Characteristics of Acute Transfusion Reactions and its related factors in Cipto Mangunkusumo Hospital Jakarta, Indonesia

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Abstrak

Latar belakang: *Reaksi transfusi akut (RTA) merupakan sekelompok kejadian yang tidak diinginkan akibat pemberian transfusi darah. Manifestasi dari RTA bervariasi dari yang ringan hingga mengancam nyawa. Saat ini, data mengenai reaksi transfusi di Indonesia masih sangat terbatas. Dalam studi ini, kami bertujuan untuk memberikan gambaran mengenai karakteristik RTA dan faktor-faktor yang mempengaruhinya.*

Metode: *Studi ini merupakan studi retrospektif yang melibatkan 288 subyek dengan RTA. Studi dilakukan di Rumah Sakit Dr. Cipto Mangunkusumo, dimulai sejak Januari hingga Desember 2017. RTA dikelompokkan berdasarkan sistem tubuh yang mengalami manifestasi, serta derajat manifestasinya.*

Hasil: *Sel darah merah merupakan produk darah utama yang ditransfusikan ke subyek, diikuti dengan konsentrat trombosit, plasma segar beku, dan kriopresipitat. Lima gejala utama dari RTA adalah gatal, demam/kenaikan suhu tubuh, menggigil, urtikaria, dan angioedema. Berdasarkan sistem tubuh yang terkena, umumnya RTA bermanifestasi sebagai gejala pada kulit (56.6%). Berdasarkan derajat manifestasinya, RTA umumnya dikategorikan dalam derajat ringan (55.9%). Anak-anak cenderung mengalami manifestasi yang ringan (64.8%) dan utamanya bermanifestasi pada kulit (65.4%). Riwayat transfusi mempengaruhi derajat RTA secara signifikan. RTA derajat sedang dan gejala konstitusional lebih banyak ditemukan pada subyek yang mendapat PRC dibanding produk darah lainnya.*

Kesimpulan: *Umumnya RTA bermanifestasi sebagai gejala dermatologi. Hanya sedikit kasus RTA yang disebabkan oleh reaksi inkompatibilitas. Manifestasi dan derajat RTA juga dipengaruhi oleh umur, riwayat transfusi, dan jenis komponen darah.* ***(Health Science Journal of Indonesia 2019;10(1):15-20)***

Kata kunci: *Transfusi darah, reaksi transfusi akut, riwayat transfuse, usia*

Abstract

Background: Acute transfusion reactions (ATRs) are a group of adverse events caused by blood transfusions. Manifestations of ATRs vary from mild to life threatening. At present, data about transfusion reactions in Indonesia are still limited. In this study, we aim to determine the characteristics of ATRs and its related factors.

Methods: This was a retrospective study of 288 subjects with ATRs. The study was conducted in Cipto Mangunkusumo Hospital, started from January to December 2017. ATRs were categorized based on the body systems affected and degree of manifestations.

Results: Packed red cells (PRC) was the predominant blood product (51.4%) which was transfused to subjects, followed by thrombocyte concentrate (TC), fresh frozen plasma (FFP), and cryoprecipitate. Five most common predominant symptoms of ATRs were pruritus/itch, febrile/increased temperature, chills, transient urticaria, and angioedema. Based on the affected body systems, the majority of ATRs manifested as dermatologic symptoms (56.6%). Based on the degree of manifestations, the majority of ATRs were categorized as mild degree (55.9%). Children tended to have milder symptoms (64.8%), which mostly manifested as dermatologic symptoms (65.4%). History of transfusion affected the degree of ATR significantly. Moderate degree of ATRs and constitutional symptoms were found more common in subjects who received PRC than other blood products.

Conclusion: Most of ATRs manifest as dermatologic symptoms, which represent allergic reactions. Only a small portion of ATRs are caused by incompatibility reactions. The manifestation and degree of ATRs are also affected by age, history of transfusion, and type of blood components. ***(Health Science Journal of Indonesia 2019;10(1):15-20)***

Keyword: Blood transfusion, acute transfusion reaction, transfusion history, age

Acute transfusion reactions (ATRs) are a group of adverse events which occur within 24 hours after starting blood transfusion. Transfusion reactions are the most common side effects related to blood products administration. Previous studies reported various incidence rate of transfusion reactions, started from 0.4% to 1.1%.[1,2] In the mild form, the most common manifestation was feeling discomfort, which was found in 0.16% patients.[2] Around 0.14% of transfusion reactions manifested as breathing problems, which is life-threatening and need immediate treatments.[2,3]

Transfusion reactions are divided into two main groups: non-hemolytic transfusion reactions and hemolytic transfusion reactions. Acute non-hemolytic transfusion reactions vary from mild pruritus, transient urticaria, febrile non-hemolytic transfusion reaction (FNHTR) to most fatal form like transfusion-related acute lung injury (TRALI). Acute hemolytic transfusion reactions are usually the result of incompatibility of red blood cell donor with patient's antibody. The symptoms are various, including sudden onset of febrile or chills, hypotension, dyspnea, hemoglobinuria, disseminated intravascular coagulation, and acute renal failure.[4]

Hemovigilance is a set of systematic procedures to detect any adverse events and incidences in the whole transfusion chain, from the collection of blood, processing blood products, until follow up of its recipients. Hemovigilance is very important to prevent any adverse events related to blood product transfusion.[5]

Understanding the characteristics of transfusion reaction and its contributing factors are important to construct plan in facing transfusion reactions. At present, there are limited data about transfusion reactions in Indonesia. Therefore, in this study, we aim to determine the characteristics of acute transfusion reactions and its relations with other contributing factors.

METHODS

This was a retrospective descriptive study conducted at Cipto Mangunkusumo Hospital, an Indonesian national referral hospital. The data of transfusion reactions were obtained from inpatients and outpatients from all unit/department in the hospital. This study started from January to December 2017. Total sampling was preferred to produce more reliable results.

In our center, transfusion reactions were categorized into three different degree: 1) mild (e.g. localized erythema, pruritus, mild rash, transient urticaria/ flushing); 2) moderate (e.g. unexplained febrile $\geq$ 39^{o}C, temperature rise $\geq$ 2^{o}C, chills, rigors, multiple rash, nausea, vomiting, myalgia, angioedema/ wheezing/persistent urticaria without signs of circulatory problems); 3) severe (e.g. hypotension, any signs of shock, dyspnea, severe stridor, angioedema, anaphylaxis, chest pain, headache, bleeding, and hemoglobinuria).

Meanwhile, based on the affected body systems, transfusion reactions were grouped into dermatologic (e.g. edema, erythema, pruritus, flushing), respiratory (e.g. dyspnea, wheezing), constitutional (e.g. chills, febrile, rigors, diaphoresis, pain), neurological (e.g. seizure, dizziness, lethargy, agitation, twitching), and circulatory symptoms (hypotension, tachycardia).

The experiment used archive materials which do not have link with patient information.

RESULTS

Transfusion reactions were occurred in 288 subjects (0.5%) from a total of 57.227 patients received blood transfusion. Table 1 showed that the number of children subjects (56.6%) were greater than adults (43.4%). No significant difference was observed between the number of male and female subjects. Packed red cells/PRC (51.4%) was the predominant blood product which caused transfusion reactions, followed by thrombocyte concentrate/TC (43.4%), fresh frozen plasma/FFP (4.2%), and cryoprecipitate (1.0%). A total of 51.4% of subjects had past transfusion history.

There were many manifestations of acute transfusion reactions (Table 1). Five most common predominant symptoms of ATRs were pruritus/itch (27.4%), febrile/increased temperature (19.1%), chills (14.2%), transient urticaria (9.7%), and angioedema (7.7%).

ATRs could be classified by several indicators. Based on the affected body system, the majority of subjects had dermatologic (56.6%) and constitutional symptoms (34.4%). Based on the degree of transfusion reaction, most of subjects had mild (55.9%) and moderate (33.0%) manifestations (Table 2).

Table 1. Characteristic of subjects

Characteristics	n (%)
Age	
≤ 18 years	163 (56.6)
> 18 years	125 (43.4)
Gender	
Male	136 (47.2)
Female	152 (52.8)
Blood products	
PRC	148 (51.4)
TC	125 (43.4)
FFP	12 (4.2)
Cryoprecipitate	3 (1.0)
Past transfusion history	
Yes	148 (51.4)
No	140 (48.6)
Predominant symptoms	
Pruritus/itch	79 (27.4)
Febrile or temperature rise	55 (19.1)
Chills	41 (14.2)
Transient urticaria	28 (9.7)
Angioedema	22 (7.7)
Flushing	20 (6.9)
Dyspnea	18 (6.2)
Rash	14 (4.9)
Hypotension	6 (2.1)
Nausea	3 (1.1)
Seizure	2 (0.7)

Table 2. Classification of transfusion reactions.

Transfusion reaction categories	n (%)
Systems involved	
Dermatologic symptoms	163 (56.6)
Constitutional symptoms	99 (34.4)
Respiratory symptoms	18 (6.3)
Circulatory symptoms	6 (2.1)
Neurological symptoms	2 (0.7)
Degree of transfusion reactions	
Mild	161 (55.9)
Moderate	95 (33.0)
Severe	32 (11.1)

Due to some limitations, we proceeded further evaluation in only 64 subjects or 50.4% of total subjects with moderate and severe manifestations. Table 3 showed that no incompatibility was found in 70.3% of the evaluations. Major incompatibility was found in two subjects with manifestation of febrile and chills. Minor incompatibility with positive donor HLA antibody was detected in one subject, which presented with TRALI. Antibodies in the rest of minor incompatibility results were undefined.

Table 3. Detection of incompatibility

Type of incompatibility	n (%)	Manifestation
Major incompatibility		
anti-E	1 (1.6)	Febrile and chills
anti-E and anti-c	1 (1.6)	Febrile and chills
Minor incompatibility		
anti-HLA antibody	1 (1.6)	TRALI
Undefined antibody	16 (25)	variative
No incompatibilty	45 (70.2)	

Most of children subjects had dermatologic symptoms (65.4%), while manifestations in adult subjects were dominated by dermatologic and constitutional symptoms (42.2%). Age of the subject affected the manifestation significantly (p=0.001). History of past transfusion did not affect the manifestation significantly (p=0.109). Mostly, subjects who got TC, FFP, and cryoprecipitate showed dermatologic symptoms (72.8%, 83.3%, and 100%, respectively). Interestingly, constitutional symptoms were the most common manifestations in patients who got PRC (Table 4).

Age of the subject also affected the degree of transfusion reactions significantly (p=0.001). Most of children subjects showed mild manifestations, while adult subjects showed mild and moderate manifestations. Past transfusion history also affected the degree of manifestations (p=0.022). Severe manifestations were found more common in patients without transfusion history (15.7%) than patients with transfusion history (6.7%). The majority of patients who got TC, FFP, and cryoprecipitate had mild manifestations. Meanwhile, patients who got PRC transfusion commonly had moderate (43.2%) and mild (42.6%) manifestations (Table 5).

DISCUSSIONS

In our study, we found PRC was the blood component that contributes the most acute transfusion reactions, followed by TC, FFP, and cryoprecipitate. The main explanation for this is the fact that the most common blood components being transfused in order are PRC, TC, FFP, and cryoprecipitate. Other studies also found similar results. Study in Japan revealed that the incidence of transfusion reaction per transfusion unit was higher in TC (3.8%), compared to FFP (1.3%), and PRC (0.6%).[6] Meanwhile, another study in India revealed that the highest incidence of transfusion reactions was occurred in patients receiving PRC (1.4%) and FFP (0.6%), but transfusion reactions never occurred in patients receiving TC.[7] These discrepancies may be explained by the fact that the transfusion reactions are affected by several factors, including ethnicity and clinical diagnosis.[8,9]

Table 4. Factors affecting predominant symptoms of transfusion reactions

	Symptoms, n(%)					p value
	Dermatologic	Constitutional	Respiratory	Circulation	Neurological	
Age						
≤ 18 years	117 (65.4)	53 (29.6)	6 (3.4)	2 (1.1)	1 (0.6)	0.001
> 18 years	46 (42.2)	46 (42.2)	12 (11.0)	4 (3.7)	1 (0.9)	
Past transfusion history						
Yes	94 (63.5)	45 (30.4)	8 (5.4)	0 (0)	1 (0.7)	0.109
No	69 (49.3)	54 (38.6)	10 (7.1)	6 (4.3)	1 (0.7)	
Type of blood products						
PRC	59 (39.9)	70 (47.3)	12 (8.1)	5 (3.4)	2 (1.4)	
TC	91 (72.8)	27 (21.6)	6 (4.8)	1 (0.8)	0 (0)	
FFP	10 (83.3)	2 (16.7)	0 (0)	0 (0)	0 (0)	N/A
Cryoprecipitate	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	

Table 5. Factors affecting the degree of transfusion reaction

	Category, n(%)			p value
	Mild	Moderate	Severe	
Age				
≤ 18 years	116 (64.8)	52 (29.1)	11 (6.1)	0.001
> 18 years	45 (41.3)	43 (39.4)	21 (19.3)	
Past transfusion history				
Yes	92 (62.2)	46 (31.1)	10 (6.7)	0.022
No	69 (49.3)	49 (35.0)	22 (15.7)	
Type of blood products				
PRC	63 (42.6)	64 (43.2)	21 (14.2)	N/A
TC	85 (68.0)	29 (23.2)	11 (8.8)	
FFP	10 (83.3)	2 (16.7)	0 (0)	
Cryoprecipitate	3 (100)	0 (0)	0 (0)	

In total, allergic reactions (pruritus/itch, transient urticaria, rash, etc) and febrile were the most common manifestations of ATR. This result was consistent with Bassi R study, which found that the most common clinical features of transfusion reactions were FNHTR and allergic reaction.[10] Allergic reactions are caused by reaction of recipient's IgE with allergen from donor, leading to release of mediators from mast cells. Several allergens that has been documented are donor's plasma protein (IgA and haptoglobin), chemical allergens (methylene blue in FFP preparation), and food allergen. Allergic reactions are also caused by passive transfer of antibodies and passive sensitization, when IgA and IgE-specific antibodies are infused from donor to patient.[11] Other studies found that allergic transfusion reactions might occur without allergen involvement, especially in platelet transfusions. Stored platelet concentrates contain accumulated inflammatory cytokines and chemokines, which directly bind to receptors in mast cells and basophils, called biological response modifiers (BRMs), including vascular endothelial growth factor, sCD40 ligand, and transforming growth factor-β1.[12,13]

Anaphylactic reactions (hypotension, bronchospasm, angioedema, etc) are the severe form of allergic reactions. It is caused by interaction of recipient's antibody with donor's plasma protein including IgA, haptoglobin, complement, and ethylene dioxide [11]. In case of anaphylaxis, IgG mediated mechanisms plays an important role, beside Ig-E mediated mechanisms. IgG specific allergen binds to FcγRs and causes subsequent release of platelet-activating factor (PAF) from basophil. In this mechanism, PAF is the major mediator for systemic anaphylaxis, rather than histamine.[12]

Febrile, rise in temperature, and chills are caused by interaction of WBC antigen – antibody and consequent cytokines release. Some cytokines that has been identified as the primary cause of febrile related transfusion are interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor α, which are released from leukocytes by acute hemolytic process (febrile hemolytic transfusion reaction/FHTR) or during storage (FNHTR).[11,14-16]

In our study, we found two cases of major incompatibility of rhesus antigen. One subject had anti-E, while the other had anti-E and anti-c, both in pre-transfusion and post-transfusion blood samples.

Interestingly, manifestations that appeared in both subject were only fever and chills. Other symptoms of acute hemolytic transfusion reactions (e.g. flank pain and hemoglobinuria), which usually appear in major incompatibility transfusion reaction cases, did not appear.[17] The symptoms resolved after transfusion was stopped and administration of acetaminophen and antihistamine IV. Goodell PP study demonstrated that 85.7% of patients with positive non-ABO incompatibility did not show any symptoms of transfusion reactions [18]. Besides, rhesus antigen C, c, E, and e are less immunogenic than antigen D.[16] The patient had underwent crossmatch analysis before transfusion, but the result was negative. Therefore, antibody screening before transfusion was conducted in our center since mid 2017.

One subject showed signs and symptoms of TRALI during administration of PRC. Further examination proved that the subject had minor incompatibility, and HLA antibody was detected in blood donor. Antibodies of a quarter of subjects with incompatibility could not be determined. They had various manifestations, including febrile, chills, urticaria, and angioedema. National Blood Bank plays an important role to assure that the donor with HLA antibody is excluded for further donation of any blood products.[11] In this study, we found that children tended to have milder ATRs than adults. Dermatologic symptoms, which represent allergic reaction, were found more common in children. The same results were also found by Oakley FD study, which demonstrated the incidence of allergic transfusion reaction between children and adults were 2.7/1000 and 1.1/1000.[19]

In this present study, we observed that from the total subjects who experienced transfusion reactions, the number of subjects with past transfusion history was almost equal to the number of subjects who never got transfusions. Moreover, subjects with transfusion history tended to have milder symptoms and mostly manifested as allergic reactions. This result can be explained by Kato H study which showed that first transfusion incidences of allergic reactions are higher than on subsequent transfusions.[20] On the contrary, Gwaram BA study showed previous transfusion history increased the risk of getting transfusion reactions.[21] Pedrosa AKKV study found that previous history of transfusion was not significantly associated with the type of transfusion reactions.[22] These discrepancies may be explained because the study population characteristics (including race) and type of blood being used in the practice are different from one study to others.

Most of subjects with PRC transfusion had constitutional symptoms, while subjects who received other blood products transfusion had dermatologic symptoms. Similar result was also found in Cho J study, which observed that the most common cause of FNHTR was RBC transfusion.[23] This can be explained by the fact that PRC has the greatest number of leukocytes, followed by TC, FFP, and cryoprecipitate.[24] Previous study proved that the prevalence of FNHTRs was reduced in the pre-storage leukocyte-reduced RBC transfusion and the prevalence of allergic reactions was reduced in the pre-storage leukocyte-reduced platelets transfusion.[15] It is hardly to determine whether allergic reactions following platelet transfusion are caused by plasma proteins or BRMs, but there is general agreement that the decreased amounts of plasma protein will reduce the risk of allergic reactions.[12]

Limitation of this study is not all subjects with moderate or severe transfusion reactions can be proceeded into further examinations. Other limitations are lack of data about leuco-filtration status for each blood component and the occurrence time of each transfusion reaction. Therefore, further studies with adding these variables are needed to fully comprehend the characteristics of transfusion reaction and its related factors, especially in Indonesian population.

In conclusion, PRC is the most common blood product received by subjects with transfusion reaction. ATRs predominantly manifest as dermatologic symptoms, which represent allergic reactions. Only a small portion of the ATRs are caused by incompatibility reactions. ATRs of PRC usually manifest as constitutional symptoms. ATRs of other blood components mostly manifest as allergic reactions. Children usually have milder ATRs, which are frequently presented as dermatologic symptoms. History of transfusion also affects the degree of ATRs.

From this study, we suggest for every blood transfusion practitioner to obtain full transfusion and adverse reactions history prior to transfusion. It is mandatory to closely monitor any adverse reactions related to transfusion, from the mildest to the most severe one. For patients receiving PRC, medical team members must be ready if any constitutional symptoms appeared, while for patients receiving other blood components, medical team members must be ready encounter allergic reactions.

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Conflict of interest

There is nothing to declare.

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