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RESEARCH ARTICLE

QUALITY CONTROL MANAGEMENT ISSUES OF ROUTINE COAGULATION TEST IN A LOW-INCOME COUNTRY (MADAGASCAR)

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Abstract

Introduction: Reliability of biological assays' results depends closely on the quality of the 3 biological stages: pre-analytical, analytical, and post-analytical. In each stage, a quality program including internal quality control (IQC) and external quality assurance (EQA) has to be assessed to ensure test result accuracy and precision. The coagulation laboratory plays an important role in the diagnosis and treatment of people with blood disorders, so though several lack of facilities in Malagasy labs, QC has to be implemented. Thus, this study aimed to analyze IQC and EQA in hemostasis tests in the Hematology laboratory of the CHU-HJRA in Antananarivo Madagascar in order to improve its analytical phase's quality.

Methods: This retrospective descriptive and analytical study was conducted from January 1st, to October 31st, 2021 in the Hematology laboratory of CHU-JRA within the routine coagulation tests (Prothrombin time PT and Activated partial prothrombin time aPTT). Regarding the EQA, percentage of deviation from the peer group's results were calculated. Then in order to analyze IQC's results, coefficient of variation and biases of IQC's results, corresponding respectively to precision and accuracy, were calculated and Levey-Jennings graphs were analyzed.

Results: Regarding global results of EQA, 50% were "within consensus" compared to peer-group. And regarding IQC, for precision, one coefficient of variation for both PT and aPTT exceeded 5%, and for accuracy, no bias exceeds 10% deviation from the expected result. Levey-Jennings's plot showed more than 90% of the results to be within M±2 SD range. A violation 10x Westgard rules, corresponding to a systematic error was observed.

Conclusion: Each out-of-control results has to be analyzed as part of strengthening quality program guaranteeing coagulation tests' reliability.

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Introduction:-

Coagulation laboratory plays an important role in the diagnosis and treatment of patients with or without blood disorders such as anti-thrombotic therapies monitoring, or biological preoperative assessment. According to the World Health Organization, "hundreds of thousands of deaths or serious illnesses worldwide are attributable each year to inaccuracies or errors in medical laboratories [1]. It is therefore essential to perform a laboratory quality program in order to get coagulation tests' results reliability [2].

« Quality » can be simply represented by 2 statements « Do the thing right » and « Do the right thing » [3]. Regarding laboratory QC program, it can be defined as the accuracy, reliability and relevance of test results and it includes Internal Quality Control (IQC) and External Quality Evaluation (EQA) [3]. In case of out-control results, corrective actions should be implemented [3].

Thus, this study aims to analyze IQC and EQA in hemostasis tests in the Hematology laboratory of the CHU-HJRA in Antananarivo Madagascar in order to improve its analytical phase's quality.

Methods:-

This is a 10-months retrospective cross-sectional and analytical study, carried out from January 1st to October 31st, 2021 within the QC program in the Hematology Laboratory CHU-JRA in Antananarivo Madagascar.

Regarding EQA, the QC program is provided by the UK-based NEQUAS (National External Quality Assurance Scheme). QC materials are received 5 times a year, and consisted on lyophilized plasma from real patients with known values so results. In, this study, 4 surveys were included. Analytical performance of the laboratory about PT and aPTT's results in each EQA survey were analyzed by calculating the percentage deviation of each test from the average of peer-group by formula seen in Table I. The result of the test was "within consensus" if the percent deviation was less than 15%, and "out of consensus" if the percent deviation was greater than 15%.

Regarding IQC, materials consisted on a pool of daily fresh plasma from 10 different samples received in the laboratory which tests' results are normal for PT, aPTT and Fibrinogen assays. Precision and accuracy of the PT an aPTT results were analyzed. IQC is performed daily before patient's samples' run. When a value is out of control, corresponding corrective action is set up. So IQC values represented in this study are from the first run, before any corrective measure. Precision's results were determined by monthly calculation of mean, standard deviation and coefficient of variation of each test's results. Accuracy's results were determined by calculating the bias or inaccuracy degree comparing to the expected result of each test (Table I).

Precision and accuracy are considered acceptable when PT and aPTT's results don't exceed 5% for coefficient of variation, and no bias exceeds 10% deviation from the expected result. Levey-Jenning's graph were analyzed using the six main Westgard rules, stating that the assay series is accepted if the results of both batches are within the acceptable limits of M ± 2SD; and rejected (or placed on watch) if the following rules are violated: 1_2s; 1_3 s, 2_2 s, R4s, 4_1 s, 10x (Table II).

Table I:- Formulas for calculating EQA and IQC parameters.

Parameters	Formula
EQA	
Percentage of deviation	$\%Dev=\frac{(\text{lab result} - \text{average of peer} - \text{group})}{\text{average of peer} - \text{group}} * 100$
IQC	
Mean (x)	$x = \frac{\sum(xi)}{n}$ $x = monthly\ mean\ of\ IQC$ $xi = daily\ results\ of\ IQC$ $n = number\ of\ IQC\ results$
Standard deviation (SD)	$SD = \frac{\sqrt{(xi - x)2}}{(n-1)}$
Coefficient of variation (CV)	$CV = 100 * SD/x$
Bias (%)	$Bias = \frac{x - v}{v} * 100 \quad v = expected\ value$

Coagulation tests are performed with a STar-T4 semi-automat from StagoDiagnostica® which measures the clotting time by a chronometric method. Reagents used for PT and aPTT are both derived from rabbit cerebral tissue and stored at +2 to +8°C. These are BIO-TP from BIOLABO® (Lot Number: 112028A, Expiry date: 11/2023) for PT; BIO-CK from BIOLABO® (Lot Number: 032042A, Expiry date: 04/2023) and Calcium chloride (Lot Number: 052157A1, Expiry date: 06/2024) for aPTT.

Table II:- Westgard rules.

Westgard rules	Details	Action
1_2s	One control measurement exceeding 2 standard deviations of control limits either above or below the mean	Warning rule to trigger careful inspection of the control data
1_3 s	Control limits are set as the mean +3 SD of control limits	Run rejected
2_2 s	Control measurements 2 SD of control limits on the same side of mean	Run rejected
R4s	2 control measurements in a group exceed the mean with a 4 SD difference between the 2 controls	Run rejected
4_1 s	4th consecutive control measurement exceeding 1 SD on the same side of the mean	Run rejected
10x	10 consecutive controls on the same side of the mean	Run rejected

Source: Hanes H. Westgard rules guidelines. John Hopkins University; April 2020

Results:-

Results of the 4 surveys of EQA are resumed in Table III, 50% were "within consensus" compared to peer-group.

Table III:- EQA results.

Survey	S50		S51		S53		S54	
	PT	aPTT	PT	aPTT	PT	aPTT	PT	aPTT
ID	W20:08	W20:09	W20:13	W20:14	W20:08	W21:09	W21:13	W21:14
Lab results	32,5%	1,9	35%	1,13	84%	1,4	93,5%	0,81
%Dev	11%	0,5%	2%	21%	12,69%	26,7%	20,1%	39,1%
Perf.	WIC	WIC	WIC	OC	WIC	OC	OC	OC

Legends:ID: Sample identity; **Perf:** Performance; **WIC:** within consensus; **OC:** out of consensus

In term of IQC, precision's analysis showed one coefficient of variation for both PT and aPTT exceeding 5% in April 2021, and accuracies showed no bias exceeding 10% deviation from the expected result (Table IV).

Table IV:- Precision and accuracy analysis.

Precision										
	J	**F**	**M**	**A**	**M**	**J**	**J**	**A**	**S**	**O**
CV (%) PT	2.75	3.06	2.51	**5.22**	4.10	2.69	2.63	2.69	2.52	2.45
CV (%) aPTT	3.82	4.23	4.43	**5.30**	4.94	4.18	4.69	4.04	4.63	4.45
Accuracy										
	J	**F**	**M**	**A**	**M**	**J**	**J**	**A**	**S**	**O**
Bias (%) PT	2.30	2.53	2.00	1.00	1.30	1.23	1.53	2.61	1.53	1.07
Bias (%) aPTT	3.52	3.09	0.90	0.58	0.65	1.38	1.67	2.54	2.90	2.18

PT Levey-Jennings graphs's analysis showed the violation of the following Westgard rules: 1_{3s} in January, 1_{2s} in February and March; 10x in August and October and aPTT Levey-Jennings graphs's analysis showed the violation 2_{2s} in March; 10x in May; 7x in August; 1_{2s} in September (Figure 2).

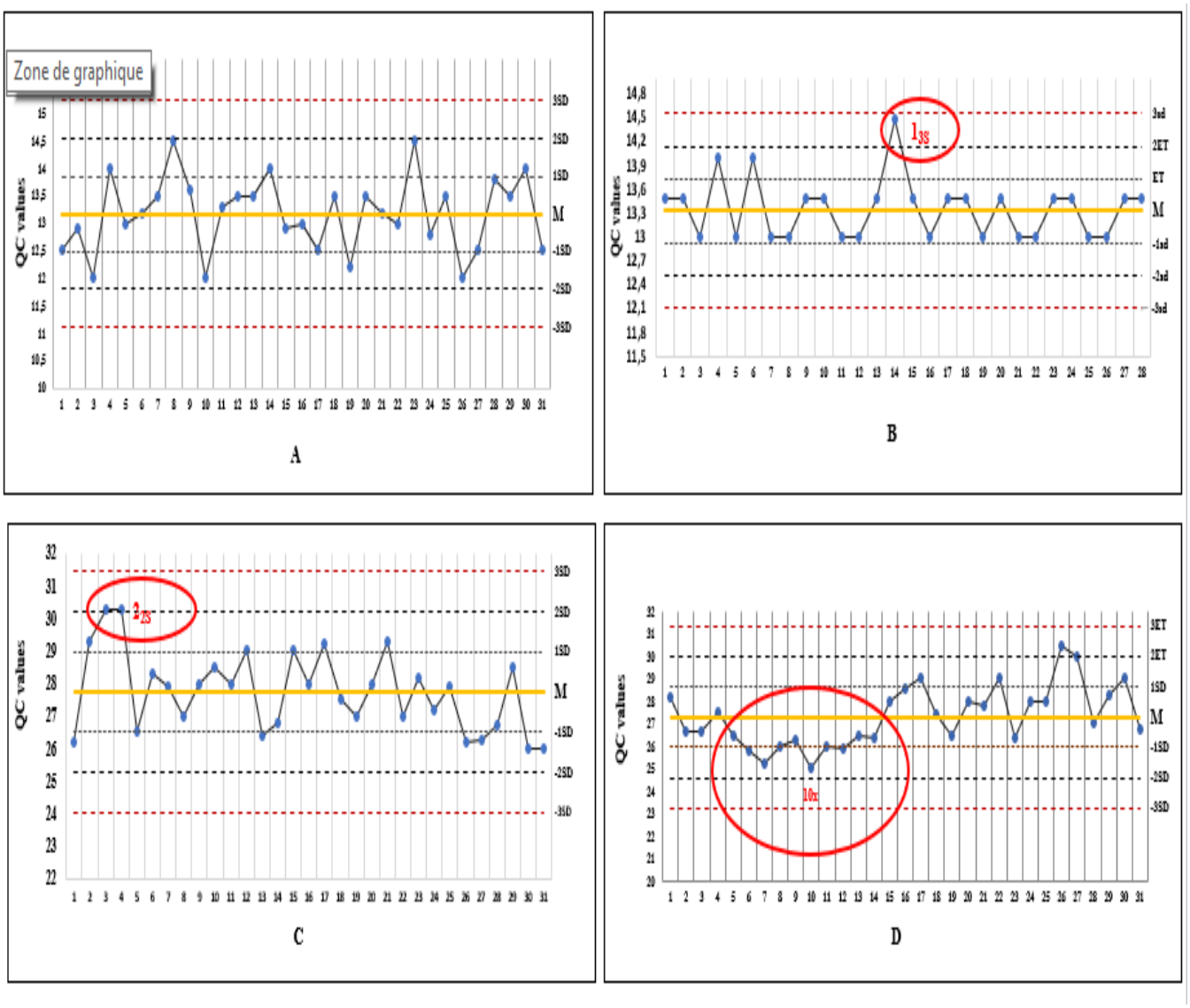

Figure 1:- Levey-Jennings graphs analysis.

Legends :A : PT Mai 2021 : No Westgard rule violated ; **B :** PT January 2021 :1_{3s} Westgard rule violated ; **C :**aPTT March 2021 : 2_{2s} Westgard rule violated ; **D :**aPTT May 2021 : 10x Westgard rule violated

Discussion:-

This study aimed to analyze routine tests QC including EQA and IQC about PT and aPTT results. Although many coagulation QC programs have been in place for decades, most of these programs begin with the evaluation of routine coagulation tests such as PT, aPTT, and fibrinogen [4]. In Madagascar, few health care system are available, so many patients have to pay for their own health care cost including biological tests that should be well ranked. Therefore, PT and aPTT are among the common tests ordered by Malagasy physicians to screen coagulation issues in preoperative patients or in suspected blood disorder. That was why these routine coagulation tests were first subjected to a QC analysis.

EQA was provided by UK-based NEQUAS which is based in Sheffield, UK, and has been inspected by the UK Accreditation Service Ltd and has received certification to ISO 17043 [5]. This program was chosen for hematology laboratory in Antananarivo Madagascar in this study thanks to the humanitarian aid program of the World Federation of Hemophilia which sustain the latter for hemophilia and blood disorder's diagnosis [5]. The QC materials are sent by mail 5 times a year. In this study, post-office issues made that only 4 surveys were received among the 5 that have been sent, and all of them were received late. In this study 4 out of 8 tests were out of

consensus for PT and aPTT that can be due to both random and systematic errors. These errors can be due to multiple factors [6] such as variations in environmental conditions (temperature, humidity) as local temperature may vary to extreme values; degradation of reagents or kits or QC materials during shipment; a manual error by the operator or a defect of the equipment and the small material (accuracy of the volumes distributed by the pipettes) or calibration error. These errors can be avoided by careful reading and following each step of the standardized operating procedure, identifying the critical points of the technical assay [7]. Advocacy to reduce the administrative procedures for customs clearance for the mail sent by EQA can be useful to reduce the issues from quality. Other studies have shown that education and training of laboratory personnel can improve the quality of test results [8].

IQC is implemented in a laboratory to detect in real time any malfunction that may occur in order to take the necessary corrective actions [9]. IQC materials must be a commercialized control plasma of known values (high, normal or low) or prepared by the laboratory and are to the closest possible from a patient's sample. In this study, the laboratory used as QC material a pool of normal plasmas. Its advantages are limitation for cost allocated for commercialized QC material, no reconstitution errors. But the disadvantage of this control is the stability and the expiration period which are not reliable. The storage condition may be affected by the laboratory environment. These labs manufactured QC are stable one month at -20°C for one month, according to a study conducted in 2021 [10].

Precision corresponds to the perfect agreement between repeated measurements on the same sample. It characterizes the dispersion of the values obtained during repeated measurements on the same sample by taking into account factors such as operator, time, reagent batches, calibrations. It can be quantified by the standard deviation (SD) or the coefficient of variation (CV). In this study, CV was used for precision's analysis and showed 2 out-of-control values (CV > 5%). Lack of precision is mostly indicative of a random error [3]. They are most often detected by the violation of 1_{2s}, 1_{3s}, R_{4s} Westgard's rules. Random errors can be related to the operator (incorrect execution of the measurement process or non-observance of instrument maintenance), to the reagents (batch change or deterioration of the reagent during storage or use), to the instruments (dysfunction of the sampling system, of the reaction medium mixing process, of the photometer, dirty cuvettes) [2]. Corrective actions have been conducted regarding the pipetting qualities and instrument's laboratory checking (temperature, reaction vessels, metal beads). This type of error in general does not reflect a defect in the analysis system, and therefore is not expected to be repeated.

Accuracy indicates the closeness of agreement between the mean value obtained from a series of test results and a value that is accepted as either a conventionally true value or an accepted reference value. It can be quantified by calculating bias which is a percentage deviation from the expected value.

In this study, all values were in-control (Bias < 10%). Lack of accuracy of the analytical process is most indicative of a systematic error [3] Systematic error is detected as soon as a change in the mean of the control value appears. This change in the mean may be gradual and appear as a drift or it may be sudden and come out as an offset. A drift indicates a progressive loss of reliability in the analytical system. Drifts are usually subtle [11]. A shift occurs when there is an abrupt change in the control mean. Shifts in quality control data represent a sudden, large, positive or negative change in the performance of the analytical system [11]. These errors are most commonly evidenced by violation of the 2_{2S}, 4_{1S}, and 10x Westgard rules. Inaccuracy of IQC results in a laboratory can also be related to reagents, equipment, personnel, calibration and internal control procedures.

Conclusion:-

Quality control program in hematology laboratory at CHU-JRA Antananarivo Madagascar is well-established despite several issues in EQA materials' transportation, lab's technical facilities resulting in random or systematic errors. Each out-of-control results have to be analyzed as part of strengthening quality program guaranteeing coagulation tests' reliability.

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Disclosure of interest:

Authors declare no conflict of interest in this manuscript's publication.

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