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In Vitro Sample Hemolysis in Chemistry Laboratories and Its Challenges

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About Article

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ABSTRACT

Hemolysis is an old and new challenging preanalytical cause of errors in chemistry laboratories, and there is a lot of controversy as regards it; also, it is the number one cause of sample rejection in chemistry laboratories. In this review, we try to spotlight the causes, how to detect hemolytic samples, how hemolysis can affect analytical assays, the biochemical effect of hemolysis on chemistry analytes, and how to reduce errors related to hemolysis. In this narrative review We aimed to understand the causes of invitro hemolysis, to clarify how to detect it precisely, to outline how hemolysis affect the chemistry lab results and its effect on clinical decision, when to accept or reject the hemolyzed chemistry sample and spotlight on how to reduce hemolysis and its effect on the chemistry results. We conclude that, Hemolysis interferes with numerous biochemical parameters, primarily potassium, AST, LDH and CK-MB, either by falsification or modification of the respective concentrations. The interference can be reduced by using standardized collection techniques, using HIL indices, and regular training of personnel.

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1. INTRODUCTION

Hemolysis is one of the most important sources of errors in clinical chemistry laboratories because of its ability to influence test reliability (Wan Azman *et al.*, 2019). Hemolysis is the major reason for rejection of samples in laboratory practice and contributes to 70% of unsatisfactory specimens (Giuseppe Lippi *et al.*, 2008; Wan Azman *et al.*, 2019). There are many challenges when dealing with a hemolyzed sample. Should the sample be accepted at the expense of the accuracy of the results, or should it be rejected, which in turn leads to delayed results? which can be dangerous, especially in critical situations that require rapid intervention or decision-making. Therefore, in this narrative review, we attempt to understand the causes and effects of hemolysis on chemical analyses and the accuracy of results. We also explore how to deal with a hemolyzed sample, when to accept and reject the sample, and its prevention strategies.

2. LITERATURE REVIEW

Hemolysis is defined as the destruction of red blood cells (RBCs) and subsequent release of intracellular constituents, such as hemoglobin (Hb), electrolytes, and enzymes, into the surrounding plasma or serum (Wan Azman *et al.*, 2019). Hemolysis can occur either in vitro or in vivo (Marques-Garcia, 2020; Wan Azman *et al.*, 2019). In vivo: Inside the body, frequently in disease conditions such as hemolytic anemias or transfusion reactions (Loriamini *et al.*, 2024). In vitro: During or post specimen collection due to inappropriate methods or handling of specimen (Heireman *et al.*, 2017) .

3. METHODOLOGY

The type of this study is a narrative review article. This study was conducted by searching relevant review literature in medical databases which include Google Scholar, PubMed, ScienceDirect, etc. We use relevant keywords (in vitro hemolysis, preanalytical errors, HIL indices, etc.); inclusion criteria consider studies in English in years between 2005 and 2025, especially peer-reviewed articles and regulatory scientific institutions standards and guidelines, such as those of the CDC (Centers for Disease Control and Prevention) and CLSI (Clinical and Laboratory Standards Institute). We aimed to understand the causes of in vitro hemolysis, to clarify how to detect hemolysis precisely, to outline how hemolysis affects the chemistry lab results and its effect on clinical decisions, to underline when to accept or reject the hemolyzed chemistry sample and to spotlight how to reduce hemolysis and its effect on the chemistry results.

4. RESULTS AND DISCUSSION

As regard Causes of Hemolysis in the Laboratory: there are Several factors contribute to in vitro hemolysis (Marques-Garcia, 2020): Improper sample extraction techniques (include Collecting samples from small veins in sites other than “antecubital area”, as veins in the antecubital area veins are larger and easy to access, use of prolonged tourniquet, using too small gauge needles, also Collecting samples from the IV catheter (Ersoy *et al.*, 2023; Ialongo & Bernardini, 2016). Sample Handling Errors (include excessive force during blood draw, excessive suction, Pulling or pushing on the plunger exerts pressure on RBC’s, causing RBCs to break, vigorous shaking, improper tube mixing, incorrect filling of tubes (Marques-Garcia, 2020; Tolan *et al.*, 2016; Wan Azman *et al.*, 2019); If not allowing antiseptics to dry can damage red blood cells (Uy *et al.*, 2024; Wan Azman *et al.*, 2019); Delayed processing or improper storage temperatures can lead to cell rupture (Marques-Garcia, 2020; Tolan *et al.*, 2016); and Automated Transportation techniques which use pneumatic tube systems in transfer of samples from wards to laboratory without proper cushioning can causevigorous shaking of samples which may lead to cell lysis (Cadamuro *et al.*, 2021; Marques-Garcia, 2020; Streichert *et al.*, 2011).

Visual inspection of samples after centrifugation inspecting for presence of pink to red discoloration of plasma or serum that implies the presence of in-vitro hemolysis. But this method uncertain and subjective, especially in mild hemolysis (Hawkins, 2002; Lippi *et al.*, 2008). CDC provides lab professionals and phlebotomists a visual aid for determining the hemolysis of serum samples by comparing sample color with a series of standardized color tabs (Figure 1) (Centers for Disease & Prevention, 2024).

Automated HIL Indices: New clinical chemistry analyzers (e.g., Roche, Abbott, Beckman) use spectrophotometric methods to detect and measurethe degree of Hemolysis (H), Icterus (I), and Lipemia (L), which is more objective assessment for the degree of hemolysis(Clinical & Laboratory Standards, 2012a). Hemolysis Index (H): measures the amount of free hemoglobinin the sample by measure absorbance at cetain wavelengths (e.g., 570 nm). These modern chemistry machines usually report HIL indices on a semiquantitative score from 0 to 4+, which in proportion with increasing concentrations of the interfering substances(Clinical & Laboratory Standards, 2012a; Lippi *et al.*, 2006).

For example, on the Abbott Alinity c system: H Index: 0 (Hb < 30 mg/dL), 1+ (Hb about 30–100 mg/dL), 2+ (Hb about 100–200 mg/dL), 3+ (Hb about 200–500 mg/dL), 4+ (Hb ≥ 500 mg/dL)(Ho *et al.*, 2021).

Manual Hemoglobin Assay: Manual methods involve quantifying free hemoglobin in serum or plasma to assess hemolysis (Whitehead *et al.*, 2019).

4.1. How hemolysis interferes with laboratory analyses

Hemolysis can interfere with chemistry test assays by several mechanisms: 1st Release of Intracellular Analytes Substances such as potassium and lactate dehydrogenase (LDH) are abundant in red cells. Their release can falsely elevate serum levels (Oostendorp *et al.*, 2012; Wan Azman *et al.*, 2019); 2nd Spectrophotometric Interference: Free Hgb absorbs light at wavelengths often used in spectrophotometric assays (340–440 nm and 540–580 nm), thereby giving false elevated results of colorimetric assays (Dolci & Panteghini, 2013; Lippi & Plebani, 2020; Wang *et al.*, 2014; Whipple, 2020); and 3rd release of certain factors that interfere with the measuring Kit. For example, enzymes like adenylate kinase and glucose-6-phosphate interfere withCK assay can cause an false increase in serum CK activity (Whipple, 2020). These interferences, if not recognized and handled properly, maylead to inaccurate and error-ridden result.

4.2. Biochemical Effects of Hemolysis

The most commonly affected is potassium (K^+). RBCs have potassium concentrations approximately 20 times higher than plasma, so hemolysis can cause significant increases in measured potassium levels, potentially leading to misdiagnosis of hyperkalemia (ClinicalBasics Editorial, 2023; Wan Azman *et al.*, 2019), lactate Dehydrogenase (LDH) is abundant in RBCs, so hemolysis can result in elevated LDH levels, which may be misinterpreted as tissue damage or other pathological conditions (Needle.Tube Editorial, 2023; Wan Azman *et al.*, 2019), Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT): these liver enzymes are present in RBCs, hemolysis can lead to increased levels, potentially confounding assessments of liver function(Needle.Tube Editorial, 2023; Wan Azman *et al.*, 2019). Also, hemolysis causes iron and phosphorus release from RBCs, falsely elevating their serum levels (Maksymyuk *et al.*, 2023). Hemolysis causes minimal or no significant changes in sodium, chloride, calcium, creatinine, and glucose levels (Koseoglu *et al.*, 2011; Perović & Dolčić, 2019). Albumin, alkaline phosphatase (ALP), amylase, HDL-cholesterol, triglycerides, unsaturated iron binding capacity (UIBC), and uric acid are affected by but remain within the CLIA limits (Koseoglu *et al.*, 2011).

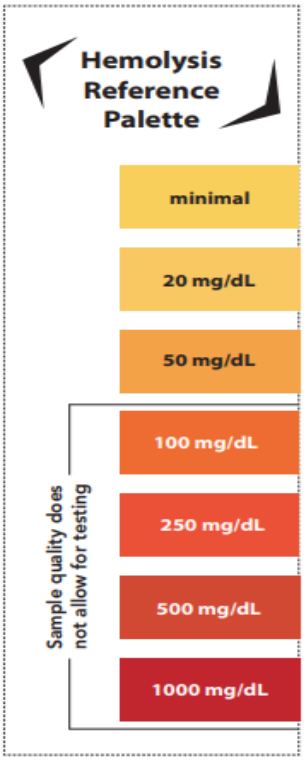

Figure 1. Color plate illustrating various degrees of hemolysis and corresponding hemoglobin (Hb) concentrations in mg/dL. Adapted from(Centers for Disease & Prevention, 2024)

4.3. The factors to consider when handling a hemolyzed sample are whether to accept or reject it

Knowing when to reject a hemolyzed blood sample is important for both accurate laboratory results and patient health. Hemolysis may cause significant interference with a number of laboratory tests, resulting in inaccurate test results. Laboratories need to weigh the value of accurate data with the potential risk of delaying reporting the result in situations when a sample is rejected (Wan Azman *et al.*, 2019). You have to take 3 considerations when you deal with a hemolyzed sample. 1st, the degree of hemolysis: Mildly hemolyzed samples are often acceptable for analysis, especially if the analyte is not significantly affected. Moderate to severe hemolyzed samples may necessitate rejection, particularly if the analyte is known to be sensitive to hemolysis (Giuseppe Lippi *et al.*, 2006). The hemolysis index (H-index) is usually used by chemistry labs to quantify the degree of hemolysis. For example, an H-index above 100 mg/dL may be considered moderate, while values exceeding 200 mg/dL are deemed severe (Goyal & Schmotzer, 2015), Adopt automated systems to objectively measure hemolysis levels, reducing reliance on subjective visual assessments (Goyal & Schmotzer, 2015; Plebani & Lippi, 2009). 2nd, the analyte sensitivity: Certain analytes are more susceptible to interference from hemolysis (Krasowski, 2019). Potassium, lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) are highly sensitive to hemolysis. Creatine kinase (CK) and alanine aminotransferase (ALT) are moderately sensitive to hemolysis(Mehmet Koseoglu *et al.*, 2011), while sodium, chloride, and glucose are less sensitive to hemolysis(Mehmet Koseoglu *et al.*, 2011; Krasowski, 2019). If the analyte in question is highly sensitive, sample rejection may mandate even with mild hemolysis (Kovacevic *et al.*, 2024). 3rd, the clinical situation: In some clinical contexts, the necessity for the data or result can be more important than the dangers of hemolysis. In order to avoid unnecessary treatment delays, results from hemolyzed specimens are sometimes reported with warnings (to discourage incorrect interpretation) in acute care or emergency settings (Badrick *et al.*, 2016; Wan Azman *et al.*, 2019). In case of repeat hemolysis or if multiple samples from the same patient are hemolyzed, in vivo hemolysis should be considered as a potential cause (Badrick *et al.*, 2016).

4.4. How to reduce hemolyzed samples

Optimizing Sample Collection Techniques: Research shows that utilizing straight needle venipuncture is better than intravenous (IV) catheter draws and significantly reduces hemolysis. Also, studies found that sample extraction from the antecubital fossa is better than distal venous sites for venipuncture, which diminishes hemolysis rates (Heyer *et al.*, 2012; Lowe *et al.*, 2008). Quality management: regular update of policies on optimizing how to deal with hemolysis regarding its detection, reporting, and specimen rejection criteria (Lippi *et al.*, 2018). At Health Care System, a 91% reduction in hemolysis rates from 9.8% to 0.88% over a three-month period was achieved by using a Lean Six Sigma project targeting the Emergency Care Center (ECC) (Damato & Rickard, 2015). Frameworks for quality improvement, such as Plan-Do-Check-Act (PDCA), should be used to show the magnitude of hemolysis-related challenges and estimate interventions' effectiveness (Taylor *et al.*, 2014). CLSI C56 advises laboratories to use clear criteria for rejecting hemolyzed samples, establish hemolysis index levels that necessitate sample rejection and describe procedures for sample recollection (Clinical & Laboratory Standards, 2012b). CLSI also states that in laboratories, HIL indices should be verified

within their chemistry machines. This includes estimating the accuracy of the automated HIL detection systems (Clinical & Laboratory Standards, 2024).

CME (Continuous medical education), training, and competency assessments: it is found that educational videos on sample collection led to a drop in the hemolysis index and in the number of hemolyzed specimens across various hospital units (de Koning *et al.*, 2023). Regular training sessions phlebotomists and nursing staff have been shown to decrease hemolysis rates significantly (Cadamuro *et al.*, 2016; Makhumula-Nkhoma *et al.*, 2019). Furthermore, evaluations of phlebotomy skills regularly to maintain high competency levels reduce the rate of hemolyzed sample (Coşkun *et al.*, 2024). Also CLSI guidelines, state that lab staff should take regular training and skill checks on how to deal with hemolysis, and they should know how to use automatic systems (HIL) that detect hemolysis (Clinical & Laboratory Standards, 2024).

Collecting Data and its Feedback: hemolysis data (number of rejections related to hemolysis, cause of hemolysis, etc.) should by collected and represented to allow laboratory mangers to identify trends and implement targeted special interventions. Sharing this data with phlebotomy teams and hospital leadership enhance hospital quality improvement (Almotairi *et al.*, 2025).

5. CONCLUSION

Hemolysis is still one of the largest preanalytical problems in clinical chemistry and causes wrong test results with subsequent incorrect diagnoses. It is caused by improper sample collection, improper preanalytical handling or processing, and transportation. Hemolysis interferes with numerous biochemical parameters, primarily potassium, AST, LDH, CK-MB, etc., either by falsification or modification of the respective concentrations. The interference can be reduced by using standardized collection techniques, using HIL indices on the automated analyzer to detect interference, and regular training of personnel. Well-defined rejection criteria and successful communication with the clinicians are necessary to obtain trustworthy results and patient safety.

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