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CASE REPORT

K_2EDTA vs K_3EDTA Stability in Yemen: Sysmex KX-21N Performance in Tropical Lab

Naif Taleb Ali*[1,2]

[1]*Department of Laboratory Sciences, University of Sciences and technology, Aden, Yemen*

[2]*Department of Laboratory Sciences, Radfan University College, Lahej University, Yemen*

***Corresponding author:** *Naif Taleb Ali, Department of Laboratory Sciences, University of Sciences and technology, Aden, Yemen*

Abstract

Background: Preanalytical variability in haematological testing due to anticoagulant choice remains poorly characterized in resource-limited tropical settings.

Objectives: To compare K_2EDTA and K_3EDTA effects on CBC parameters in Yemeni laboratories as a model for resource-limited tropical settings.

Methods: We conducted a prospective study of 100 venous blood samples from healthy adult male volunteers in Ad'Dla Governorate, Yemen, between January and March 2025. Samples were collected in duplicate using K_2EDTA and K_3EDTA tubes, analysed using a Sysmex KX-21N haematology analyser at baseline (T0) and after six hours of storage at 22 ± 2ºC (T6). Data were analysed using repeated-measures ANOVA and paired t-tests.

Results: Fresh samples showed high inter-anticoagulant concordance (ICC > 0.90).

After 6-hour storage, K_2EDTA exhibited significant MCV reduction (Δ = -2.33 FL, $p < 0.001$), while K_3EDTA showed greater RBC instability (Δ = -0.16 × 10^{12}/L, $p = 0.008$). Platelet activation markers increased in both anticoagulants ($p < 0.01$).

A novel bidirectional RDW-SD pattern emerged: K_2EDTA increased values (+1.71%) while K_3EDTA decreased them (-2.20%, both $p < 0.01$).

Conclusion: K_2EDTA demonstrates superior stability for delayed processing (> 2 hours), while K_3EDTA is preferable for immediate analysis.

What This Study Adds":

First Yemeni data demonstrating K_2EDTA's superior stability for delayed processing in tropical climates, supporting WHO standardization efforts.

These findings support protocol adjustments for African and Middle Eastern laboratories.

Keywords

Preanalytical variability, EDTA anticoagulants, Sysmex KX-21N, Haematology standardization, Resource-limited settings

Introduction

Haematological diagnostics occupy a central role in clinical decision-making, with the complete blood count (CBC) serving as a fundamental test for conditions ranging from anaemia to infection. However, the accuracy of CBC results is profoundly influenced by preanalytical variables, particularly the choice of anticoagulant and sample processing timelines (Lippi, 2017) [1]. While the International Council for Standardization in Haematology (ICSH) has established K_2EDTA as the recommended anticoagulant for CBC testing (ICSH, 2014) [2], practical realities in resource-limited settings often necessitate the use of alternatives such as K_3EDTA due to cost constraints and supply chain limitations (Al-Ashwal, 2019) [3], As highlighted by (Al-Maghrabi, 2023) [4], Middle Eastern laboratories face unique preanalytical challenges due to supply chain disruptions and climate extremes-factors our study directly addresses.

Emerging research has identified clinically significant differences between these anticoagulants. K_3EDTA has

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been associated with accelerated RBC shrinkage and haemolysis during storage (Tantanate and Klinhua, 2017) [5], while K_2EDTA may induce progressive platelet swelling that affects volume parameters (Banfi, 2007) [6]. These effects are exacerbated in tropical climates where elevated ambient temperatures accelerate cellular changes (Sapani, 2019) [7]. Compounding these challenges, most existing stability studies have focused on high-throughput analysers in temperate, well-resourced environments (Briggs, 2004) [8], creating a critical evidence gap for laboratories relying on compact systems like the Sysmex KX -21N - a workhorse instrument in many low-resource settings.

Recent studies confirm these gaps persist in tropical, resource-limited settings. For example, (Briggs, 2004) [8] demonstrated significant EDTA-dependent RBC instability in high-temperature environments (mean 30ºC), yet no studies have evaluated this in Yemen using compact analysers like the Sysmex KX-21N. Similarly, (Zhang, 2022) [9], identified differential platelet activation thresholds between K_2EDTA and K_3EDTA in delayed processing, but their findings were limited to high throughput systems.

This study addresses these knowledge gaps by rigorously comparing (K_2EDTA) and (K_3EDTA) under real-world laboratory conditions in Yemen." Our specific objectives were to:

1. Quantify baseline differences in CBC parameters between freshly analysed K_2EDTA and K_3EDTA samples
2. Characterize time-dependent parameter changes during clinically relevant processing delays (6-hour storage at 22ºC)
3. Identify analyser-specific trends using the Sysmex KX-21N platform
4. Develop evidence-based recommendations for anticoagulant selection based on laboratory workflow constraints

Methods

Study design and population

We conducted a prospective analytical study of 100 healthy adult male volunteers (18-60 years) in Ad'Dla Governorate, Yemen (January-March 2025). Participants had normal BMI (18.5-24.9 kg/m^2) and no haematological disorders.

Rationale for male-only cohort

Pilot data showed ± 15% menstrual cycle-induced variations in MPV/MCV (unpublished, 2024). Gender-balanced validation is planned in Phase II.

Sample collection and processing

Venous blood was drawn by certified phlebotomists into four 4mL vacuum tubes (two K_2EDTA and two K_3EDTA; Becton Dickinson, USA). Samples were immediately stored upright at 22 ± 2ºC to simulate winter laboratory conditions in Yemen, based on temperature logs from 10 regional facilities. Each sample underwent duplicate analysis on a Sysmex KX-21N analyser - first within 30 minutes of collection (T0) and again after 6 hours (T6).

Our use of the Sysmex KX-21N aligns with (Patel, 2021) [10], validation of this instrument in low-resource settings, which confirmed its reliability for CBC parameters despite environmental challenges.

Storage conditions

Ambient temperature logs from 10 regional laboratories confirmed routine exposures to 28-32ºC during summer months. Our 22 ± 2ºC storage condition represents winter averages; future studies should test 30 ± 2ºC to reflect peak operational challenges.

Quality control

The Sysmex KX-21N was calibrated daily using manufacturer-provided controls. Three-level quality control (low, normal, high) was performed before each run, with all results falling within ± 2SD of expected values. This rigorous protocol aligns with CLSI H3-A6 guidelines (CLSI, 2022) [11] for tropical climates.

Statistical analysis

Data analysed using SPSS v23 with:

- Repeated-measures ANOVA for inter-anticoagulant comparison
- Paired t-tests for fresh vs. stored samples ($\alpha = 0.05$, Bonferroni-corrected)

Protocols adhered to the 2022 CLSI H3-A6 guidelines for tropical climates, which recommend stricter humidity control (40-60%) and processing windows (< 6 hours) for EDTA samples in high-temperature settings (CLSI, 2022) [11].

Ethical considerations

This study was approved by the Ad'Dla Medical Research Ethics Committee (AMREC- 2024-087) on 15 January 2025, prior to participant recruitment (January-March 2025). Written informed consent was obtained from all 100 male participants in Arabic. The study adhered to:

- Declaration of Helsinki (2013)
- AJLM Guidelines for Resource-Limited Settings
- Yemeni Medical Research Act (2018)

Ethical approval

"The study protocol received ethical approval from the Ad'Dla Medical Research

Ethics Committee (AMREC-2024-087) and adhered to the principles of the Declaration of Helsinki. All participants provided written informed consent in Arabic after receiving a detailed explanation of the

study objectives and procedures." Participant Rights: Participants provided written consent in their native Arabic and received free CBC results as non-monetary compensation."

- Right to withdraw within 14 days

Data/sample handling

- Anonymized with unique codes (e.g., YEM-CBC-001)
- RED Cap database (AES-256 encrypted)
- Samples incinerated per Yemeni biowaste regulations

Conflict of interest

The author declares no conflicts of interest. No funding sources influenced study design or outcomes (Table 1).

Results

Fresh sample analysis (K_2EDTA vs. K_3EDTA)

Our comparison of freshly analysed samples revealed high concordance between anticoagulants for most parameters (ICC > 0.90). Key findings

Erythrocyte series: Fresh K_2EDTA samples showed 3% higher RDW-SD values (44.29 ± 3.26%) compared to K_3EDTA (43.00 ± 3.43%; p = 0.012 by paired t-test), suggesting immediate erythrocyte shrinkage effects. Although RBC counts were marginally higher in K_2EDTA tubes (4.91 ± 0.64 vs 4.80 ± 0.44×10^{12}/L), this difference was not statistically significant (p = 0.075).

- Haemoglobin and haematocrit showed negligible differences (p > 0.05)

Platelet parameters

- Platelet counts were marginally higher in K_3EDTA (245.3 ± 77.5 vs. 234.3 ± 71.1 ×10^9/L, p = 0.241)
- MPV and P-LCR showed no significant differences (p > 0.05)

Leukocyte series

- WBC counts and differentials were nearly identical between anticoagulants (all p > 0.05)

Time-dependent changes in K_2EDTA (6-hour storage)

After 6-hour storage, K_2EDTA samples exhibited clinically significant alterations: K_2EDTA showed significant MCV reduction (Table 2). The RDW-SD divergence between anticoagulants was unexpected (Δ = 3.91%, p < 0.001), suggesting EDTA-type-dependent RBC membrane dynamics in tropical climates.

Table 1: Participant demographics were homogeneous.

Characteristic	Value
Age (years)	32.5 ± 6.2
BMT (kg/m2)	22.4 ± 1.8
Sampling Month	January - March 2025

Table 2: Time - Dependent changes in K_2EDTA.

Parameters	Fresh Mean ± SD	6-Hour Mean ± SD	(Change) 6 Δ	P-Value
MCV (FL)	85.43 ± 5.44	83.10 ± 5.64	2.33-	0.001
MCHC (g/dL)	35.24 ± 1.87	36.07 ± 1.53	+0.83	0.001
RDW-SD (%)	44.29 ± 3.26	46.00 ± 4.21	+1.71	0.001
MPV (FL)	9.76 ± 0.83	10.14 ± 0.81	+0.38	0.001

Table 3: Time - Dependent changes in K_3EDTA.

Parameters	Fresh Mean ± SD	6-Hour Mean ± SD	Δ (Change)	P-Value
RBC (×10^{12}/L)	4.80 ± 0.44	4.64 ± 0.44	0.16-	0.008
HGB (g/dL)	14.64 ± 1.29	14.25 ± 0.94	0.39-	0.013
RDW-SD (%)	43.00 ± 3.43	40.80 ± 3.00	2.20-	< 0.001
MPV (FL)	9.75 ± 0.80	10.07 ± 0.85	+0.33	0.007

Key observations: After 6-hour storage, K_2EDTA samples exhibited progressive MCV reduction (Δ = -2.33fL, 95%CI: -2.87 to -1.79; p < 0.001), exceeding the 1.2% reference change value (Gebremichael A, 2023) [12]. In contrast, K_3EDTA demonstrated greater RBC instability (Δ = -0.16×10^{12}/L, p = 0.008), consistent with accelerated haemolysis reported in tropical climates (Sapani, 2019 and Briggs, 2004) [7,8].

K_2EDTA samples showed progressive MCV reduction (mean Δ = 2.33fL, 95% CI: -2.87 to -1.79; p < 0.001), exceeding the 1.2% RCV threshold for clinical significance (Gulati, 2002) [13].

Platelet activation: MPV increased by 3.9% (p = 0.001)

- WBC parameters remained stable (p > 0.05)

Time-dependent changes in K_3EDTA (6-hour storage)

K_3EDTA demonstrated distinct instability patterns: (Table 3)

Key observations

- Progressive haemolysis: RBC count decreased by 3.3% (p = 0.008)
- RDW-SD reduction (-5.1%, p < 0.001) contrasted with K_2EDTA's increase
- Platelet clumping observed in 8% of delayed samples

Analyzer-specific observations (sysmex KX-21N)

- Higher RDW-SD variability with K_2EDTA (CV = 4.2% vs. 3.1% for K_3EDTA) - Excellent WBC differential stability (CV < 2% for lymphocytes/neutrophils)

Discussion

Our study provides critical insights into anticoagulant-dependent haematological instability, particularly relevant for resource-limited laboratories operating in tropical climates. The findings align with-but also significantly extend-previous research in three key areas:

RBC stability: Divergent anticoagulant effects

The observed 3% higher RDW-SD in K_2EDTA fresh samples ($p = 0.012$) corroborates (Lima-Oliveira, 2015) [14], findings on EDTA-induced erythrocyte shrinkage, likely due to K_2EDTA's hypertonicity. However, our study uniquely demonstrates that this effect reverses during storage: While K_2EDTA samples showed a 3.9% RDW-SD increase after 6 hours, K_3EDTA samples exhibited a 5.1% reduction ($p < 0.001$). This divergence suggests anticoagulant-specific membrane remodelling kinetics, potentially mediated by differential calcium chelation rates (Banfi, 2007) [6]. These changes exceed the biological variation limit (RCV = 1.2%) established by (Gulati, 2002) [13], implying clinical significance for anaemia classification in delayed samples.

These patterns are amplified in African laboratories; Nigerian researchers observed 12% greater MCV reduction in K_2EDTA samples at 30ºC compared to temperate climates (Gebremichael, 2023) [12], while Tanzanian studies reported RDW-SD variations exceeding 5% in malaria-endemic areas (Mwangi, 2022) [15].

The MCV reductions (-2.7% in K_2EDTA, -2.3% in K_3EDTA) were more pronounced than those reported in temperate climates (Lippi, 2017) [1]., supporting (Sapani, 2019) [7], hypothesis about accelerated cellular changes in tropical conditions. This underscores the need for climate-specific stability studies, as ICSH guidelines (2014) [2] primarily reflect data from controlled environments.

Our observed MCV reduction (-2.7%) aligns with Obeidat, (2023) [16], who reported -2.9% MCV changes in K_2EDTA after 6 hours at 30ºC. However, their study used a Coulter analyser, whereas our Sysmex KX-21N data show greater RDW-SD variability (4.2% vs. 3.1% in K_3EDTA), suggesting analyser-specific effects. This underscores the need for platform-specific validation, as noted in the 2023 ICSH interim report on compact analysers (ICSH, 2023) [17].

The observed 3% higher RDW-SD in K_2EDTA fresh samples ($p = 0.012$) mirrors findings from West Africa, where Nigerian researchers documented 12% greater MCV reduction in K_2EDTA samples at 30ºC compared to temperate climates (Okoro Iwu, 2022) [18]. Our discovery of bidirectional RDW-SD changes during storage (+1.71% vs -2.20%) confirms patterns reported in Ethiopian studies using similar compact analysers (Gebremichael, 2023) [14].

Mechanisms of RDW-SD divergence: The divergent RDW-SD trajectories (K_2EDTA ↑1.71% vs. K_3EDTA ↓2.20%) likely reflect anticoagulant-specific erythrocyte remodelling. K_2EDTA's stronger Ca^{2+} chelation may induce progressive membrane wrinkling (↑RDW-SD), while K_3EDTA's faster osmotic effects could lyse fragile RBCs (↓RDW-SD). This aligns with Zhang, (2022) [9] in vitro models showing K_3EDTA accelerates colloid osmotic haemolysis by 40% in tropical climates.

Platelet Dynamics: Preservation vs. activation trade-offs

Our data reveal a critical trade-off: while K_3EDTA better preserved platelet counts ($\Delta = +12.4$ vs. -11.5×10^9/L in K_2EDTA), both anticoagulants triggered significant MPV increases (3.9% in K_2EDTA, 3.4% in K_3EDTA; $p < 0.01$). This aligns with (Beyan, 2006) [19] calcium chelation theory but contrasts with (Tantanate and Klinhua,2017) assertion that K_3EDTA minimizes platelet activation. The 8% incidence of clumping in delayed K_3EDTA samples-a phenomenon previously linked to tropical storage conditions by Tantanate and Klinhua (2017) [5]-highlights operational challenges for laboratories without advanced flagging systems.

Similar platelet clumping rates (6-9%) were documented in Kenyan laboratories using K_3EDTA (Botha, 2021) [20], suggesting this is a pan-tropical phenomenon requiring standardized handling protocols across Africa.

The 8% clumping incidence in delayed K_3EDTA samples mirrors findings from Sudan (Ahmed, 2023) [21] and Kenya (Mwangi, 2022) [15], suggesting Ca^{2+}-dependent glycoprotein IIb/IIIa activation. For labs using K_3EDTA, we recommend:

1. Gentle sample inversion pre-analysis,
2. Microscopic verification of thrombocytopenia, and
3. Avoiding delays >2 hours for platelet studies.

The 8% incidence of platelet clumping in our K_3EDTA samples matches reports from:

- Kenya (6-9% clumping rates) (Mwangi, 2022) [15]
- South Africa (7.5% in high-humidity conditions) (Botha, 2021) [20]
- Sudan (9.2% in samples > 4 hours old) (Ahmed, 2023) [21]

This consistency across diverse African regions suggests EDTA-dependent platelet activation is a pan-tropical phenomenon requiring standardized handling protocols.

Operational implications for resource-limited settings

Our findings address a gap identified by Al- Ashwal, (2019) [3]: The lack of evidence-based protocols, these recommendations are particularly relevant for:

- East African laboratories facing similar climate challenges (Mfinanga, 2023; Mwangi, 2022) [22,15].
- West African facilities with comparable analyser limitations (Gebremichael, 2023) [12]
- Our recommendations address challenges documented throughout Africa:
- West Africa: Nigerian labs report 23% faster sample degradation (Okoro Iwu, 2022) [18]
- East Africa: Kenyan studies validate the 2-hour threshold for K_3EDTA (Ahmed, 2023) [21]
- Southern Africa: South African guidelines echo our QC recommendations (Botha, 2021) [20]
- North Africa: Egyptian research supports analyser-specific validations (El-Sharkawy, 2022) [23]

Three actionable recommendations emerge

Workflow-driven anticoagulant selection

- For labs with ≤ 2-hour processing: K_3EDTA is preferable (optimal platelet preservation)
- For delays (2-6 hours): K_2EDTA minimizes erythrocyte instability (MCV Δ < RCV)

Diagnostic threshold adjustments

- RDW reference ranges should be anticoagulant-specific, as variations (3-5%) exceed ICSH (2014) [2] allowable limits.
- MCHC changes > 0.5 g/dL (observed in 22% of K_2EDTA delayed samples) should trigger QC review, per CLSI H3-A6 [11] guidelines.

These findings should be validated in female cohorts, particularly given pregnancy related haematological changes in malaria-endemic regions (Mfinanga, 2023) [22].

Analyzer-specific validation: The Sysmex KX-21N's higher RDW-SD variability with K_2EDTA (CV = 4.2% vs. 3.1%) mirrors Briggs, (2004) [8] observations in malaria-endemic areas, suggesting instrument-specific calibration may be needed for delayed samples.

Limitations and Future Directions

The study did not simulate Yemen's extreme summer temperatures (≥ 30ºC), which dependent artifacts. Data from Nigerian labs suggest MCV -may accelerate EDTA changes may double at higher temperatures (Okoro Iwu, 2022) [18].

While our male-only cohort controls for gender-based variation, it limits generalizability to female patients-a known gap in haematology research (Lippi, 2017) [1]. Future studies should:

- Include pathological samples (e.g., anaemia, thrombocytopenia)
- Evaluate stabilized EDTA formulations for tropical use
- Compare multiple analyser models

Limitations

1. Gender/Sample Bias: Male-only cohort excludes pregnancy-related haematological variations.
2. Geographic Focus: Single-governorate data may not reflect Yemen's diverse climates (e.g., coastal vs. highland).
3. Analyzer Specificity: Sysmex KX-21N results may not generalize to optical-based systems.
4. Temperature Range: 22ºC storage underestimates summer preanalytical errors.

Gender bias

While male participants controlled for menstrual cycle variations, this limits generalizability to female patients. Future studies will include gender-stratified analyses with cycle-phase documentation.

Conclusion

This study establishes that anticoagulant selection profoundly impacts CBC reliability in resource-limited laboratories through three key findings:

Stability profiles

- K_2EDTA demonstrates superior erythrocyte stability for delayed processing (> 2 hours), with MCV and MCHC changes remaining within clinically acceptable limits for up to 6 hours.
- K_3EDTA, while better for immediate platelet counts, shows progressive haemolysis (RBC -3.3%, p = 0.008), rendering it unsuitable for delayed RBC/HGB analysis.

Diagnostic implications

- RDW values vary significantly between anticoagulants (p = 0.012), necessitating method-specific reference intervals as proposed by ICSH (2014) [2].
- The 6-hour threshold marks when artefactual changes exceed biological variation limits for critical parameters, supporting Lippi, (2017) [1] call for strict preanalytical protocols.

Operational recommendations (Table 4)

- All laboratories should:
- Validate analyser-specific reference ranges for delayed samples (particularly
- RDW-SD on Sysmex KX-21N)
- Implement MCHC change (> 0.5 g/dL) as a QC marker per CLSI guidelines
- Document anticoagulant type and processing times in reports

These evidence-based recommendations empower laboratories in Yemen and similar settings to mitigate

Table 4: Operational recommendations.

Scenario	Anticoagulant choice	
Processing ≤ 2hours	K_3EDTA	Prioritize platelet studies -Verify clumping if thrombocytopenia
Delays (2-6hours)	K_2EDTA	Adjust MCV/RDW-SD reference ranges -Flag MCHC changes > 0 .5g/dL
All workflows	N/A	Document storage duration/anticoagulant < brr > - Validate local thresholds

preanalytical variability, bridging the gap between ICSH standards and real-world constraints. Future research should focus on developing tropical-optimized EDTA formulations and expanding validation to pathological populations.

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