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Is it true hypoparathyroidism? A root cause analysis of unusually low Intact Parathyroid Hormone (iPTH) at a clinical laboratory

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ABSTRACT

Introduction

Intact Parathyroid Hormone (iPTH) has a short half-life i.e. two to four minutes therefore the sampling regimen has to pass through a stringent pre-analytical process control. The aim of this study was to identify the causes of apparently falsely low iPTH encountered while signing out Laboratory reports by the Clinical Chemistry professionals.

Material and methods

This report was conducted at the section of Clinical Chemistry, The Aga Khan University Hospital (AKUH) Karachi Pakistan from July to December 2017. Audit tool utilized was Plan-Do-Check-Act Cycle. After correlating with available clinical details and lab parameters, all low iPTH values (<16 pg/ml) were investigated by phone interview. A fresh sample was requested for non-correlating cases.

Appropriate interventions were undertaken and a re-assessment was done from January to March 2018.

Results

During the audit, 2559 iPTH samples were analyzed. 110 (4.3%) were identified as apparently falsely low. After recollection, the above 110 samples were immediately centrifuged, and cold chain maintained until re-analysis. 60 (2.4%) resulted with normal or elevated levels. The causes identified were poor compliance of staff with pre-analytical steps including delayed sample separation and unfavorable temperature chain maintenance. Interventions included online meetings with the staff country-wide and circulation of flyers detailing the pre-analytical steps via emails and hard copies. Re-audit showed reduction in number of apparently falsely low results to 30 out of a total of 1448 samples and 14 (0.96%) were investigated to be falsely low.

Conclusion

Stringent pre-analytical process control is vital for quality reporting and patient safety.

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INTRODUCTION

Parathyroid hormone (PTH) is a biologically active 84 amino acid peptide hormone, which serves various vital physiological roles in the human circulation but more extensively appraised in literature as a regulator of bone metabolism. Specifically, it functions to enhance renal reabsorption of calcium, bone resorption and activation of vitamin D, whereas has inhibitory effect on renal phosphate reabsorption, bone turnover and mineralization (1).

A number of circulating molecular forms of PTH have been identified namely the fragment containing carboxyl (C) - or amino (N)-terminal portions of the molecule that results from either intra-glandular or peripheral degradation of the hormone, but their biological significance is ill-defined (2). Starting from the second half of the 20th century the first generation of radioimmunoassays were pioneers to measure PTH activity but suffered from certain limitations including lack of diagnostic accuracy. Second generation immunometric assays (IMAs) are graded as specific for the whole PTH molecule (3).

From a global perspective, PTH measurements are now routinely carried out on the second-generation assays for the diagnosis and management of hypo-parathyroidism and hyperparathyroidism (4, 5). The widely used IMA two-site sandwich assays, characteristically termed as “intact PTH” (iPTH) assays, recognize the intact as well as large C-terminal fragments as they employ a capture antibody against the C-terminal part of the PTH molecule and a radioiodinated detection antibody directed towards the N-terminal portion of PTH (6). Improved clinical specificity of third generation assays has not yet been widely established and they are not in widespread use (7).

Addressing the pre-analytics, iPTH is a relatively unstable hormone possessing a plasma half-life of two to four minutes (8). Stability differs depending on sample type, whether fresh frozen or lyophilized etc. It is therefore imperative for clinical laboratories to specify the preferred specimen type and to provide clear advice about storage if specimens are not assayed immediately (9). A study has reported bovine thrombin in rapid serum tubes to decrease PTH compared to serum separator tubes by 14.1% after 4 hours at room temperature (10). Furthermore, there is inconsistent evidence in literature regarding the potential effects of serum separator tubes on iPTH measurement. Other potential influences beyond the control of laboratory are prior

food intake, vegetarian diet, strenuous exercise, gender, race and menopausal status (1).

While signing out laboratory reports the Clinical Chemistry Consultants were encountering an unusually high number of iPTH results that were below the reference interval and not correlating with other laboratory parameters and clinical details. The aim of this audit was to identify the causes of apparently falsely low iPTH and rectify the root cause.

MATERIAL AND METHODS

This study was conducted within the section of Clinical Chemistry, Department of Pathology and Laboratory Medicine, The Aga Khan University Hospital (AKUH) Karachi Pakistan from July to December 2017. The clinical laboratory of AKUH is accredited by the College of American Pathologists and has more than 10 stat laboratories and a network of 264 phlebotomy stations and collection points across Pakistan. This study was approved by the departmental quality management committee (DQMC) of Pathology & Laboratory Medicine, AKUH. Samples for iPTH analysis from across the country are transported following the appropriate protocol i.e. 3-5 cc of venous blood sample in ethylenediaminetetraacetic acid (EDTA K_2) tube is collected and subjected to immediate centrifugation at 3000 *g* for 15 minutes, frozen and sent in dry ice to main campus in Karachi. Main campus is the hub of AKU clinical laboratories for analysis at the clinical chemistry section.

The iPTH was analyzed on Siemens IMMULITE 2000 a solid-phase, two-site chemiluminescent enzyme-labeled immunometric assay (Siemens diagnostics USA). In our laboratory all internal quality control, validation and proficiency testing are accomplished according to Clinical and Laboratory Standards Institution (CLSI) guidelines (11). Two levels of commercially available controls were run with each batch.

Audit tool utilized was Plan-Do-Check-Act Cycle. In the planning phase the audit team comprising of three Consultant Chemical Pathologists and a laboratory technologist prospectively reviewed and discussed all cases with low iPTH (<16 pg/ml). In the next phase after correlating with available clinical details and laboratory parameters including 25-OH-Vitamin D and serum calcium, clinical history was obtained by phone call for all low iPTHs (<16 pg/ml). In order to appropriately correlate the clinical history with the iPTH results the sectional post graduate residents were trained using direct lecture methodology and an hour teaching session by a Consultant Chemical Pathologist was taken. This session was centered across a refresher of the pre-analytical and analytical steps for serum iPTH and clinical indications of iPTH alongside causes of low iPTH were also reviewed. They were further directed to request a fresh sample for confirmation of the results for non-correlating cases based on the clinical history and other laboratory parameters after independent consultation by at least two Consultant Chemical Pathologists. The findings were presented in the DQMC meeting as a potential patient safety issue and meetings minutes were recorded. Grounded on the findings analyzed appropriate interventions were undertaken and implemented for the entire network of the clinical laboratory and re-audit was done from January to March 2018 to check the compliance and the outcome. Data was analyzed using Microsoft Excel version 2013.

RESULTS

Audit findings

During the audit period, 2559 iPTH samples were analyzed, 2242 were out-patients and 317 were in-patients. Inpatients' samples were collected at the main AKUH and outpatients' samples were received from phlebotomy centers

in Karachi and also from phlebotomy centers across Pakistan for the months of July to December 2017.

The audit tool utilized i.e. the Plan-Do-Check-Act Cycle is summarized in Figure 1. After correlating with available clinical details and laboratory parameters including 25-OH-Vitamin D, serum calcium and, based on telephonic history, 110 (4.3%) were identified as apparently falsely low by the two independent Pathologists.

On re-analysis of a fresh sample under instructions of immediate centrifugation and cold chain maintenance, 60 (2.4%) were found to have normal or elevated levels with respect to reference intervals used.

Gap analysis

A few Phlebotomy centers staff were not aware regarding the sample stability of plasma iPTH, furthermore delayed centrifugation was also evident in most cases. Specimens collected at main campus laboratory were not being delivered to the laboratory labelled as STAT leading to delayed centrifugation and analysis. Samples drawn and collected outside the laboratory collection unit i.e. at different patient care facilities and home were being received at the collection units with unfavorable temperature control and without appropriate transportation protocol. The root causes are depicted with the Ishikawa diagram in Figure 2.

Corrective actions

An online meeting regarding iPTH sampling collection and transportation issues was held by the audits team and laboratory manager with regional managers/coordinators in which refresher was given on sample collection of iPTH; all people were asked to reinforce it in their respective areas. In this meeting detailed pre-analytical steps were outlined, and number of discordant results were shared with the respective regions. The regional managers/coordinators were directed to take a verbal pre-test of the phlebotomist at their respective regions regarding the pre-analytical steps of iPTH and provide feedback and educate. The flyer with pictorial description of pre-analytical steps of iPTH for easy comprehension was circulated to all phlebotomy centers by laboratory manager via email and hard copy as shown in Figure 3. The flyer was designed in line with ACB recommendations for iPTH which emphasize that as PTH is labile; serum or plasma should be separated as soon as possible, preferably using a refrigerated centrifuge (12).

Furthermore, it encompasses the step-by-step process from collection of 3-5 cc blood sample in EDTA k_2 (purple top) tube, followed by cold chain maintenance as specimen must be kept cold (2–8°C) through the collection & separation process. Separated Plasma specimen should be stored at -20°C and should be transported to the laboratory for analysis in frozen condition with dry ice.

Two follow-up meetings were repeated in the subsequent months and compliance data was shared and feedback was given. The laboratory manager issued a memo that all inpatient iPTH samples should be transported directly to the Clinical Chemistry section for immediate processing and analysis rather than being transported to the main laboratory and further routed to the section.

Phlebotomy staff at main laboratory were reinforced to send all iPTH samples collected from outpatients at main laboratory to the section of Clinical Chemistry in ice immediately labelled as STAT. Clinical Chemistry processing bench staff were reinforced to processes all iPTH specimens immediately as STAT specimen on receipt in the section for immediate analysis.

Figure 1 Plan - Do - Check - Act - Cycle

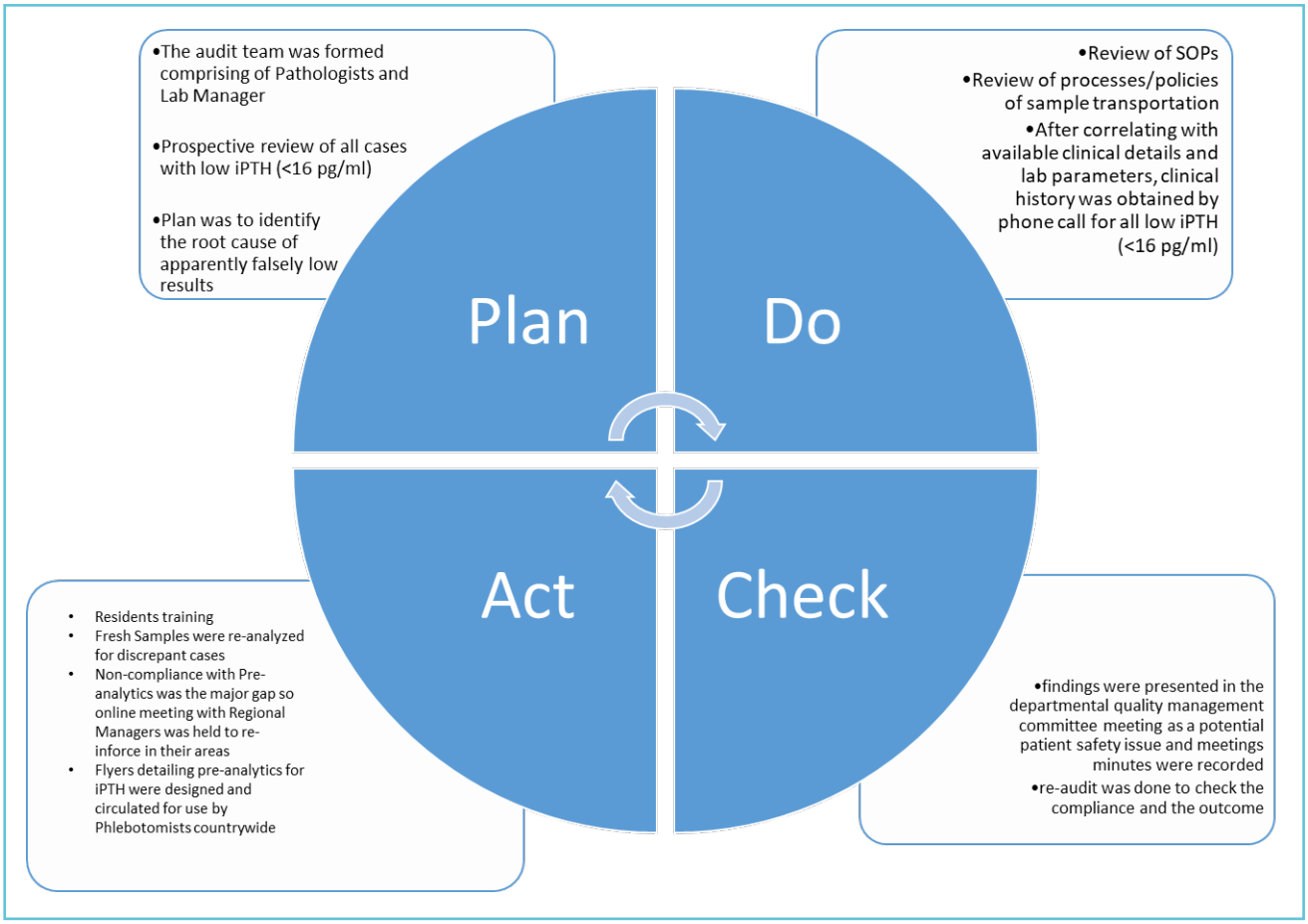


Figure 2 Ishikawa diagram depicting the major causes and consequences

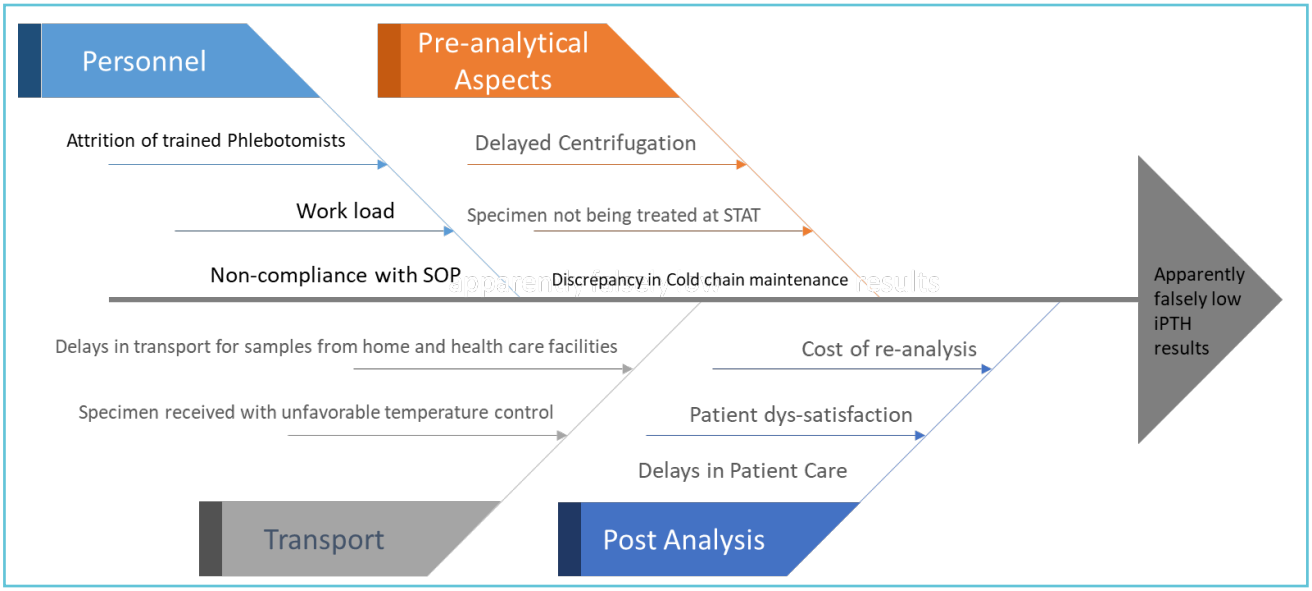
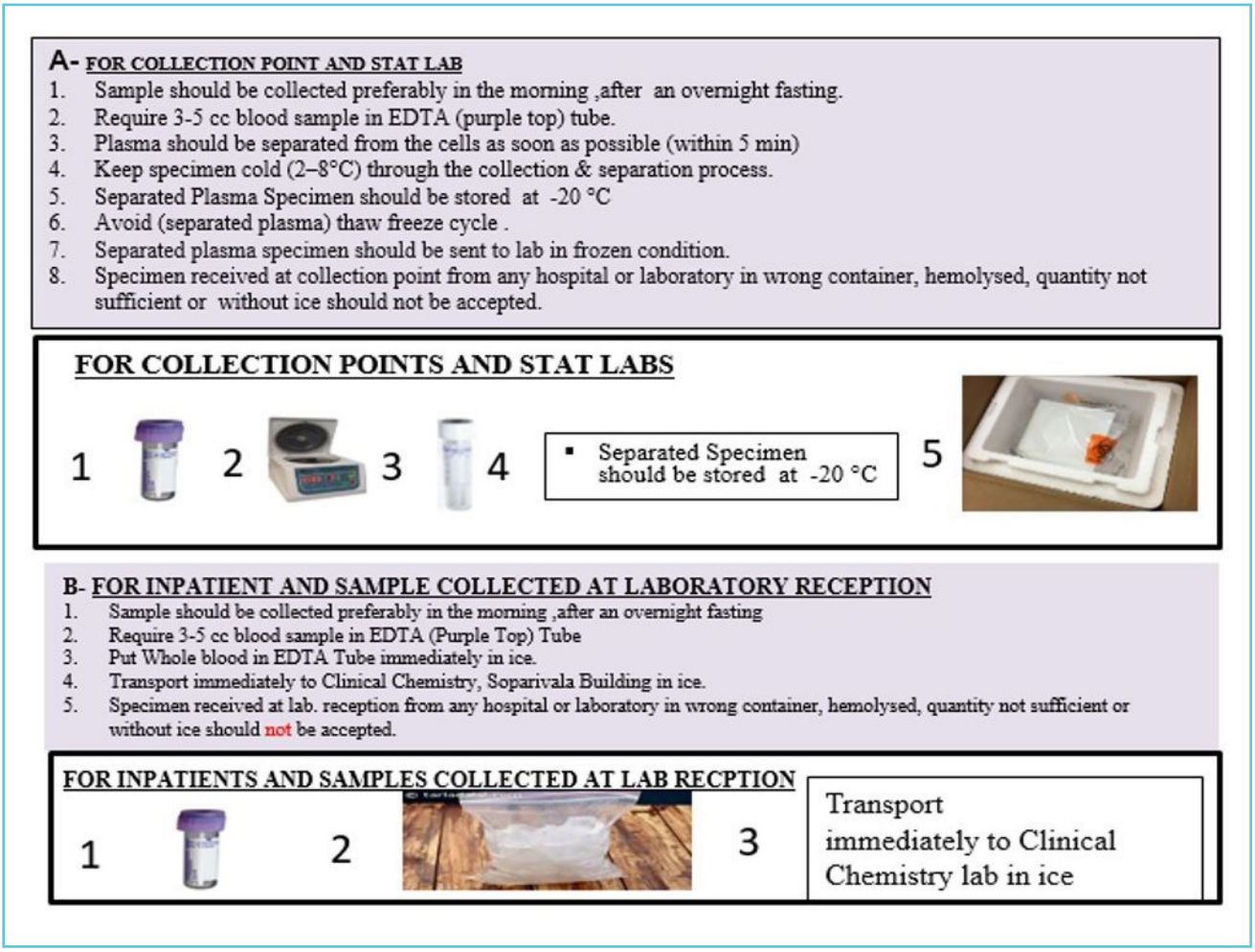


Figure 3 iPTH (Intact Parathyroid Hormone) specimen collection guide – flyer circulated for staff countrywide



Re-audit

A re-audit was done in April, 2018 and data collected from January to March 2018 was critically reviewed and analyzed by the audit team.

During the re-audit period 1448 samples were analyzed for iPTH. After the implementation of corrective actions identified by the audit team a reduction in number of apparently falsely low results to 30 (2.1%) was recorded.

Furthermore, the rate of change in report was reduced by more than 50% from a total of 60 (2.4 %) in the audit phase to 14 (0.96%) in the re-audit phase. A significant difference was observed in the median iPTH before and after the corrective action from the different blood collection sites, being 58.4 (IQR: 25.02-265) and 66.2 (IQR: 30.6-221) respectively.

DISCUSSION

The backbone of a high-volume clinical laboratory functioning is laid on the pillars of total quality management in the laboratory process involving the pre-analytic, analytic, and post-analytic phases. It ensures the integrity of all the stages involved in producing laboratory results, initiating from test order entry to the final interpretation of reports issued, with attention

to reduce or eliminate the errors that may arise during the various steps (13). Establishment of ideal sample collection and processing protocols and compliance with the sample transport guidelines are a pre-requisite for the standard operating protocols (SOPs) for a clinical laboratory (14).

Pre-analytical errors have been reported in literature as a leading proportion of errors in laboratory processes and cause disruption in the assurance of patient safety (15). Moreover, failures in following the best practices of quality management can inflict potential harm to patient safety and dys-satisfaction of requesting physicians (16). The International Federation of Clinical Chemistry (IFCC) Working Group on laboratory errors and patient safety has defined a number of quality indicators for the pre-analytical stage in order to ensure continual quality improvement (17).

This study was planned in keeping with the view that the clinical audits are an essential element of a laboratory's quality management system and should include scheduled and timely inspections (18). Our audit showed a rate of 2.4% pre-analytical errors as depicted in Figure 2, pertaining to varied phlebotomy practices with non-adherence to pre-requisites, transportation errors particularly for specimens brought to the phlebotomy centers from homes and other patient care facilities and samples received from in-patient areas without cold chain maintenance.

The knowledge gaps of phlebotomists were linked with the high attrition rate, as with a widespread network of phlebotomy centers where the staff turnover is a potential confounder.

When planning corrective actions to control error rates, a 'system'-based approach has been shown to be effective rather than an 'individual' approach (19). This study was undertaken accordingly, with emphasis on the check of total laboratory processes, and after collecting data on the flaws that in the pre-analytical processes were identified as opportunities for improvement.

Previous research has shown that online learning and use of effective teaching modalities, like flyers with pictorial depiction of the process for awareness and reinforcement of key steps, prove effective and improves productivity (20, 21). Using the same strategy the timely online meetings with the staff by the audit team and circulation of flyers proved to be effective as unveiled by the reduction in error rates, able to improve patient safety.

Furthermore, repeat test requests lead to patient dissatisfaction and increase laboratory expenditure with negative effects on patient outcomes particularly linked to delays in reporting (22). The corrective actions can lead to substantial improvement in the rate of errors and patient safety can be improved alongside cost cutting of repeat analysis for the clinical laboratory.

Although the re-audit showed noteworthy improvement, still the highest benchmark was not achieved. The audit team recommended that as quality improvement should be a continuous process, timely checks should be done and staff education and reinforcement of appropriate pre-analytics should be regularly scheduled to achieve the highest targets of quality. This strategy based on regular online meetings at virtually no cost and circulation of flyers served as a possible resource pack for continued education in order to attain highest levels of quality and compliance.

The results were shared in the departmental quality management committee meeting and it was decided to include monitoring of falsely low iPTH in the key performance indicators in order to ensure compliance and achieve a near zero target of falsely low results.

CONCLUSION

Since iPTH has a short life, stringent pre-analytical process control is vital for appropriate analysis and result reporting. For improving the pre-analytical quality control regularly scheduled clinical audits, online feedbacks and meetings with staff at outreach phlebotomy centers and refresher based educational activities proved to be beneficial and led to attainment of optimal outcomes alongside a momentous and sustained reduction in laboratory errors. The clinical audit driven interventions catalyzed a commitment to improve pre-analytical error control across the umbrella of a high-volume clinical laboratory, ultimately leading to improved patient safety, end user satisfaction and cost-effectiveness for all stakeholders.

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Disclosure

This study was presented as a poster presentation at the 5th EFLM Conference on Pre-analytical Phase, held in Zagreb, Croatia, 22-23 March 2019.

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