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ORIGINAL ARTICLE

Efficacy of Oscillation-Induced Depolymerization for Pseudothrombocytopenia Management Under Varying Conditions

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SUMMARY

Background: **The aim of this study is to examine the effectiveness of oscillation-induced depolymerization in mitigating pseudothrombocytopenia (PTCP) under varying oscillatory conditions.**
Methods: **A total of 161 patients diagnosed with PTCP and admitted between May 2020 and November 2023 were included in the study. The patients were categorized into four groups based on oscillation parameters: 1,500 rpm for 1 minute, 1,500 rpm for 3 minutes, 3,000 rpm for 1 minute, and 3,000 rpm for 3 minutes. Platelet (PLT) depolymerization was assessed pre- and post-oscillation in each group, and peripheral blood smears were examined to evaluate platelet distribution. Additionally, the Mindray BC-6800 Plus hematology analyzer, in combination with a special stain, was utilized to verify depolymerization and identify the most appropriate depolymerization method for clinical application.**
Results: **PLT counts were significantly higher in the 3,000 rpm for 3 minutes and the 3,000 rpm for 1 minute groups compared to the 1,500 rpm for 1 minute group ($p < 0.05$). However, no significant differences in white blood cell and red blood cell counts were observed across the oscillation conditions ($p > 0.05$). Depolymerization rates in the 3,000 rpm groups were significantly higher than those in the 1,500 rpm groups ($p < 0.05$). The oscillation-induced depolymerization rate in the 3,000 rpm for 3 minutes group reached 93.79%, which was significantly greater than that in the special stain group (11.80%) ($p < 0.05$). Logistic regression analysis identified elevated lymphocyte count and potassium level as risk factors for incomplete depolymerization, while total bilirubin, direct bilirubin, and indirect bilirubin levels were found to be protective factors ($p < 0.05$).**
Conclusions: **Oscillation at 3,000 rpm for 3 minutes resulted in the highest rate of platelet depolymerization and demonstrated favorable clinical efficacy for PTCP management. Monitoring of lymphocyte count, potassium, total bilirubin, direct bilirubin, and indirect bilirubin levels is essential to facilitate timely implementation of the oscillation method, thereby reducing the incidence of PTCP and enhancing the accuracy of clinical detection.**
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LIST OF ABBREVIATIONS

PTCP - pseudothrombocytopenia
PLT - platelet
EDTA-PTCP - pseudothrombocytopenia induced by EDTA

KEYWORDS

clinical examination, clinical value, depolymerization, oscillation method, pseudothrombocytopenia

INTRODUCTION

Platelets (PLTs) are essential for maintaining vascular health, facilitating hemostasis, supporting immune response, and regulating normal blood flow. Abnormal platelet function can contribute to various conditions, including bleeding and thrombotic disorders, underscoring the importance of accurate assessment and management of platelet activity to maintain overall health [1,2]. Pseudothrombocytopenia (PTCP) refers to the *in vitro* aggregation of platelets that does not result from physiological processes occurring *in vivo*. This phenomenon often results from laboratory-related conditions or technical factors rather than underlying physiological or pathological processes [3,4].

Previous studies have reported associations between PTCP and factors such as the type of anticoagulant used, blood collection and processing conditions, extracorporeal circulation systems, and the presence of antithrombin [5]. When PTCP is detected, interventions such as substituting anticoagulants and performing manual platelet counts may correct deviations. However, these approaches often require repeated blood draws, leading to poor patient compliance, increased strain on the healthcare system, and even medical disputes.

A well-documented subtype of PTCP is EDTA-induced pseudothrombocytopenia (EDTA-PTCP). Since the clinical adoption of EDTA, its potential role in platelet aggregation has been increasingly recognized, prompting increased awareness among medical professionals regarding its implications. In clinical laboratory settings, automated hematology analyzers and flow cytometry may have limited ability to distinguish between aggregated and individual platelets, thereby complicating accurate diagnosis of PTCP [6,7].

Epidemiological studies have reported that the clinical incidence of EDTA-PTCP ranges from 0.07% to 0.20% in the general population and from 0.1% to 2.0% among hospitalized patients [8,9]. This condition has been observed across various disease states, health statuses, and age groups, and may be associated with malignancies, altered immune function, and medication use. Additionally, some individuals without clinically apparent symptoms have exhibited EDTA-PTCP over more than a decade of follow-up.

The present study evaluates the effectiveness of a simple oscillation-based method for improving the detection of PTCP in clinical practice. The results aim to inform optimization strategies for laboratory diagnostic procedures. The findings are reported as follows.

DATA AND METHODS

General data

A total of 161 individuals diagnosed with PTCP, based on the diagnostic criteria for EDTA-induced PTCP, were selected from the hospital's examination center between May 2020 and November 2023. Informed consent was obtained from all participants prior to inclusion in the study. The cohort comprised 122 males and 39 females, with an age range of 34 to 74 years (mean age: 53.98 ± 10.23 years). Whole blood samples were collected in EDTA-K2 anticoagulant tubes and analyzed using an automated hematology analyzer. If the platelet count was below 125 x 10^9/L, the analyzer triggered an alarm for platelet aggregation, which was subsequently confirmed through blood smear examination. The aggregation was corrected by substituting sodium citrate as the anticoagulant [10]. None of the patients exhibited skin purpura, mucosal bleeding, or significant hepatosplenomegaly. Additional causes of thrombocytopenia were excluded.

Methods

Three methods - oscillation, special staining, and microscopic examination - were utilized to assess the effect of depolymerization and to categorize the study groups. Microscopic examination served as the gold standard for evaluating the depolymerization rate by preparing two blood smears from each sample, and platelet distribution was assessed under a microscope. Observations were conducted using a high-powered 1,000 x magnification lens (100 x objective lens with a 10 x eyepiece). Evaluation was focused on the tail region, bilateral edges, and evenly distributed regions of the blood smear. A minimum of 10 fields of view were assessed. Platelet count (PLT), red blood cell count (RBC), and white blood cell count (WBC) were compared before and after oscillation, and the platelet distribution in the blood smear was analyzed. The microscopic evaluation of platelet distribution was used as the criterion to determine whether platelet aggregation had resolved. All specimens were tested within 30 minutes of collection. Oscillation was performed prior to re-analysis, and all testing was completed on the day of sample collection.

Evaluation of depolymerization under various oscillation conditions

An IKA MS3 circumferential oscillator and a Mindray BC-6800 Plus hematology analyzer were utilized to evaluate the depolymerization effect under different oscillation parameters. Blood samples were categorized into four groups based on oscillation speed and dura-

tion: 1,500 rpm for 1 minute, 1,500 rpm for 3 minutes, 3,000 rpm for 1 minute, and 3,000 rpm for 3 minutes. PLT, WBC, and RBC counts were measured under varying oscillation conditions, and the depolymerization rate was evaluated.

Evaluation of the depolymerization effect of special stain

Whole blood samples were collected in EDTA-anticoagulated tubes to reconfirm the presence of platelet aggregation. Analysis was performed using the Mindray BC-6800 Plus hematology analyzer and the M-68P FR stain reagent. This reagent contains a specialized dye that selectively binds to various blood cell components (Figure 1).

Univariate and logistic regression analysis

A baseline data questionnaire was used to collect variables potentially associated with the depolymerization effect in PTCP. Collected data included gender, body mass index, age, presence of underlying disease, history of myocardial infarction, and hematological indicators to statistically assess the factors influencing the depolymerization effect of PTCP.

Statistical analysis

Statistical analysis was conducted using SPSS version 22.0. Categorical data were expressed as percentages, and comparisons between groups were conducted using the chi-squared or Fisher's exact test. Continuous variables were presented as mean ± standard deviation (SD), with independent samples *t*-tests used for two-group comparisons. One-way analysis of variance (ANOVA) was utilized for comparisons among three or more groups, with Bonferroni correction applied for subsequent multiple comparisons. A $p < 0.05$ was considered statistically significant.

RESULTS

Comparison of platelet and other hematological parameters under varying oscillation conditions

A statistically significant difference was observed in PLT values across different oscillation conditions ($p < 0.05$). PLT counts observed under oscillation conditions of 3,000 rpm for 3 minutes and 3,000 rpm for 1 minute were significantly higher than those recorded at 1,500 rpm for 1 minute ($p < 0.05$). However, no significant differences were observed in WBC and RBC counts across the different oscillation conditions ($p > 0.05$) (Table 1).

Comparison of depolymerization rates under varying oscillation conditions

A statistically significant difference was observed in the depolymerization rate across different oscillation conditions ($p < 0.05$). Depolymerization rates at 3,000 rpm for 3 minutes and 3,000 rpm for 1 minute were significantly higher than those recorded at 1,500 rpm for 1 minute and 1,500 rpm for 3 minutes ($p < 0.05$) (Table 2).

Comparison of the depolymerization effects between special stain and oscillation methods

The depolymerization rate achieved using the oscillation method at 3,000 rpm for 3 minutes was 93.79%, which was significantly higher than the 11.80% observed with the special stain method ($p < 0.05$) (Table 3).

Univariate and logistic regression analysis of factors affecting the depolymerization effect of oscillation method in PTCP

The cases were categorized into an incomplete depolymerization group ($n = 10$) and a complete depolymerization group ($n = 151$) under the optimal oscillation condition of 3,000 rpm for 3 minutes. Statistically significant differences were observed in lymphocyte count, potassium, total bilirubin, direct bilirubin, and indirect bilirubin between the two groups ($p < 0.05$). Logistic regression analysis further indicated that elevated lymphocyte count and potassium were significant risk factors for incomplete depolymerization, whereas higher levels of total bilirubin, direct bilirubin, and indirect bilirubin were identified as protective factors ($p < 0.05$) (Tables 4 and 5).

DISCUSSION

PTCP is a pre-analytical artifact characterized by *in vitro* platelet aggregation, leading to falsely decreased platelet counts when assessed using automated hematology analyzers. Clinically, PTCP presents a diagnostic challenge, as it can mimic true thrombocytopenia and result in unnecessary diagnostic procedures and treatments [11]. The mechanism underlying PTCP is believed to involve naturally occurring antibodies binding to platelets in the presence of anticoagulants, thereby inducing platelet aggregation. Thus, accurate identification of PTCP is crucial to prevent misdiagnosis and inappropriate interventions [12]. Common approaches to addressing PTCP include repeating blood cell counts using alternative anticoagulants (such as sodium citrate or heparin), performing manual platelet counts, or microscopic evaluation of blood smears. However, these methods are either labor-intensive or lack sufficient precision. Clinical evidence indicates that the oscillation method effectively disperses platelet aggregates, improving the accuracy of automated platelet counting. However, its efficacy is influenced by multiple factors, including oscillation speed, duration, and environmental factors such as sample temperature [13,14].

The Mindray BC-6800 Plus Hematology Analyzer utilizes flow cytometry and optical scattering techniques to accurately determine platelet counts, independent of PTCP, thereby enhancing the reliability of hematological analysis in clinical laboratories [15]. The M-68P FR

Table 1. Comparison of PLT values, WBC and RBC counts under different oscillation conditions ($\bar{x} \pm s$).

Oscillation conditions	Specific parameters	PLT values (x 10^9/L)	White blood cell count (x 10^9/L)	Red blood cell count (x 10^{12}/L)
1	1,500 rpm, 1 minute	143.23 ± 48.81	6.91 ± 0.81	4.72 ± 0.56
2	1,500 rpm, 3 minutes	151.09 ± 50.81	6.82 ± 0.77	4.81 ± 0.62
3	3,000 rpm, 1 minute	168.28 ± 50.22 *	6.80 ± 0.84	4.83 ± 0.66
4	3,000 rpm, 3 minutes	179.02 ± 44.73 *	6.74 ± 0.73	4.77 ± 0.50
	F	15.763	1.284	1.098
	p	0.000	0.279	0.349

Compared to oscillation condition 1, * - $p < 0.05$.

Table 2. Comparison of depolymerization rates under different oscillation conditions [n (%)].

Oscillation conditions	Depolymerization rate
1,500 rpm, 1 minute	92/161 (57.14)
1,500 rpm, 3 minutes	105/161 (65.22)
3,000 rpm, 1 minute	142/161 (88.20) *
3,000 rpm, 3 minutes	151/161 (93.79) *
χ^2	82.919
p	0.000

Compared to oscillation condition 1, * - $p < 0.008$.

Table 3. Comparison of the depolymerization rates between special stain and oscillation methods [n (%)].

Different depolymerization methods	Depolymerization rates
Special stain	19/161 (11.80)
Oscillation method (3,000 rpm, 3 minutes)	151/161 (93.79)
χ^2	217.126
p	0.000

staining reagent is specifically formulated for blood cell analysis, reacting with platelet components to render them clearly visible under a microscope. This staining reagent typically contains DNA-binding dyes such as methylene blue or other nucleophilic stains, which bind to platelet nucleic acids. These agents enhance contrast under microscopy by producing distinct coloration. However, the depolymerization rate associated with the staining method in this study was significantly lower than that achieved using the oscillation method [16].

Clinical observations from this study indicate that the oscillation method provides a practical and more effective alternative to anticoagulant substitution or other complex interventions for correcting PTCP [17]. Moderate oscillation rapidly disperses platelet aggregates, eliminating the need for repeated blood draws and potentially decreasing conflicts between patients and healthcare providers. In this study, depolymerization rates were significantly higher under oscillation conditions of 3,000 rpm for 3 minutes and 3,000 rpm for 1 minute compared to 1,500 rpm for 1 minute and 1,500 rpm for 3 minutes ($p < 0.05$). The data indicate that the oscillation method effectively disperses platelet aggregates through mechanical vibration, minimizing platelet adhesion and aggregation. Increased oscillation velocity and duration may enhance kinetic shear forces, preventing platelet clumping and maintaining their dispersed state, thereby improving depolymerization rates [18].

Table 4. Univariate analysis of factors influencing the depolymerization effect of the oscillation method in PTCP.

Groups	Incomplete depolymerization group (n = 10)	Complete depolymerization group (n = 151)	t/χ^2	p
Gender			0.194	0.660
Male	7	115		
Female	3	36		
Body mass index (kg/m^2)	25.01 ± 4.02	24.87 ± 3.89	0.110	0.913
Age (years)	54.52 ± 9.98	53.91 ± 10.51	0.178	0.859
Underlying disease				
Diabetes	3	18	2.703	0.100
Hypertension	4	24	3.794	0.052
Coronary heart disease	3	21	1.915	0.166
History of myocardial infarction	2	17	0.689	0.407
Lymphocyte count x 10^9/L)	5.23 ± 1.04	3.18 ± 0.82	7.528	0.000
Potassium (mmol/L)	6.23 ± 2.09	4.20 ± 0.59	3.063	0.013
Total bilirubin (μmol/L)	8.15 ± 1.33	14.21 ± 3.38	12.059	0.000
Direct bilirubin (μmol/L)	1.99 ± 0.29	5.21 ± 1.06	25.576	0.000
Indirect bilirubin (μmol/L)	3.05 ± 0.91	7.14 ± 1.02	12.352	0.000

Table 5. Logistic regression analysis results.

Variables	Regression coefficient β	Standard error S.E.	Wald value	p-value	OR value	95% CI
Lymphocyte count	0.432	0.198	4.760	0.029	1.540	1.045 - 2.271
Potassium	0.519	0.202	6.601	0.010	1.680	1.131 - 2.497
Total bilirubin	-0.251	0.127	3.906	0.048	0.778	0.607 - 0.998
Direct bilirubin	-0.438	0.191	5.259	0.022	0.645	0.444 - 0.938
Indirect bilirubin	-0.495	0.241	4.219	0.040	0.610	0.380 - 0.978
Constant	-0.679	0.287	5.597	0.018	-	-

Further analysis categorized cases into incomplete and complete depolymerization groups based on the optimal oscillation condition (3,000 rpm for 3 minutes). Lymphocyte count and potassium were identified as risk factors for incomplete depolymerization in PTCP, while total bilirubin, direct bilirubin, and indirect bilirubin levels were identified as protective factors ($p < 0.05$). Lymphocytes play a key role in immune and inflammatory responses and may contribute to enhanced platelet aggregation under inflammatory conditions when present at elevated levels [19]. Potassium, an essential ion for maintaining cell membrane potential, influences platelet activation and cohesion, thereby affecting platelet function. Bilirubin, particularly direct bilirubin, exhibits strong antioxidant properties that neutralize free radicals and oxidative agents, reducing intracellular oxidative stress and mitigating platelet aggregation. The findings indicate that oxidative stress may contribute to platelet aggregation in PTCP, and bilirubin's antioxidant properties help preserve platelet integrity, lowering the likelihood of aggregation. These factors collectively influence platelet aggregation through mechanisms such as antioxidation, anti-inflammation, membrane stabilization, and coagulation regulation [20].

In clinical laboratory practice, PTCP can be effectively prevented and managed by the selection of appropriate anticoagulants, optimization of oscillation parameters, consideration of patient clinical history, implementation of quality control measures, and targeted training of laboratory staff. These strategies contribute to improved accuracy in platelet count and improve the reliability of diagnostic results. The oscillation method has emerged as the preferred clinical approach for correcting PTCP. However, in cases where adequate platelet depolymerization is not achieved through oscillation alone, substitution with an alternative anticoagulant may be nec-

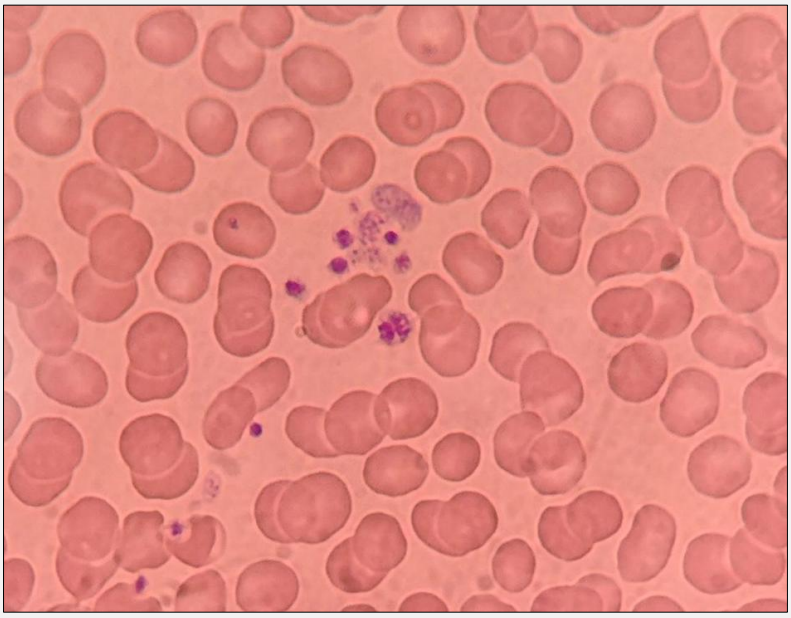

Figure 1. Visualization of platelet aggregation using special staining reagent (x 1,000).

essary to enhance the accuracy of platelet count measurements.

In summary, platelet depolymerization achieved under the oscillation condition of 3,000 rpm for 3 minutes demonstrated favorable clinical efficacy and may be considered the preferred method for addressing PTCP in clinical practice. Additionally, monitoring lymphocyte count, potassium, total bilirubin, direct bilirubin, and indirect bilirubin levels is essential to facilitate timely blood sample processing, reduce the incidence of PTCP-related artifacts, and improve the accuracy of platelet count measurements in clinical settings.

Declarations:

This study was conducted with approval from the Ethics Committee of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine on May 9th, 2020 (No. 183). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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Data Availability:

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of Interest:

The authors declare that they have no conflict of interest regarding this work.

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