

Original article

Acetaminophen and chlorpheniramine maleate premedication among patients with chronic transfusion: a prospective, randomized controlled trial

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Abstract:

Introduction: Patients with chronic transfusion, especially those with transfusion-dependent thalassemia, are susceptible to transfusion reactions. Acetaminophen and/or chlorpheniramine maleate (CPM) are commonly used as premedication in Thailand, although their efficacy in preventing transfusion reactions remains unclear. This study aims to evaluate the efficacy of acetaminophen and CPM in preventing febrile nonhemolytic transfusion reaction (FNHTR) and allergic transfusion reaction (ATR) before leukocyte-poor packed red cells (LPRC) transfusion. **Methods:** This study is a prospective, randomized controlled trial involving patients with chronic transfusion aged ≥ 18 years. Patients were randomly assigned to either receive oral acetaminophen and intravenous CPM or placebo (calcium carbonate and normal saline) before LPRC transfusion. The primary endpoint was the combined incidence of FNHTR and ATR among patients receiving premedication compared with those receiving placebo. This study was registered at Thai Clinical Trial Registry Study (TCTR20221011002). **Results:** Ninety-four patients were recruited, with 46 in the premedication arm and 48 in the placebo arm. The incidence of FNHTR and allergic transfusion reaction in the premedication arm and the placebo arm was 0% and 2.1%, respectively ($p = 0.33$). FNHTR occurred in one patient in the placebo arm, and no patients presented ATR. No adverse events were reported with any medication. **Conclusions:** Among patients with chronic transfusion receiving LPRC, the incidence of FNHTR or ATR is low. Premedication with oral acetaminophen and intravenous CPM did not have benefits in preventing transfusion reactions. Therefore, acetaminophen and CPM could be safely omitted in chronic transfused patients without a history of transfusion reactions.

Keywords : ● Premedication ● Leucocyte poor packed red cells ● Transfusion reaction

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นิพนธ์ต้นฉบับ

การศึกษาแบบสุ่มมีกลุ่มควบคุมในการให้ยาพาราเซตามอลและคลอร์เฟนิรามีน มาลีเอตเป็นการให้ยานำในผู้ป่วยที่ได้เลือดเป็นประจำ

ศุภณัฐ จรรยางาม^{1,2} พลภัทร โรจน์นครินทร์^{2,3} พรรณดี วัฒนบุญยงเจริญ⁴ ปราวณี สุจริตจันทร์² และ กฤษณา ปานรงค์^{2,3}
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บทคัดย่อ

บทนำ ผู้ป่วยที่ได้เลือดเป็นประจำมีความเสี่ยงที่จะเกิดปฏิกิริยาจากการให้เลือด การให้ยานำก่อนที่จะให้เลือดด้วย acetaminophen และ/หรือ chlorpheniramine maleate (CPM) เป็นแนวทางปฏิบัติที่พบบ่อยในประเทศไทย ถึงแม้ว่าจะไม่ได้มีหลักฐานสนับสนุนประสิทธิภาพที่ชัดเจน การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาประสิทธิภาพของ acetaminophen และ CPM เป็นยานำเพื่อป้องกันการเกิด febrile nonhemolytic transfusion reaction (FNHTR) และ allergic transfusion reaction (ATR) ก่อนให้ leukocyte poor packed red cell (LPRC) **วิธีการศึกษา** ทำการศึกษาในผู้ป่วยที่ได้เลือดเป็นประจำ โดยกำหนดด้วยวิธีสุ่ม ซึ่งผู้ป่วยจะได้รับยานำเป็น acetaminophen และยา CPM ก่อนที่จะให้เลือดชนิด LPRC หรือยาหลอก โดยตัวชี้วัดหลักของการศึกษาคือ อุบัติการณ์ของการเกิด FNHTR และ ATR ในผู้ป่วยที่ให้นำเปรียบเทียบกับยาหลอก **ผลการศึกษา** มีผู้ป่วยเข้าร่วมการศึกษาทั้งหมด 94 ราย เป็นกลุ่มที่ได้รับยานำ 46 ราย และ ยาหลอก 48 ราย อุบัติการณ์ของ FNHTR และ ATR ในกลุ่มที่ได้รับยานำและยาหลอก ร้อยละ 0 และ ร้อยละ 2.1 ($p = 0.33$) ตามลำดับ โดยพบ FNHTR เพียงหนึ่งรายในผู้ป่วยที่ได้รับยาหลอก และไม่พบการเกิด ATR ในผู้ป่วยทั้งสองกลุ่ม ไม่พบปฏิกิริยาอันไม่พึงประสงค์จากยาที่ใช้ในงานวิจัย **สรุป** อุบัติการณ์ของการเกิด FNHTR และ ATR นั้นต่ำมากในผู้ป่วยที่ได้รับเลือดชนิด LPRC เป็นประจำ การให้ยานำด้วย acetaminophen และ CPM จึงไม่ได้มีประโยชน์ในการช่วยลดอุบัติการณ์ที่ต่ำมากดังกล่าว ดังนั้นจึงสามารถพิจารณางดการให้ยา acetaminophen และ CPM ได้อย่างปลอดภัยในผู้ป่วยที่ได้รับเลือดเรื้อรังและไม่มีประวัติปฏิกิริยาของการให้เลือดมาก่อน

คำสำคัญ : ● Premedication ● Leucocyte poor packed red cells ● Transfusion reaction

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2567;34:187-94.

Introduction

Many patients, such as those with thalassemia, myelodysplastic syndrome and aplastic anemia, require chronic red cell transfusion, which can lead to chronic complications and poor outcomes including shortened survival among these patients.¹⁻⁴ Thalassemia syndromes are prevalent in Thailand, with varying degrees of severity, from mild to severe anemia requiring regular red blood cell transfusions.^{1,2} However, despite their general safety, transfusions still carry certain risks. Frequent transfusions can increase the likelihood of adverse effects such as transfusion reactions including febrile nonhemolytic transfusion reactions (FNHTR) and allergic transfusion reactions (ATR), demonstrating an incidence of 86.4 and 104.1 per 100,000 transfused units, respectively.⁵ The recent multicenter study among patients with transfusion-dependent thalassemia in Thailand demonstrated an FNHTR prevalence of 5.4% and an ATR prevalence of 13.0%.²

In Thailand, leukocyte-poor packed red cells (LPRC) are the primary component used for red blood cells, along with leukodepleted packed red cells (LDPRC). LPRC is obtained through centrifugation, which reduces white blood cells (WBC) by approximately 90% ($< 1.2 \times 10^9$ cells/unit). LDPRC, on the other hand, are prepared using pre-storage filtration, resulting in a WBC reduction to $< 1 \times 10^6$ cells/unit, lower than LPRC.⁶ This filtration process improves the safety and quality of the blood product, reducing the risk of transfusion reactions and alloimmunization among recipients. Potential causes of FNHTR include the presence of cytokines in cellular blood components or the reaction of recipient HLA antibodies with antigens on transfused lymphocytes, granulocytes, or platelets.⁷ Reducing leukocyte concentrations in blood products to less than 5×10^6 cells/unit can prevent primary HLA immunization, which, in turn, helps prevent FNHTR.⁸ The retrospective data from a single hospital in the US indicates that the implementation of universal prestorage leukoreduction can significantly reduce the incidence of FNHTR but not

ATR.⁹ ATR is caused by pre-existing IgE antibodies in the recipient reacting to allergens present in the blood component.⁷ Antihistamines are commonly used to prevent ATR, while antipyretics are used to prevent fever in FNHTR. Despite their widespread use, related studies have failed to demonstrate the benefits of routine premedication with antipyretics and antihistamines. Most patients in related studies including those with hematologic malignancies and solid tumors, received mainly leukodepleted blood products.¹⁰⁻¹³

In Thailand, access to LDPRC is limited due to its higher cost, which is not covered by most medical benefit schemes. This leads to an additional cost for patients receiving LDPRC, which can be a significant financial burden, especially for those requiring regular transfusions. As a result, LPRC is the most commonly used blood product.

Based on a related randomized study among children and adolescent patients with thalassemia, where patients were premedicated with oral acetaminophen and intravenous chlorpheniramine maleate (CPM) before receiving either LPRC or LDPRC, significant differences in the incidence of febrile reactions and urticarial rash were found. Specifically, the premedication arm had a lower incidence of 6.9 and 22%, compared with those receiving placebo with an incidence of 9.5 and 35.2%, respectively.¹⁴ Despite this evidence, premedication before transfusion in Thailand remains mainly based on the physician decision. Therefore, we have decided to conduct a randomized controlled trial to investigate the effects of premedication on LPRC products in patients with chronic transfusion.

Materials and methods

Study designs and participants

We conducted a single-blind, randomized, controlled study at King Chulalongkorn Memorial Hospital in Bangkok, Thailand. The study involved patients aged 18 years and older with chronic red blood cell transfusion requirements, with a focus on those with transfusion-

dependent thalassemia and other conditions requiring regular red blood cell transfusions. The eligibility criteria included patients with a specific cause for red blood cell transfusions having received at least two units of packed red blood cells in the previous three months, with a hemoglobin level of 8 g/dL or lower. Patients having received blood transfusions due to acute blood loss, trauma-related injuries or surgery were excluded from the study. Additionally, patients with a history of transfusion reaction within three months before enrollment were excluded. Patients with allergies to acetaminophen or CPM, fever or allergic rashes within 24 hours before transfusion, and those receiving acetaminophen, CPM, other antihistamines or corticosteroids equivalent to at least 5 mg of prednisolone within 48 hours before transfusion were also excluded. All participants were given informed consent, and the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No. 461/64), approved this study

The primary objective of the study was to investigate the incidence of FNHTR and ATR among patients with chronic transfusion receiving premedication with acetaminophen and CPM, compared with the control group. The study also evaluated secondary endpoints including the incidence of FNHTR and ATR in the study and control groups separately, differences in the diagnosis of other transfusion-related complications between the two groups, the incidence of other transfusion reactions, adverse reactions from the premedication drugs and other complications related to blood transfusions in the study.

The definitions of FNHTR and ATR used in the study were obtained from the Biovigilance Component Hemovigilance Module Surveillance Protocol of the National Healthcare Safety Network (NHSN) (v2.6, 2021).¹⁵ This trial was registered at Thai Clinical Trial Registry Study (TCTR20221011002).

Randomization

Eligible patients were randomly assigned to receive either premedication or placebo before their red blood cell transfusion, in a 1:1 ratio using block randomization

with a block size of 4. The allocation was communicated to the medical personnel involved in the transfusion procedure, while the patients were blinded to their treatment assignment. This single-blind design was implemented to minimize bias and maintain the integrity of the study.

Procedures

At the time of enrollment, patient vital signs and the quantity of LPRC received were documented. The treatment arm received 500 mg of acetaminophen if their weight was less than 67 kg, or two tablets if their weight was 67 kg or greater, along with 10 mg of CPM intravenously 30 minutes before the first LPRC. The placebo arm received 350 mg of calcium gluconate and 0.9% NaCl as a placebo. Only LPRC was used in this study, and administration followed the standard protocol for ambulatory patients. During the transfusion, vital signs were monitored hourly, and patients were instructed to immediately report any abnormal symptoms such as fever, itchy rashes, allergic symptoms or shortness of breath to a medical staff. Patients were also provided with a thermometer, and a trained staff instructed them on proper body temperature recording methods. An emergency phone number was provided to the patients to contact the investigator in case of any abnormal symptoms. After 24 hours, the investigator was followed up with the patient to inquire about any occurrences of fever, rashes, allergic symptoms or other abnormal symptoms.

Statistical Analysis

The sample size for the study was determined based on a minimal clinically important difference of 20%, with a power of 80% at a significance level of 0.05. A total of 94 patients were determined to be necessary for the study. The chi-square test was used to analyze categorical data, while the t-test was used for analyzing continuous data regarding demographic information. Fisher's exact test was used to assess the association of risk between the treatment arm and placebo group.

Results

Patient Characteristics

During the enrollment period spanning December 2, 2021 to January 1, 2023, a total of 104 patients were screened for eligibility. Of those, 9 patients declined to participate, and 95 patients were randomized in the study. However, due to missing data, one patient was excluded from the analysis, resulting in a final sample size of 94 patients. The study flow is summarized in Figure 1. Baseline characteristics of the patients were almost similar between both treatment arms, except for age (Table 1). The majority of patients had transfusion-dependent thalassemia, with only a few requiring red cell transfusions for other conditions.

Primary endpoint

No significant differences were noted in the incidence of FNHTR and ATR between the premedication and the placebo arms, with rates of 0 and 2.1%, respectively ($p = 0.33$). The mean peak body temperature during transfusion was similar in both groups, with a mean body temperature of 36.9°C in the premedication arm and 37.0°C in the placebo arm. Only one patient in the placebo arm experienced an episode of fever (BT 39.1 °C),

occurring 1 hour after the transfusion ended, and no episodes of fever were detected in the premedication arm. No ATR events were detected in either arm (Table 2).

To assess the impact of missing data on our study outcomes, we conducted a sensitivity analysis focused on the premedication arm, where data for one patient were missing. Initially, the intention-to-treat analysis was performed including the participant with missing data. No significant differences were observed in the incidence of FNHTR and ATR between the two arms, with rates of 0% and 2.1%, respectively ($p = 0.32$). In the worst-case analysis, the missing patient was assumed to have experienced FNHTR or ATR, so the incidence rates remained at 2.1% in both arms ($p = 0.99$).

Secondary endpoints

No ATR events including hemolytic transfusion reactions, bacterial contaminations, transfusion-associated lung injury and transfusion-associated circulatory overload, were reported in either the premedication or placebo arms of the study. The incidence of FNHTR was 1.1%, while no other transfusion-related complications were observed. Furthermore, no adverse events were reported from the premedication administered in the study.

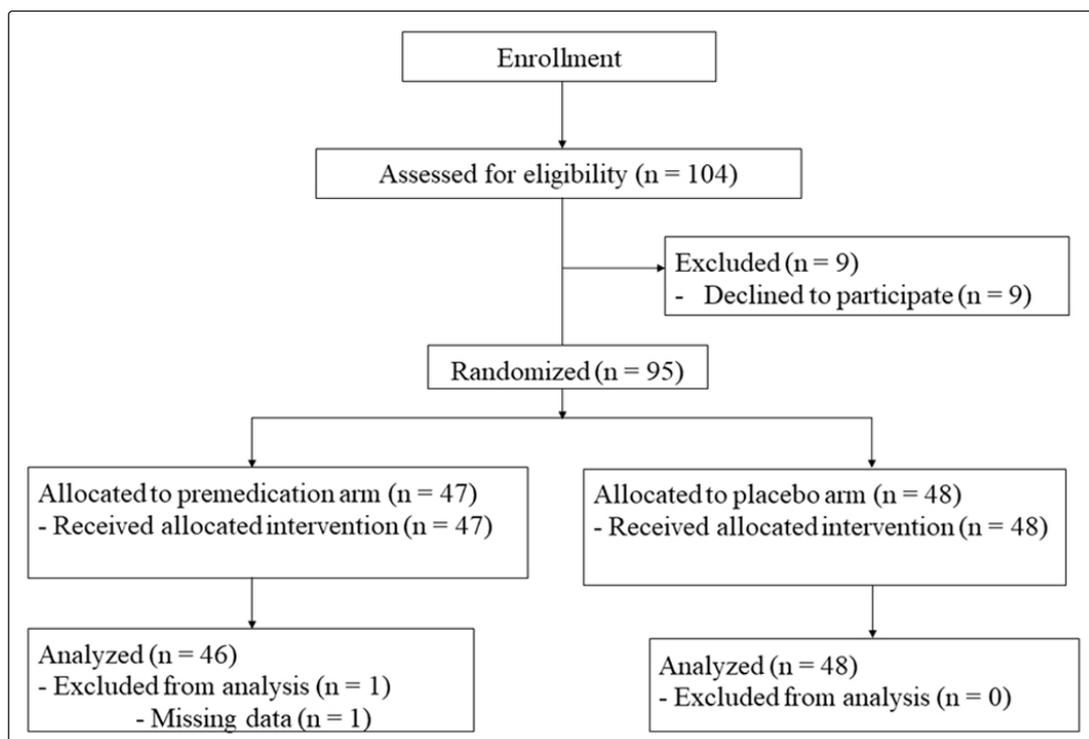


Figure 1 The study flow diagram

Table 1 Patients' Baseline Characteristics

	Premedication (n = 46)	Placebo (n = 48)
Sex		
- Male	12	14
- Female	34	34
Age		
- Mean \pm SD	38.6 \pm 15.1	33.2 \pm 11.0
- Min - Max	19-87	19-59
Weight (kg)		
- Mean \pm SD	51.4 \pm 7.4	49.8 \pm 7.1
- Min - Max	39-67	40-67
Disease		
- β -thalassemia-HbE	29	38
- β -thalassemia major	13	8
- HbEA Bart's disease with CS	0	1
- Hb H disease	1	0
- Hb H-CS	1	1
- MDS	1	0
- PRCA	1	0
Pretransfusion Hb		
- Mean \pm SD	6.90 \pm 0.83	7.10 \pm 0.78
- Min - Max	4.30-7.90	5.10-8.00
Unit(s) of transfused LPRC		
1	13	12
2	33	36

CS, Constant Spring; Hb, hemoglobin; LPRC, leukocyte poor packed red cell; MDS, myelodysplastic syndrome; PRCA, pure red cell aplasia

Table 2 Body temperature, fever, rashes and allergic symptoms recorded between patients receiving premedication and placebo

	Premedication (n = 46)	Placebo (n = 48)	p-value
Peak body temperature			
- Mean \pm SD	36.9 \pm 0.2	37.0 \pm 0.4	0.827
- Min - Max	36.3 - 37.5	36.0 - 39.1	
Fever within 24 hours	0	1 (2.1%)	0.33
Rashes and allergic symptoms within 24 hours	0	0	-

Discussion

In this single-blind, randomized, controlled study, we aimed to investigate the incidence of FNHTR and ATR in patients with chronic transfusion, with or without premedication. Our study showed no significant differences in the incidence of FNHTR and ATR between the premedication and placebo arms. The sensitivity analysis also confirmed the reliability of our primary find-

ings. The incidence of FNHTR in our study was much lower compared with that of related studies, possibly due to the relatively low sample size or current improvement in the procedure of preparing LPRC. Although the limited sample size may have contributed to the absence of reported cases of ATR, our study suggests that the current incidence of ATR is extremely low. Based on our findings, we conclude that premedication

with oral acetaminophen and intravenous CPM prior to LPRC transfusion did not provide significant benefits in preventing very low transfusion events. Therefore, we recommend that premedication with acetaminophen and CPM can be safely omitted in patients with chronic transfusion without any history of severe transfusion reactions. However, almost all patients involved in this study comprised patients with thalassemia. Therefore, the results of this study may be safely applied to chronically transfused thalassemia patients, but they might not be generalized to other patients requiring chronic transfusions such as those with bone marrow failure and chemotherapy-induced anemia.

In our randomized controlled trial, we did not observe any transfusion reactions, transfusion-related complications or adverse events associated with the premedication used in the study. The absence of such occurrences can be attributed to the inherently low incidence of these events as well as the limited sample size of our study population.

To our knowledge, only one related study was conducted in Thailand by Rujkijyanont and colleagues, which investigated the efficacy of acetaminophen and CPM premedication in preventing transfusion reactions among chronically transfused thalassemia patients. However, the incidence of both FNHTR and ATR in that study was significantly higher than what we observed in our study. In that study, the overall incidences of febrile reaction and urticarial rash were 6.9 and 22% among the patients randomized to receive active drugs, compared with 9.5 and 35.2% among patients receiving placebo.¹⁴ The population in that study contained 73 pediatric and adolescent patients, while our current population contained only adult patients. Related studies from two hospitals in Thailand demonstrated the low incidences of FNHTR and ATR, both of which were less than 1%, similar to our current study. The majority of patients in these two hospitals constituted adults. Thus, transfusion

reactions may occur differently between pediatric and adult patients.^{16,17} Additionally, the amount of WBC in LPRCs was not measured in both the related study and our current study. Therefore, the difference in WBC amounts in LPRCs might explain the lower incidence of FNHTR and ATR in our study.

Our study encountered limitations. The sample size was relatively small; and therefore, the small benefit of premedication could not be totally excluded. However, the efficacy is unlikely to have been clinically relevant as the incidence of transfusion reactions without prophylaxis was low. Further study involving patients with chronic transfusion and indications other than thalassemia is warranted before extrapolating the results of this study to routine practice.

Conclusion

The current incidence of FNHTR or ATR is very low among adult patients with chronic transfusion with LPRC. Premedication with oral acetaminophen and intravenous CPM before LPRC transfusion did not have benefits in preventing very low transfusion events. Therefore, acetaminophen and CPM may be safely omitted among chronic transfused patients without a history of transfusion reactions.

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Conflicts of interest statement

None of the authors disclose any potential conflict of interest related to the present article.

References

1. Paiboonsukwong K, Jopang Y, Winichagoon P, Fucharoen S. *Thalassemia in Thailand*. *Hemoglobin*. 2022;46:53-7.
2. Teawtrakul N, Songdej D, Hantaweepant C, Tantiworawit A, Lauhasurayotin S, Torcharus K, et al. *Red blood cell alloimmunization and other transfusion-related complications in patients with transfusion-dependent thalassemia: A multi-center study in Thailand*. *Transfusion*. 2022;62:2039-47.
3. de Swart L, Crouch S, Hoeks M, Smith A, Langemeijer S, Fenaux P, et al. *Impact of red blood cell transfusion dose density on progression-free survival in patients with lower-risk myelodysplastic syndromes*. *Haematologica*. 2020;105:632-9.
4. Lee SE, Yahng SA, Cho BS, Eom KS, Kim YJ, Kim HJ, et al. *Impact of pretransplant red cell transfusion on outcome after allogeneic stem cell transplantation in adult patients with severe aplastic anemia*. *Bone Marrow Transplant*. 2016;51:1323-9.
5. Pool MD. *Adverse Effects of Blood Transfusion*. In: Harmening D, editor. *Modern Blood Banking & Transfusion Practices*. 7th ed. Philadelphia: F.A. Davis Company; 2019.
6. Leelarungsun T, Klomiamsira A, Kitisapkanjana S, Wittayawiwat P, Prungchaiyaphum C, Worachun N, et al. *Effect of the separation time by using an automated blood separator on the hemolysis of leukocyte poor packed red cells*. *J Hematol Transfus Med*. 2019;29:195-203.
7. Fung MK, Grossman BJ, Hillyer CD, Westhoff CM. *Technical Manual*. 18th ed: AABB; 2014.
8. Brand A. *Passenger Leukocytes, Cytokines, and Transfusion Reactions*. *N Engl J Med*. 1994;331:670-1.
9. Paglino JC, Pomper GJ, Fisch GS, Champion MH, Snyder EL. *Reduction of febrile but not allergic reactions to RBCs and platelets after conversion to universal prestorage leukoreduction*. *Transfusion*. 2004;44:16-24.
10. Ezidiegwu CN, Lauenstein KJ, Rosales LG, Kelly KC, Henry JB. *Febrile nonhemolytic transfusion reactions. Management by premedication and cost implications in adult patients*. *Arch Pathol Lab Med*. 2004;128:991-5.
11. Kennedy LD, Case LD, Hurd DD, Cruz JM, Pomper GJ. *A prospective, randomized, double-blind controlled trial of acetaminophen and diphenhydramine pretransfusion medication versus placebo for the prevention of transfusion reactions*. *Transfusion*. 2008;48:2285-91.
12. Sanders RP, Maddirala SD, Geiger TL, Pounds S, Sandlund JT, Ribeiro RC, et al. *Premedication with acetaminophen or diphenhydramine for transfusion with leucoreduced blood products in children*. *Br J Haematol*. 2005;130:781-7.
13. Wang SE, Lara Jr. PN, Lee-Ow A, Reed J, Wang LR, Palmer P, et al. *Acetaminophen and diphenhydramine as premedication for platelet transfusions: A prospective randomized double-blind placebo-controlled trial*. *Am J Hematol*. 2002;70:191-4.
14. Rujkijyanont P, Monsereenusorn C, Manoonphol P, Traivaree C. *Efficacy of Oral Acetaminophen and Intravenous Chlorpheniramine Maleate versus Placebo to Prevent Red Cell Transfusion Reactions in Children and Adolescent with Thalassemia: A Prospective, Randomized, Double-Blind Controlled Trial*. *Anemia*. 2018;2018:9492303.
15. National Healthcare Safety Network: *Blood Safety Surveillance: US Centers for Disease Control and Prevention; 2021* [Available from: <https://www.cdc.gov/nhsn/acute-care-hospital/bio-hemo/>]
16. Urairong K, Yeekian C. *Transfusion reactions and transfusion associated errors*. *J Hematol Transfus Med*. 2013;23:195-202.
17. Chanachaisuwan P, Suwattanadecha K. *Transfusion reactions in Police General Hospital patients during 2006-2012*. *J Hematol Transfus Med*. 2014;24:353-60.