurement variation in an inspection process. However, in spite of such safe guards, human error continues to be the main source of errors in pre-analytic, analytic and post-analytic processes. At the same time, the monitoring of operational variations caused by laboratory personnel is still being neglected in most hospital laboratories. As such, laboratories are urged to focus on the quality of such analytic processes in order to improve patient safety (13). With regard to variations caused by a given gauge or reagent, variations in repeatability can be reduced by continuously updating the instruments, or by further developing testing methods. However, the natural variations caused by personnel have seldom been discussed. In this study, we incorporated the daily QC data of a given hospital laboratory and used measurement system analysis (MSA) to quantitatively determine the QC of the laboratory's biochemistry-related measurements, and to further explore the manual factors which could affect the quality of those measurements.

[1] Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), and HHS. Medicare, Medicaid, and CLIA programs; laboratory requirements relating to quality systems and certain personnel qualifications. Final rule. *Fed. Regist.* 68: 3639, 2003.

Materials and Methods

Daily QC data were collected from a large teaching hospital in northern Taiwan. The clinical biochemistry laboratory of the hospital uses an Olympus AU640 automation machine in its analyses of clinical biochemistry test items. Five biochemical substances that the laboratory measures on a daily basis are blood glucose (GLU), aspartate aminotransferase (AST), blood sodium (Na), blood chloride (Cl) and uric acid (UA); as such, the laboratory also generates daily QC data levels for measurements of these substances, and these data were collected for the same QC reagent lot from August 2008 through December 2008. The measurement variations in terms of repeatability and reproducibility that were calculated from the QC data of five individual medical technicians were evaluated. In order to ensure quality, the reagent of a standard QC solution lot for each biochemistry item was prepared by the same technician twice a week. During the aforementioned 5-month period, 15 sample runs were collected randomly from each technician for GLU, AST and UA, while 10 runs were collected randomly from each technician for Na and Cl. QC data for both the normal and abnormal ranges were analysed twice a day for each biochemistry test item. In the other words, 150 pieces of data (15 runs*5 technicians*2 times) for GLU, AST and UA, and 100 pieces of data (10*5*2) for Na and Cl were collected, respectively. In total, two samples containing 650 QC data values in the normal and abnormal levels were composed to analyze the GR&R. The total variation in measurements derived from clinical biochemistry data which were recorded by automatic analysis instruments can be constructed with the following 3 variance components: (a) variation of product (*i.e.* reagent), (b) variation of different measurements, and (c) variation of different operators (*i.e.* technicians). The variance of measurement is defined as follows:

$$\hat{\sigma}^2_{Total} = \hat{\sigma}^2_{part} + \hat{\sigma}^2_{gauge} \quad (1)$$

Where $\hat{\sigma}^2_{part}$ is the product variance and $\hat{\sigma}^2_{gauge}$ is the gauge measurement variance. The gauge measurement variance can be defined as follows:

$$\hat{\sigma}^2_{gauge} = \hat{\sigma}^2_{repeatability} + \hat{\sigma}^2_{reproducibility} \quad (2)$$

An experiment used to measure the components of $\hat{\sigma}^2_{gauge}$ is called a GR&R study.

In order to quantify the effects of human errors, two components of measurement error are investigated in determining the $\hat{\sigma}^2_{gauge}$ value, namely, the gauge repeatability and reproducibility, which consist of the measurement variation caused by the actions of repeated measurements and the measurement variation caused by the different operators, respectively. In an ideal situation, almost all variations come from product differences, with only a very small degree of measurement variation caused by repeatability and reproducibility. By minimizing the operation variation among operators, the credibility of the measurement system can be maximized. It is a common practice to compare the estimate of gauge capacity to the width of the tolerance band [upper specification limit (USL) - lower specification limit (LSL)] for the part that is being measured (12, 14, 16). The ratio of $6\sigma_{gauge}$ to the total tolerance band, which is called the precision-to-tolerance (P/T) ratio, can be calculated as follows:

$$P/T = \frac{6\sigma_{gauge}}{USL - LSL} \quad (3)$$

where USL denotes the upper specification limit and LSL denotes the lower specification limit. $6\sigma_{gauge}$ accounts for 99.73% of measurement system variation based on the normal distribution for underlying gauge error. Values for the estimated P/T are used to estimate gauge capability in most industries. A small value for the estimated P/T is often taken to imply adequate gauge capability (12). According to the Automotive Industry Action Group, a P/T value of 0.1 or less indicates that the measurement system should be considered acceptable. In contrast, a P/T value of 0.3 or more indicates that the measurement system is unacceptable[2]. In this study, we used the P/T ratio as an indicator of the technicians' capability in measuring the aforementioned five biochemical substances.

This study used Minitab, version 17, to process the QC variation. The traditional QC indicator, coefficient of variance (CV), was also calculated and compared for each item. The variance contributions of the different factors were calculated to determine the main source of total variation. For instances in which the gauge capacity was found to be inadequate, a two-way analysis of variance (ANOVA) was derived to estimate the significance of variation of repeatability and reproducibility. The level of statistical significance was set at 0.05. This study determined whether the measurement variation levels of the aforementioned biochemistry test items conformed to the specifications of MSA and of six sigma QC practice. In order to verify the source of operation variation, individual mean and normalized standard deviations of QC data among the technicians were also compared for subsequent issue improvement. The Levene's test was used to estimate the heterogeneity of variance among the different technicians. A visual pattern of the variation for each technician was also created to better illustrate individual deviations (10). In addition, a probability density function was used to describe the relative likelihood for the QC data to take on a given value (2).

[2] AIAG 2010. Measurement system analysis. Detroit, New York: Automotive Industry Action Group.

Table 1. Variance and tolerance values for the five biochemical test items in the normal and abnormal QC levels

	Normal Level					Abnormal Level				
Statistics	GLU	AST	Na	Cl	UA	GLU	AST	Na	Cl	UA
Mean	80.68	32.42	143.57	98.04	4.93	271.43	181.33	84.25	124.92	10.20
SD	1.87	0.71	1.92	1.37	0.08	5.97	2.71	1.29	1.95	0.15
CV(%)	2.32	2.18	1.33	1.39	1.57	2.20	1.49	1.53	1.56	1.45
P/T	0.69	0.32	1.45	0.85	0.28	0.66	0.23	1.45	0.92	0.27

GLU: glucose; AST: aspartate aminotransferase; NA: sodium; CL: chloride; UA: uric acid. SD: standard deviation; CV: coefficient of variance. P/T: The ratio of 6 σ gauge to total tolerance band.

Table 2. Contribution of GR&R components of the five biochemical test items in the normal and abnormal QC levels

GR&R	Normal Level (%)					Abnormal Level (%)				
Components	GLU	AST	Na	Cl	UA	GLU	AST	Na	Cl	UA
Repeatability	59.64	83.44	2.72	81.16	76.73	66.31	64.76	55.31	63.55	75.94
Reproducibility	40.36	16.56	21.83	11.35	23.27	33.69	34.14	13.45	36.45	24.06
Part-to-part	0.00	0.00	75.45	7.49	0.00	0.00	1.10	31.24	0.00	0.00

Definitions of the biochemical test item abbreviations are the same as indicated in the footnote for Table 1.

Results

Using the traditional QC indicator, we found that the Na and GLU measurements had the smallest and the largest CV values, respectively (Table 1). All the CV values ranged from 1.33% to 2.32% for the normal and abnormal QC levels. This implied that the daily QC data for the Na measurements were more stable than those for the other items. On the other hand, the larger P/T values of Na, Cl and GLU indicated less adequate gauge capability in measuring those items than in measuring the other two items. The GR&R components and contribution percentages for each of the 5 test items are shown in Table 2. The product variation, *i.e.* part-to-part, values reveal the differences among the different items. The product variation contribution of Na was 75.45% and 31.24% in normal and abnormal QC levels, respectively. Excluding Na, the product variation contributions of all other items were lower than 10%. With regard to reproducibility, the study found high contributions of more than 30% of variation for these selected items. The high operator variation implied that the possibility of inadequate gauge capacity could not be excluded. The two-way ANOVA analysis results of the GR&R study are shown in Table 3. The operator variations for the GLU measurements were significant (F= 5.296 in the normal level and 3.399 in the abnormal level, respectively). Similar results were also found for the Na measurements. In addition to operator variations, the product variations of Na were also significant in both QC levels. The heterogeneity of variance for the five technicians is shown in Table 4. There were statistically significant differences ($P < 0.05$) for Na and Cl measurements in the normal level. As indicated in Figs. 1 and 2, the five technicians had different accuracy levels for their QC data. Technician B exhibited a good accuracy in the normal QC levels of Na measurements, while technician A exhibited both poor reliability and validity. In the normal level of Cl measurements, good reliability but poor validity could be observed for technician D.

Discussion

This study showed that using the MSA method with GR&R data derived from daily QC monitoring data can be used to evaluate reagent quality, measurement reproducibility of medical technicians, and repeatability of repeated gauge measurements conducted in hospital

Table 3. ANOVA for GR&R components of the five biochemical test items in the normal and abnormal QC levels

	Normal Level			Abnormal Level		
Items	Part	Operator	Part* Operator	Part	Operator	Part*Operator
GLU						
F (df)	0.529(14)	5.296(4)	1.829(56)	0.463(14)	3.399(4)	1.738(56)
p value	0.906	0.001	0.007	0.943	0.015	0.013
AST						
F (df)	0.992(14)	1.582(4)	1.345(56)	1.087(14)	1.767(4)	1.954(56)
p value	0.474	0.192	0.115	0.389	0.148	0.003
Na						
F (df)	37.803(9)	13.621(4)	7.535(36)	5.521(9)	2.898(4)	1.249(36)
p value	< 0.001	< 0.001	< 0.001	<0.001	0.035	0.231
Cl						
F (df)	1.725(9)	1.052(4)	1.273(36)	0.569(9)	0.577(4)	2.147(36)
p value	0.119	0.394	0.213	0.813	0.681	0.006
UA						
F (df)	0.374(14)	2.621(4)	1.450(56)	0.653(14)	2.510(4)	1.484(56)
p value	0.977	0.050	0.066	0.809	0.052	0.055

Parts denote product variation; Operators denote operator variation; Parts*Operators denote the interaction of variation between operator and product. F denotes statistics of ANOVA test; df denotes degree of freedom. See also Table 1 footnote.

Table 4. Levene's test among the medical technicians for the five biochemical test items in the normal and abnormal QC levels

		Normal Level			Abnormal Level		
Items	Technician	Mean	SD	F (*p* value)	Mean	SD	F (*p* value)
GLU	A	80.27	1.89		272.80	6.61	
	B	81.77	1.74	0.408	272.43	5.81	0.831
	C	81.20	1.73	(0.803)	273.83	5.36	(0.507)
	D	80.67	1.71		268.77	5.28	
	E	79.53	1.57		269.33	5.28	
AST	A	32.23	0.73		181.20	2.61	
	B	32.37	0.76	0.680	180.40	2.54	0.202
	C	32.63	0.72	(0.607)	182.27	2.18	(0.937)
	D	32.30	0.60		180.93	3.11	
	E	32.57	0.68		181.87	2.78	
Na	A	142.70	2.43		124.10	2.10	
	B	143.50	1.79	2.740	124.80	1.82	0.364
	C	144.20	1.32	(0.033)	125.30	2.00	(0.834)
	D	144.45	1.23		125.75	1.68	
	E	143.00	2.08		124.65	1.90	
Cl	A	97.95	1.79		83.90	1.25	
	B	97.70	1.17	2.928	84.25	0.97	1.564
	C	98.10	1.29	(0.025)	84.20	1.51	(0.190)
	D	98.55	0.83		84.65	0.99	
	E	97.90	1.52		84.25	1.62	
UA	A	4.95	0.07		10.22	0.13	
	B	4.92	0.08	1.131	10.22	0.19	2.233
	C	4.95	0.07	(0.344)	10.25	0.10	(0.068)
	D	4.89	0.07		10.12	0.14	
	E	4.95	0.08		10.21	0.14	

SD: Standard Deviation; F denotes statistics of Levene's test. See Table 1 footnote.

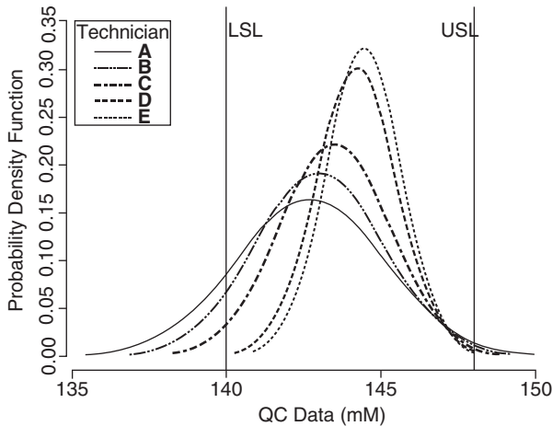

Fig. 1. Distribution of QC accuracy by five medical technicians for normal levels of Na. USL denotes the upper and LSL the lower specification limits. A to E represent the five individual medical technicians. Probability density function: $f(x)=\frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{(x-\mu)^2}{2\sigma^2}}$.

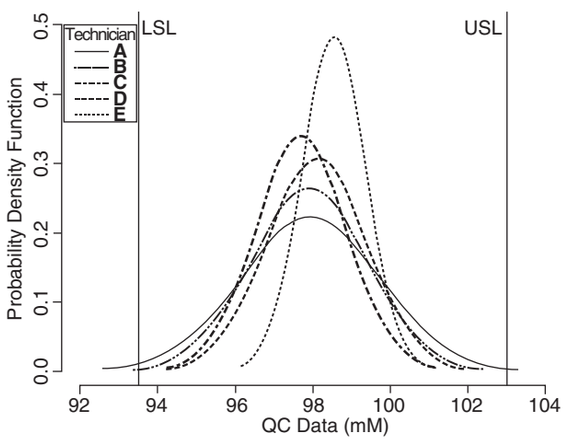

Fig. 2. Distribution of QC accuracy by five medical technicians for normal levels of Cl. See also legend to Fig. 1.

biochemistry laboratories. A previous study reported that most of the industries conducting MSA are finding it difficult to investigate the root causes behind poor GR&R and, consequently, to take proper corrective actions (6). Our study establishes an evaluation procedure which can explore the cause of poor quality estimated by GR&R. With regard to reagent quality, our results showed that Na measurements exhibited higher product variation effects than the measurements of other test items. While reviewing the reagent preparation process, as the Na QC reagent was diluted with reverse osmosis (RO) water and used for three consecutive days, the concentration of the infused serum was found to increase as the RO water gradually evaporated. Therefore, the volume of RO water in the relevant test tube needs to be monitored continuously to avoid affecting the quality of the reagent. With regard to the effects on overall accuracy caused by operators, the present study reported that significant variation among the operators could be observed in the GLU and Na measurements, as well as in the Na and Cl measurements. Estimating individual variation further, we found that the errors were contributed mainly by specific technicians. After further interviewing the laboratory director, we suspected that the errors might have been caused by a lack of personal experience or capability. For example, one of the technicians was on a fixed night shift and studied during the daytime, while the other was a junior technician who had been working in the laboratory for less than half a year.

To ensure patient safety, continuous improvements in the quality of laboratory reports is crucial (17). In recent years, in order to maintain the quality of laboratory reports, most of the high-quality laboratories have obtained ISO 15189 certification. Through the normalized operation requirements of collection and transportation of inspection items stipulated by the ISO 15189 standards, as well as the establishment of standards of inspection regarding item acceptance, pre-analytic procedures have greatly reduced the probability of abnormal reports. For post-analysis, as most laboratories use LIS standards to establish guidelines and review mechanisms, the proportion of manual reporting errors has been greatly reduced. Recently, efforts have also been made to apply well-known industrial QC tools or indices in healthcare. For example, after using statistical process controls and the process capability (Cp) and process capability index (Cpk), two previous studies suggested that developed tools could improve process capabilities in biochemical laboratories (1, 4). To ensure optimal testing, laboratories should develop their own QC procedures to account for the precision and accuracy of measurement and the quality required to provide good care to their patients (21).

Biochemistry inspections of QC in laboratories in Taiwan have been universally established, and the variations in laboratory measurements mainly derived from equipment and reagents have been given a good degree of attention. However, the variances in reproducibility contributed by personnel have received less concern. Generally, middle- or large-scale medical biochemistry laboratories in Taiwan have three to six technicians executing daily QC inspections over different shifts. The daily laboratory report is produced and released by multiple technicians, so there may be measurement variations among the different operators. Therefore, identifying analytic errors caused by personnel, and determining which technicians are relatively inconsistent in their work, can be helpful

in efforts to reduce the degree of variation caused by individual technicians. While controlling measurement variations caused by laboratory personnel may make little difference in terms of specific diagnoses, if relatively inconsistent personnel can be identified, reeducated and retrained, potential pre-analytic and post-analytic errors can also be reduced.

Nonetheless, two limitations to the current study should be noted. First, we used the same QC lot to monitor measurement quality for five months. Due to the short study period, small and unequal sample sizes for the five biochemical test items were collected; as such, selection errors may have affected our analyses when comparing the variances of all the items together. It is suggested that in future studies data should be collected for analysis over longer periods to avoid the problem of incomparable variables. Moreover, values for the estimated P/T of 0.1 or less are often taken to imply adequate gauge capability in most of industries (12). As such, the large P/T values shown in our study could be considered to be indicators of inadequate QC performance. Recently, a revised P/T ratio for multivariate MSA with correlated quality characteristics was proposed. Nonetheless, in performing GR&R studies, most industries today are still using the approval criteria for P/T ratios stipulated in QS9000 (15). A similar issue can be observed in the variation contribution of GR&R components. In industrial QC practices, contributions of less than of 10% are considered acceptable (3). However, whether criteria requiring high precision can be applied in biochemistry laboratories needs to be assessed further.

In the healthcare sector, measurement tools should be developed in order to come up with useful instruments to measure the process orientations of relevant employees (7). A system for assessing and improving healthcare organizations should be applied to promote overall service quality (5). This study provides evidence that MSA can be used to evaluate product and personnel errors and to improve the quality of biochemical laboratory work through proper corrective actions. Future research should focus on the development of MSA index criteria in clinical laboratories. Objective criteria can be applied and judged by laboratory authorities to continuously improve their measurement quality.

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