Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:382-388
DOI: 10.4274/BMJ.galenos.2023.2023.4-3

Research

Non-infectious Causes of Blood Transfusion Reactions: A Tertiary Hospital Review

Kan Transfüzyon Reaksiyonlarının Bulaşıcı Olmayan Nedenleri: Bir Üçüncü Basamak Hastane İncelemesi

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ABSTRACT

Objective: Blood transfusion is a life-saving medical intervention. Transfusion reactions are undesirable consequences of this intervention and may present with various findings. Using data from our hospital and hemovigilance procedures that included electronic recording, our aim was to evaluate non-infectious transfusion reactions.

Methods: We present reaction data from electronic recordings of blood products transfused between January 2017 and December 2021. Gender, age, symptoms and findings, blood pressure, fever, respiratory and heart rates before and after transfusion were analyzed according to reaction types. Reactions were classified according to clinicians definition. Analysis of the data was carried out using the SPSS 25 package program.

Results: While allergic transfusion reactions and febril nonhemolitic transfusion reactions were common transfusion reactions, the most common reaction products were fresh frozen plasma, erythrocyte suspension and platelet suspension respectively. Chills, restlessness, fever, were common signs and symptoms. While allergic transfusion reactions were higher in pediatric patients, there was no difference between genders. The high number of patients who had a previous transfusion among the patients who developed a reaction suggested that exposure did not reduce the risk. More notifications were made after the use of electronic records than in previous years.

Conclusion: Electronically recorded hemovigilance data can contribute to an increase in accurate classification and reporting of transfusion reactions and monitoring of blood processes.

Keywords: Transfusion reactions, allergic reactions, febrile reactions, electronic hemovigilance, transfusion related adverse events

ÖZ

Amaç: Kan transfüzyonu hayat kurtarıcı bir tıbbi müdahaledir. Transfüzyon reaksiyonları bu girişimin istenmeyen sonuçlarıdır ve çeşitli bulgularla karşımıza çıkabilir. Amacımız; hastanemizden elde edilen verileri ve elektronik kaydı içeren hemovijilans prosedürlerini kullanarak enfeksiyöz olmayan transfüzyon reaksiyonlarını değerlendirmekti.

Gereç ve Yöntem: Ocak 2017 ile Aralık 2021 tarihleri arasında transfüze edilen kan ürünlerinin elektronik kayıtlarından elde edilen reaksiyon verileri incelendi. Transfüzyon öncesi ve sonrası cinsiyet, yaş, semptom ve bulgular, kan basıncı, ateş, solunum ve kalp hızları reaksiyon tiplerine göre analiz edildi. Reaksiyonlar klinisyen tanımına göre sınıflandırıldı. Verilerin analizi SPSS 25 paket programı kullanılarak yapılmıştır.

Bulgular: Alerjik transfüzyon reaksiyonları ve hemolitik olmayan febril transfüzyon reaksiyonları sık görülen transfüzyon reaksiyonları iken, en sık reaksiyon görülen ürünler sırasıyla taze donmuş plazma, eritrosit süspansiyonu ve trombosit süspansiyonuydu. Titreme, huzursuzluk, ateş yaygın

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Cite as: Karabela ŞN, Canbolat Ünlü E, Pamak Bulut S, Yılmaz D, Altungayular S, Baydili KN, Alacahan R, Taşpolat İ, Gedik H, Kart Yaşar K. Non-infectious Causes of Blood Transfusion Reactions: A Tertiary Hospital Review. Med J Bakirkoy 2023;19:382-388

Received: 22.04.2023
Accepted: 17.10.2023

belirti ve semptomlardı. Alerjik transfüzyon reaksiyonları pediatrik hastalarda daha fazla görülürken, cinsiyetler arasında fark yoktu. Reaksiyon gelişen hastalar arasında daha önce transfüzyon geçirmiş hasta sayısının fazla olması maruziyetin riski azaltmadığını düşündürdü. Elektronik kayıtların kullanılmasından sonra geçmiş yıllara göre daha fazla bildirim yapılmıştır.

Sonuç: Elektronik olarak kaydedilen hemovijilans verileri, transfüzyon reaksiyonlarının doğru sınıflandırılmasında ve raporlanmasında ve kan süreçlerinin izlenmesinde artışa katkıda bulunabilir.

Anahtar Kelimeler: Transfüzyon reaksiyonları, alerjik reaksiyonlar, ateşli reaksiyonlar, elektronik hemovijilans, transfüzyonla ilişkili istenmeyen olaylar

INTRODUCTION

Transfusion reactions (TRs) are adverse events associated with the transfusion of blood products and findings such as fever, chills, pruritus, and urticaria are common (1). Reactions after blood transfusion can be listed as acute hemolytic transfusion reactions (AHTR), febrile non-hemolytic transfusion reactions (FNHTR), allergic transfusion reaction (ATR), transfusion related acute lung injury (TRALI) and transfusion associated circulatory overload (TACO) (2-4).

AHTRs are rare life-threatening reactions including fever, chills, flank pain and leakage from intravenous sites caused by ABO incompatibility due to labeling errors or reactions against the alleles of other red blood cell antigen systems (2).

FNHTRs including chills, flushing, headache, tachycardia, mild dyspnea, and nausea/vomiting defined as the body temperature is ≥38 °C during or within 4 hours or a rising more than 1 °C from the onset of transfusion without symptoms of hemolysis and no evidence of infectious/ environmental reason (3).

ATR is a common form of acute TR and present with by urticaria, pruritus, erythematous rash, angioedema, bronchospasm, and/or hypotension (4). The best known and relatively rare pulmonary complications of transfusion are TRALI (<0.01%) and TACO (<1%). TACO is a type of pulmonary edema due to volume excess or circulatory overload. TRALI is a life-threatening form of acute lung injury that includes fever, chills, and respiratory distress (5).

Electronic records are effectively used for routine health data such as demographic information, diagnosis, imaging and laboratory findings in healthcare services (6). Hemovigilance systems also take advantage of this opportunity through intrahospital and national networks. The use of electronic technologies can speed up data collection and feedback thus enabling hemovigilance centers to access transfusion-related information early. It has been reported that, electronic records powered by clinical decision support systems increase the verified reaction reporting (7,8). It has been reported that repeated exposure, rather than the total volume of transfused blood product, may influence the incidence of ATRs (9).

In addition the incidence of reactions, when evaluated per patient transfused, may differ from that calculated based on the number of blood products (10).

The aim of this retrospective study is to evaluate blood transfusion reactions in a tertiary care hospital based either on product or patient via the data of hemovigilance center. The data obtained after the electronic hemovigilance records were started to use were compared with the previous period. In addition, the changes in the clinical findings of the patients before and after the transfusion and the relationship between the reactions and repeated exposure are presented.

METHODS

A total of 200,256 transfusion forms reported to the hemovigilance center in 2017-2021 were evaluated retrospecvtively. Reactions were classified as "Anaphylactic, AHR, ATR, FNHTR, TACO, TRALI and Unidentified" according to clinicians' definition. The data of the patients such as gender, age, symptoms and findings, blood pressure, fever, respiratory and heart rates before and after transfusion were analyzed according to reaction types.

Figure 1 depicts the flow of requests and notifications for blood products at our institution. The feedback rate in our hospital is over 98% (11). Reaction definitions have been categorized by clinicians according to Turkish National Hemovigilance guidelines (12). The data of our study was obtained from these digital forms by two different researchers.

Transfused blood products were classified as erythrocyte suspension (ES), fresh frozen plasma (FFP), whole blood, platelet suspensions (PSs) (random, pooled, apheresis), cryoprecipitate and others. TRs incidence according to blood product types was defined as the number of reactions divided by the total number of products transfused and the number of patients. For each TR, the average of the clinical findings (blood pressure, body temperature, respiration

and heart rate) was taken into account whether there was a difference between before and after transfusion. Types of reactions and causative blood products were listed according to previous transfusion status. Hamidiye Clinical Research Ethics Committee of Health Sciences University approval was obtained for the research and ethical rules were followed (decision no: 35/20, date: 19.11.2021).

Statistical Analysis

Analysis of the data was carried out using the SPSS 25 package program. Frequency and percentage values for qualitative variables, median, minimum and maximum values for quantitative variables are presented. Chi-square test was used for comparisons between two qualitative variables. In order to compare the difference before and after transfusion, the difference score was calculated for the discrete variables and the percentage change for the continuous variables. The Kruskal-Wallis H test was used for comparisons between qualitative and quantative variables containing more than two categories. If there was a significant difference in the Kruskal-Wallis H test, the categories were compared in pairs with the Mann-Whitney U test. In the study, the type error rate was taken as 0.05.

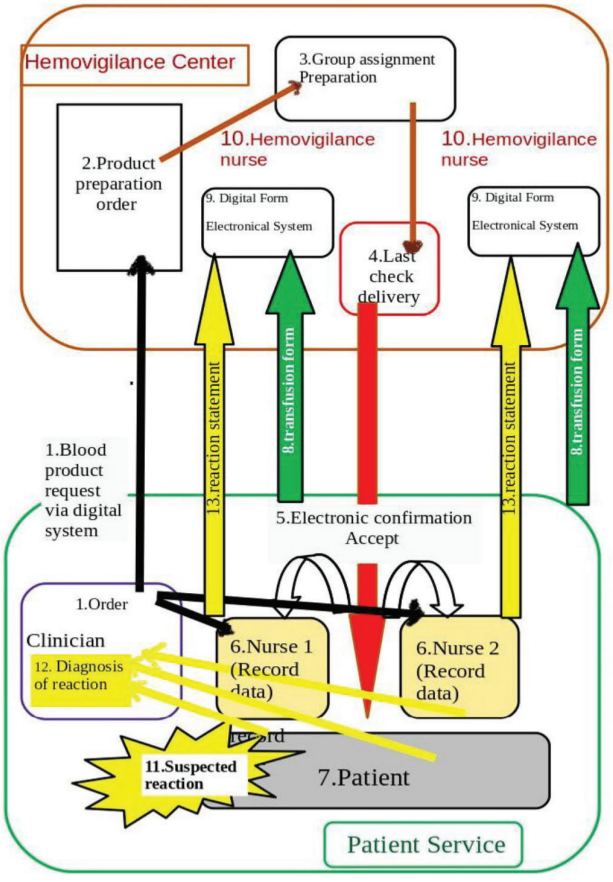

Figure 1. Demand and feedback flow for blood products. 1. The blood product is digitally ordered from the Hemovigilance Center for the patient. 2-4. When the group of the blood product is verified by the system, it is approved and delivered to the service nurse. 5. The blood product is received by scanning the barcode. 6. Transfusion is started under the control of two nurses. 7. The vital signs of the patient are recorded electronically every 15 minutes. 8. When the transfusion is finished, the form is transmitted electronically to the hemovigilance center. 9-10. The hemovigilance nurse evaluates electronic forms. 11,12. If a transfusion reaction is suspected, the clinician is informed. The reaction is diagnosed. 13. The characteristics of the reaction, the type of blood product, the patient's symptoms and signs are recorded. It is delivered to the transfusion center through the system. Steps 9 and 10 are repeated

RESULTS

Between January 2017 and December 2021, 43,516 patients received 200,256 blood product transfusions in our hospital. The frequency of transfused blood products is 46.2% with ES, 37.2% with FFP and 15% with PS, respectively. A total of 261 TRs were reported in 234 patients. Table 1 displays the distribution by product.

TRs were most frequently seen with FFP (48.3%), followed by ES (41.7%) and PSs (9.6%). When evaluated according to product, the incidence of TR was found to be the highest (0.17%) with FFP and whole blood. When evaluated according to the number of transfused patients, the incidences of reactions were 0.72% in FFP, 0.66% in random PSs and 0.44% in ES.

The mean age of the patients who developed a TR was 46.56 (±24.15) years. The most common TR was ATR (63.9%) and FHTR (13%). Types of reactions are shown in Figure 2. There were no AHTR and fatal reaction. In 44 patients (16.85%) TRs could not be classified. Mild allergic reactions appeared to be the most common TR for each blood product.

Between 2017 and 2021, the annual TR numbers that were recorded by years were 42, 76, 66, 41, and 36. Notifications grew from 22 to 52 on average per year. In patients who experience a TR, chills (17.9%), restlessness (6%), fever (16.2%), skin rash (15.7%), and itching (7.2%) were the most prevalent symptoms and findings (Figure 3).

Table 2 compares vital indicators before and after transfusion in accordance with the different forms of reaction. Patients who were classified as having a febrile reaction had higher post-transfusion fever levels than other patients ($p<0.001$).

In patients with mild allergic reaction, pre-transfusion systolic arterial blood pressure was lower than the others ($p=0.018$). Generally, the type of reaction could not be defined in patients with a significant increase in pulse values after transfusion ($p=0.002$). There was no difference between reaction types in terms of other variables examined. There was no difference in reaction types according to gender ($p=0.34$). However, mild allergic reactions were more common in pediatric patients (n=29, 87.9%) compared to adults (n=129, 66.5%) ($p=0.044$). One hundred and fifty-nine

Table 1. Numbers of reactions and ıncidence according to blood products

Blood component	N. of transfused products	N. of reactions	Incidence of product (%)	N. of transfused patients	N. of patients who had a reaction	Incidence of patient-reaction (%)
Erythrocyte suspension	92,609	109	0.12	23,580	105	0.44
Fresh frozen plasma	74,502	126	0.17	14,674	107	0.72
Platelet suspension (random)	22,304	19	0.08	2,400	16	0.66
Platelet suspension (pooled)	5,748	4	0.07	1,411	4	0.28
Cryoprecipitate	2,176	0	0	247	0	0
Platelet suspension (apheresis)	2,130	2	0.09	647	2	0.3
Whole blood	574	1	0.17	415	1	0.24
Other*	213	0	0	142	0	0
Total	**200,256**	**261**	**0.13**	**43,516**	**234****	**0.53**

N.: Number, *Apheresis granulocyte, apheresis immune fresh frozen plasma, **One patient had a reaction with both erythrocyte suspension and fresh frozen plasma

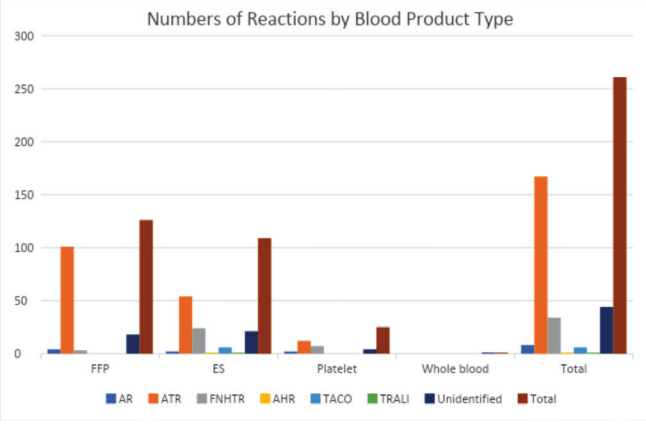

Figure 2. Numbers of reactions by blood product type
AR: Anaphylactic reaction, ATR: Allergic transfusion reaction, FNHTR: Febrile non-hemolytic transfusion reaction, AHR: Acute hemolytic reaction, TACO: Transfusion-associated circulatory overload, TRALI: Transfusion-related acute lung injury, FFP: Fresh frozen plasma, ES: Erythrocyte suspension

(67.9%) of the 234 individuals who experienced a response had previously received a blood product transfusion. Table 3 contains distributions by products and reaction.

DISCUSSION

While the risk of infection in transfusions is reduced thanks to the good examination of donors, non-infectious complications continue to be a clinical problem. These complications are usually TRs (13). The information gathered by reporting the reactions to the hospital's hemovigilance unit may be useful in the future.

Hemovigilance is dependent on the nurse and clinician notifying the transfusion center of information pertaining to transfusions. The typical transfusion process or the diagnostic results of an emerging response may be included in this information. The formats in which the information is delivered, however, take time to get to the center. Data collection and feedback can be accelerated by the deployment of electronic technologies that allow hemovigilance centers to quickly access transfusion-related information (7).

The hemovigilance system's inclusion of a decision support system and the development of electronic algorithms in response to the findings boost the reporting of TR (6). There is no such warning system in our study. However, the requirement to complete the form on the computer screen and the standardization of reporting, including clinical findings, provided for more frequent and extensive reporting of reactions.

While the rates were between 0.05% and 0.18% in previous studies of the incidence of reactions, this rate was found to be 0.13% in our study (14,15). We think that the reason why no hemolytic reaction was observed in our follow-ups is our strict control strategies. Our findings support studies showing that the ratio of reactions by product or patient changes the incidence results (10).

Our research revealed that non-serious transfusion responses shared similar symptoms. Clinicians may have difficulty correctly identifying the reaction as a result.

According to the literature, febrile nonhemolytic and allergic reactions are reported more frequently than other (15-20).

In line with the literature, we discovered that allergic reactions to transfusions occurred more frequently (0.4%)

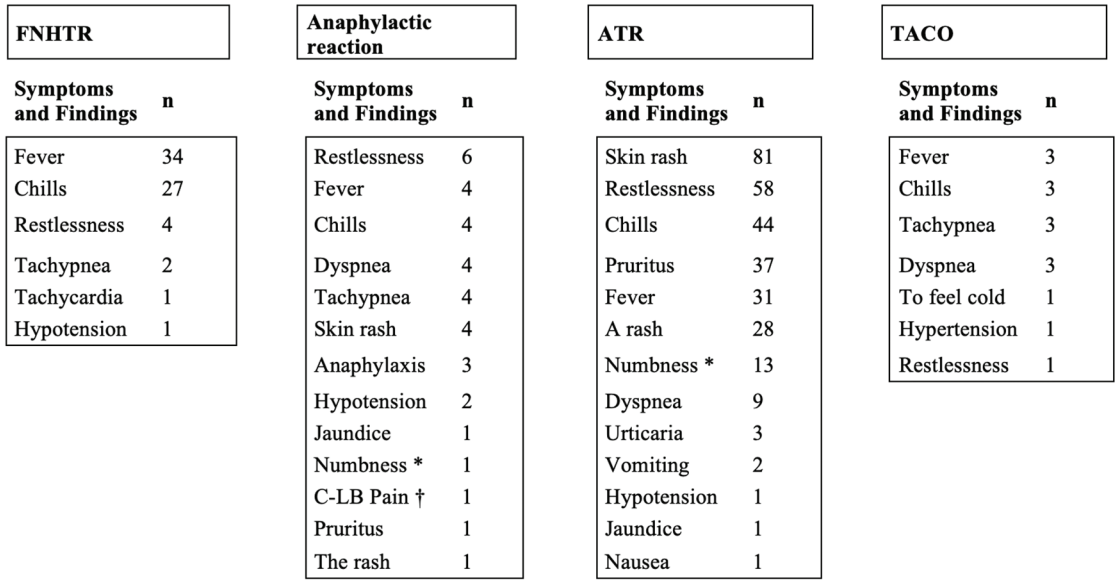

Figure 3. Symptoms and findings

FNHTR: Febrile non-hemolytic transfusion reaction, ATR: Allergic transfusion reaction, TACO: Transfusion-associated circulatory overload, TRALI: Transfusion-related acute lung injury, *Numbness (in the finger and around the mouth), †Chest and lower back pain

Table 2. Clinical findings by reactions

	FNHTR	ATR	Unidentified reaction	Kruskal-Wallis H	p-value
Temperature before transfusion/°C	36.7 (36-38,8)	36.5 (35.4-38)	36.6 (36-37.2)	3.267	0.195
Temperature after transfusion/°C	37.8 (36.2-39.1)	36.6 (35.5-39.4)	36.7 (35.6-39)	35.283	<0.001*
Pre-transfusion systolic blood pressure/ mmHg	117 (66-154)	112.5 (65-189)	120 (65-180)	8.001	0.018*
Pre-transfusion diastolic blood pressure/ mmHg	70 (39-92)	70 (10-94)	70 (22-85)	1.591	0.451
Post-transfusion systolic blood pressure/ mmHg	117 (66-177)	118 (65-186)	118.5 (60-175)	0.305	0.858
Post-transfusion diastolic blood pressure/ mmHg	70 (28-93)	71 (24-100)	70 (20-90)	4.144	0.126
Pre-transfusion peripheral pulse beats/ minute	88 (73-150)	87 (21-179)	91.5 (62-172)	5.062	0.080
Post-transfusion peripheral pulse beats/ minute	92 (75-172)	88 (18-193)	100.5 (60-196)	12.554	0.002*
Pre-transfusion respiratory rate/minute	20 (15-58)	20 (12-52)	20 (14-98)	0.882	0.643
Post-transfusion respiratory rate/minute	20 (16-60)	20 (12-61)	20 (14-98)	2.473	0.290
Difference temperature/°C	2,459 (-0.79-7.44)	0 (-100-6.94)	0.2743 (-2.2-5.98)	29.332	<0.001*
Difference systolic/mmHg	3.7736 (-45.9-55)	4.6537 (-100-96.63)	-7.5599 (-50-84.62)	5.665	0.059
Difference diastolic/mmHg	6.9444 (-53.33-1.54)	0 (-100-600)	-6.4583 (-71.43-263.64)	5.090	0.078
Difference peripheral pulse beats/minute	2 (-8-24)	0 (-83-47)	4 (-35-76)	6.865	0.032*
Difference respiratory rate/minute	0 (-2-5)	0 (-16-13)	0 (-5-33)	1.240	0.538

*p<0.05 Kruskal-Wallis H: Kruskal-Wallis H test calculation value. ATR: Allergic transfusion reaction, FNHTR: Febrile non-hemolytic transfusion reaction

Table 3. Previous exposure to blood products and reaction type

		Previously transfused patient (n)	Patient not transfused before (n)
Blood product	ES	77	28
	FFP	65	41
	PS	17	5
	Whole blood	0	1
Total		**159**	**75**
Reaction type	ATR	99	46
	FNHTR	22	8
	Anaphylactic	8	0
	TACO	4	1
	TRALI	1	0
	AHR	1	0
	Unidentified	24	20
Total		**159**	**75**

AR: Anaphylactic reaction, ATR: Allergic transfusion reaction, FNHTR: Febrile non-hemolytic transfusion reaction, AHR: Acute hemolytic reaction, TACO: Transfusion-associated circulatory overload, TRALI: Transfusion-related acute lung injury, FFP: Fresh frozen plasma, ES: Erythrocyte suspension, PS: Platelet suspensions

than other reactions. According to several research, the incidence of allergic responses may exceed 3% (20-22). The frequency of ATR development linked with the use of these products is related to the highest incidence of responses following transfusions of whole blood and FFP. It is known that plasma proteins play a role in the reactions. TR risk is increased by recipient features, such as atopic susceptibility and high immunoglobulin E levels (21).

To minimize whole blood responses, it has been deemed crucial to carry out the proper predonation screening, particularly by assessing mean blood pressure (23). One patient experienced a reaction following a transfusion of whole blood, however the type of reaction could not be defined. We suspected that low systolic blood pressure before to donation would be a risk factor for allergic reactions when we assessed the systolic and diastolic blood pressures of our patients with other reactions.

Febrile nonhemolytic reactions were found to be lower than the literature (28-61%) (22,24). In the presence of symptoms such as rash and redness, it is possible to define an allergic reaction and also fever can be seen in other reactions. In the presence of additional findings, it was thought that clinicians were undecided about the type of reaction. Unfortunately; the similarity of signs and symptoms in conditions such as tremor, restlessness, itching resulted in the unclassification of the reaction in some patients. Anaphylactic reactions which is a severe state of allergic reactions, and serious reactions such as TACO, TRALI and hemolytic reactions were also rare in our hospital comparing with the others (5,25).

In 44 patients (16.85%) TRs could not be classified. It is a high number that the reaction could not be classified in 44 patients. Despite the standards for classification, this high rate may be due to the confusion in the findings and the clinician's lack of knowledge in the definition of TR.

Our results were consistent with earlier research that did not discover a relationship between gender and reaction development (22,24,26). Having a previous transfusion history does not eliminate the risk of ATRs (27). Patients who had previously received transfusions accounted for 67.9% of our reported responses. This bolsters the idea that individuals who have previously received blood products may experience transfusion responses.

The use of retrospective hemovigilance data, diagnosis by various doctors, and single-center design are the study's weaknesses. A comparison with those who did not develop a reaction was also impossible because only the transfusion exposure of those who experienced a reaction was known.

CONCLUSION

In our investigation, we demonstrated that despite good classification, doctors may struggle to differentiate between reactions because of overlapping clinical symptoms. Allergic TRs were thought to be common in patients with low blood pressure. Our results confirm that the use of electronic technology and the implementation of a rigorous hemovigilance system can facilitate TR follow-up by expediting reporting. The monitoring of TRs is crucial despite the serious reactions declining with excellent medical procedures.

ETHICS

Ethics Committee Approval: Study was approved by the Hamidiye Clinical Research Ethics Committee of Health Sciences University (decision no: 35/20, date: 19.11.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: Ş.N.K., E.C.Ü., S.P.B., H.G., K.K.Y., Design: Ş.N.K., E.C.Ü., S.P.B., H.G., Data Collection or Processing: E.C.Ü., D.Y., S.A., K.N.B., R.A., İ.T., Analysis or Interpretation: D.Y., S.A., K.N.B., R.A., İ.T., Literature Search: Ş.N.K., E.C.Ü., S.P.B., D.Y., S.A., K.N.B., R.A., İ.T., H.G., K.K.Y., Writing: Ş.N.K., E.C.Ü., K.K.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

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