Journal of Diabetic Association Medical College 2023;7(1)34-39

Review Article

Pre-analytical Variables: A Potential Source of Laboratory Error

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Abstract

Clinical laboratories have a great role in the management of patients. To ensure quality test results laboratories need to maintain standards in all the three phase of total testing process- pre analytical, analytical and post-analytical. With the advancement of modern technologies analytical and post-analytical errors have been reduced significantly but pre-analytical errors are still very common, which can be as high as 71% of total error rate. This is because; many of the steps in this phase are related to human activities and outside of the laboratories that are not under the direct control of laboratory. Pre-analytical errors can occur during test ordering by the physicians, patient preparation, sample collection, transportation or during processing of the sample. Though most of the errors in this phase remain within the reference limit but 25% can produce erroneous results that can affect patient health. In order to minimize errors in this phase it is mandatory to check and identify the sources of pre-analytical errors.

Key words: Pre-analytical variables, Laboratory error, Interference

Introduction

Laboratory test results play very important role in the clinical decision making process. Any errors in the test results have serious consequences in terms of diagnosis, treatment and prognosis of the patients. With the increasing number of laboratory tests day by day, the opportunity of error also increases. These errors can occur in any of the three phases of total testing process: the pre-analytic, analytic and post analytic phases. This process begins as the clinician determines the need for a laboratory test and ends with the interpretation of test results. The paper highlights errors in various steps of pre- analytical phases, sources of pre-analytical variation and its impact on patient's health.

Pre-analytical phase

Pre-analytical phase extends from the time of test ordering by the clinician until the sample is ready for analysis. With the advancement of the instrument technology and automation, analytical error rate has been reduced remarkably but the pre-analytical phase remains the most vulnerable part of the total testing process.Pre-analytical error may occur at any step of this phase- like during test requesting, patient preparation, sample collection, sample transport, handling and storage.[1]Some of these steps are performed outside the laboratory and are not under the direct supervision of laboratory stuff. These wide ranges of activities, location and personnel involved in this phase increase the chance of error to occur. According to some study pre-analytical error accounts for 46% – 71%of all the errorsoccurring in the laboratory services.[2,3]A clear understanding about the sequence of events in laboratory testing is essential to identify the sources of pre-analytical error.

Sources of pre-analytical variation are as follows:

A) Test order: Errors in the laboratory order commonly occurs due to-

- Inappropriate laboratory test requisition which may originate from similarities of the test name or improper use of synonyms.
- Incomplete laboratory request form also can contribute to the laboratory error especially for the tests that require additional clinical information.
- Incomplete entry of orders into the hospital electronic computer system.
- Transcription entry error occurs where orders are manually transcribed from written notes or requisition, such as outpatient location or specimen receiving section. Also, physicians sometimes verbally dictate their test orders to interns or nursing stuffs who transcribe the tests onto requisition form.College of American Pathologists (CAP) Q-probes studied upon 660 institutes and estimated that 4.8% of physician requests were associated with one or more data entry errors.[4] In a single centered study done in Australia it was found that 75% of total laboratory error were caused by transcription error which ultimately led to wrong test or missing test.[5]

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B) Patient preparation: After placing a correct order, patient must be prepared for the specific test so that results can be properly interpreted. There are many factors regarding patientthat can affect the test results.

- Diet: Diet (number of meal, sources and proportion of a nutrient in diet, vegetarianism, starvation etc) is well known variable that can affect plasma composition. There are both long term and acute effects of diet on many analytes. After ingestion of cooked fish serum creatinine concentration increasessignificantly while eGFR decreases from the baseline value[6]. It also increases blood urea level. Now it is well known that ahigh calorie diet increases serum triglyceride level.[7]Serum triglyceride and cholesterol level is also influenced by physical activity, smoking, consumption of alcohol and coffee.[8]Moreover, activity of some enzymes like ALT, AST, and ALPmay also increaseup to 20% following a meal.

- Fluid intake: Intake of various fluid may also exert acute and chronic effect. Caffeine which is found in tea & coffee increases plasma glucose concentration by increasing free cortisol level. It also induces diuresis with loss of electrolytes through urine. Urinary loss of water and electrolytes specially calcium and magnesium increases within 2 hours after caffeine ingestion.[9] Caffeine also increases lipid catabolism thus increases the plasma total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol.[10]Another important factor is alcohol that markedly affect the concentration of some analytes depending on the duration and extent of its consumption. Plasma glucose decreases and lactate increases significantly after consumption of alcohol.[11] Alcohol also stimulate hepatic uric acid synthesis by enhancing adenine nucleotide degradation thus increasing plasma uric acid level.[12]Chronic alcohol ingestion is associated with an increase in serum GGT, AST & ALT level. Serum ferritin level also increases in chronic alcoholism.[13-15]

- Tobacco smoking: Smoking leads to a number of acute and chronic changes in some analyte concentration. Glucose concentration dramatically rises by 10 mg/dl after 10 minutes of smoking a single cigarette and it can persist for one hour. Current smokers also showed high fasting and post prandial plasma glucose concentration than ex-smokers or non-smokers.[16,17]Smoking also leads to acute increase in serum triglyceride, LDL and total cholesterol concentration whereas it decreases plasma HDL cholesterol.[18-20]Heavy smokers have high level of liver enzymes in plasma but low total plasma protein and albumin.[21,22] Smoking tobacco also have chronic effect on leukocyte count, some tumor marker, vitamins, heavy metals etc.

- Muscular activity: Physical activity also affects several plasma analytes. They are markedly influenced by the type, intensity and duration of exercise, level of training and time of recovery after training.[23]Simply, repeated clenching of fist during venous blood collection may increase the plasma potassium concentration by 1-2 mmol/L.[24]Intensive exercise transiently increases many common biochemical markers like cardiac biomarkers, markers of muscle damage.Exercise greater than 12 hours per week may increase plasma CK-MB & LDH. After bicycle stress test cardiac troponin also rises.[25-27]It should be remembered that in case of professional sportsman a large proportion of laboratory results may fall outside the usual reference range to avoid the misinterpretation.

- Influence of circadian rhythm: Several hormones and other analytes tend to change in plasma concentration throughout the course of the day due to various reason. Some of them may vary up to maximum 30%.[28] It is well known that serum cortisol level increases in the morning than decline throughout the day. Serum potassium and iron levelsare also found to be high in the morning than the evening.[29,30]

- Menstrual cycle: Analytes can show significant changes due to the hormonal fluctuations during the menstrual cycle. Aldosterone could be high as twice just before ovulation while plasma cholesterol decreases during ovulation. Plasma iron and phosphate level decreases during menstruation.[31]

- Influence of therapeutic procedures: Severaltherapeutic procedureslike- infusions &transfusions, dialysis and ionizing radiation have significant effect on laboratory tests. To ensure maximum quality the exact time regarding procedure should be documented and interpretation must be done accordingly.

C) Specimen collection: Once the patient is appropriately prepared for the test, a proper specimen must be collected at a suitable time. During specimen collection there are many small steps which can be a source of wrong test results.

- Patient identification:It is mandatory before any specimen collection. The Joint Commission recommends the use of two unique identifiers to confirm the identity of a patient.[32]

- Body position of patient during sample collection: Body posture influences blood constituents. Changing posture from supine to upright position may lead to increase in serum albumin, total protein, ALP,GGT, LDH, total bilirubin, triglyceride level by more than 10%.[33]

- Labeling of the container: Wrong labeling of the

sample is another area of pre-analytical error that ultimately warrant to recollect the specimen.

- Tube type or order of draw: There are a number of tubes available for specimen collection. Some of them contain additives or clot activator, other contain preservative or anticoagulant. Color of the stopper indicates different types of additives each poses specific test limitations. Collection of specimen in the correct tube is mandatory. False hyperkalemia or hypocalcemia may be seen when blood is collected in potassium EDTA tube.[34,35]During collecting multiple specimens proper order should be maintained to avoid cross contamination. Wrong order of tube used for specimen collection can lead to further pre-analytical error.

- Prolonged use of tourniquet: Use of a tourniquet for over 1-3 minutes can cause elevation in protein, calcium and potassium. After 5 minute total calcium level rises significantly.[36]

- Collection from IV line or catheter: Collection of specimen from a IV line results indilution effect for most of the analytes.[37] It also can cause contamination and hemolysis of the samples.[38]

- Inadequate tube filling: Inadequate or incomplete tube filling specially in vacuum tube where vacuum may persist causes micro hemolysis and affect some test results.[39]

D) Transportation, processing and storage of sample: After collection of specimen it should be transported and processed as soon as possible. Transportation is a major part of pre-analytical phase & can be crucial in delaying laboratory results.[40]If transport to a referral laboratory take longer time, then serum should be separated &the temperature should be maintained because in room temperature many analytesare unstable in unprocessed blood.[41]After receiving specimen in the laboratory it should be centrifuged and serum or plasma are separated. Centrifugation must be done only once because re-centrifugation can release cellular components.Laboratory should seek to process blood by centrifugation within 30 to 60 minute of collection and stored at 4°C in the refrigerator until analysis.If longer storage is required, then serum is stored at -20°Cwith maintaining the temperature. Whole blood should not be stored in the refrigerator rather it should be preserved in room temperature if centrifugation is delayed. Prolonged storage of sample leads to alterations in the concentration of analytes.[42]

E) Noncontrollable variables: There are some biological factors that cannot be avoided rather they should be considered during the interpretation of results.Due to changes during growth and development reference ranges differ with respect of an individual's age and gender. Some biological markers increase while others decrease within first two weeks of life. Some changes are significant during puberty. Gender differences are related to lower metabolic demand, decreased muscle mass etc.[43,44]

F) Interference factors: These factors interfere with the analytical procedure and alter the test results. Common interference factors are hemolysis, lipemia, icterus and drugs.

- Hemolysis: It is the most common pre-analytical error which can be as high as 3.8% of all the routine samples, accounting for 40% to 70% of all unsuitable specimen.[45,46]Frequency of hemolysis largely depends on the collection facility, characteristics of patient population and type and skill of professional who is doing the phlebotomy. Highest hemolysis frequency has been found in samples from emergency department, pediatric department and internal medicine. Lowest frequency was found in outpatient phlebotomy center where trained phlebotomist draws the blood.[47,48] Hemolysis can occur in vivo or in vitro though in vivo hemolysis is not common. In vitro hemolysis ismainly caused by the factors associated with collection of blood, whereas transportation, processing and storage of blood specimen account for a minority of cases. Most frequently found cause of specimen hemolysis is vigorously drawn blood through needle.[49]It affects the laboratory results by releasing the cell components into the sample.Grossly hemolyzed sample alter almost all the analytes. Clinically meaningful variations of AST, LDH and potassium can be observed in samples with mild or almost undetectable hemolysis by visual inspection.[50]

- Lipemia: It is the most common and important endogenous interference which affect laboratory results. Turbidity in lipemic sample iscaused by the presence of large lipoprotein particles which may occur due to postprandial triglyceride increase, parenteral lipid infusion or some lipid disorder.[51] Lipemia causes interference by light absorption & light scattering, volume depletion effect and partitioning effect.[52] All the serum analytes are affected by lipemia at varying levels but it causes clinically significant interferences for phosphorus, creatinine, total protein, calcium and iron.[53-55]

- Icterus:Increased bilirubin in serum interferes by two mechanism- spectrophotometric interference and chemical reaction. It interferes with numerous biochemical tests like enzymes (ALT, ALP), electrolytes, creatinine,total protein, cholesterol, triglyceride etc.[52,56]

- Drug interference:Drugs as exogenous substance can interfere by different mechanisms and influence test results. Most of the drugs invariably interfere with different analytes: either by falsely increasing

or decreasing the concentration or affecting the actual concentration. Some commonly prescribed antibiotics and analgesics interfere with analytese.g. cephalosporin can falsely elevate serum creatinine level after its intravenous administration, paracetamol can increase serum uric acid level.[52,57,58]

Impact on patient health

It can be easily understood that the effect of pre-analytical errors on patient health can be dangerous in respect to misdiagnosis which may lead to unnecessary operative procedures, prolonged hospital stays or repetition of test. Though 75% errors can produce results within reference range that cannot be easily identified but 12.5% may have effect on patient management and another 12.5% produce wrong results that are so illogical to be considered clinically and are rejected.[59]

Conclusion

Most of the errors in laboratory services occur in the pre-analytical phase; therefore, it is very important to identify them in order to prevent errors in test results. All the laboratory personnel should have adequate knowledge about each step of pre-analytical phase. Proper test ordering, ideal patient preparation, correct and adequate specimen collection, rapid processing and transportation of sample can reduce the pre-analytical error rate thus helps towards improved interpretations of test results.

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