REVIEW ARTICLE

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Timing of onset of intraoperative transfusion anaphylaxis: a literature review

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ABSTRACT

Clinical diagnosis of intraoperative transfusion anaphylaxis using clinical symptoms is challenging and should be made carefully, as an incorrect clinical diagnosis can exacerbate surgical bleeding secondary to stopping a clinically indicated blood transfusion. The timing of onset of anaphylaxis to start of transfusion may be the key to correctly diagnosing intraoperative transfusion anaphylaxis clinically. However, the reliability of this measure remains unknown. A literature search was conducted using MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials up to June 29, 2021. No language restriction was applied. Two pairs of review authors independently reviewed intraoperative transfusion anaphylaxis cases and extracted data on the timing of onset of anaphylaxis to start of transfusion. A total of 8,918 articles were reviewed, the full texts of 186 articles were assessed, and 20 intraoperative transfusion anaphylaxis cases were included in this study. The 20 intraoperative transfusion anaphylaxis cases included a precise timing of onset. With nine cases, cardiovascular surgery was the most prevalent, and one case was fatal. Fifteen cases had a timing of onset in minutes, and of those, 14 reported timeframes within 30 minutes of initiation of transfusion (median: 15.5, 5–30 minutes). Almost all cases of intraoperative transfusion anaphylaxis occurred within 30 minutes of the transfusion initiation. This timeframe may be helpful in the clinical diagnosis of intraoperative transfusion anaphylaxis.

Keywords: transfusion anaphylaxis, intraoperative, timing of onset

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INTRODUCTION

Blood products are a lifesaving resource and are transfused in hospitals. Although blood transfusion is safer than ever,[1] blood products can trigger various adverse reactions.[2,3] Allergic reactions are one of the most common transfusion reactions and are clinically diagnosed by symptoms related to organ systems and the timing of the reaction.[3-5] Transfusion anaphylaxis occurs when the reaction is severe and should be treated immediately. The initial treatment of transfusion anaphylaxis is stopping transfusion of the suspected causative blood product.[6] However, stopping transfusion in a suspected case of transfusion anaphylaxis may be difficult in specific conditions.

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Since hemorrhagic shock or coagulopathy during surgery can complicate surgical attempts to stop bleeding, blood products are transfused to treat coagulopathy, anemia, and low platelet count.[7,8] When the clinical picture is suggestive of transfusion anaphylaxis after transfusion, the clinician should carefully diagnose and treat the anaphylaxis. Stopping a transfusion may treat the anaphylaxis but worsen the surgical bleeding.[9] In the intraoperative period, the diagnosis of anaphylaxis can be difficult. Side effects of various drugs or surgery complications, such as severe hypotension induced by surgical bleeding, can resemble symptoms of anaphylaxis.[10,11] Thus, incorrect diagnosis of transfusion anaphylaxis based on clinical symptoms can occur. The timing of symptom onset from the start of transfusion may be the key to an accurate clinical diagnosis of intraoperative transfusion anaphylaxis.[12] If the onset time of anaphylaxis is far from the start of transfusion, it is more likely to be another disease or anaphylaxis due to drugs other than blood products. According to the definition of hemovigilance, transfusion anaphylaxis usually occurs during or shortly after transfusion.[4,5] However, considering that the infusion rate of transfusion depends on the bleeding situation and urgency, the timing of "during" or "very shortly after transfusion" varies, and the timing of onset to the start of transfusion can be more useful in the intraoperative period. This study aimed to review the literature on intraoperative transfusion anaphylaxis and determine the timing of its onset to the start of transfusion, which may be helpful in clinically diagnosing intraoperative transfusion anaphylaxis.

MATERIALS AND METHODS

Data sources and searches

A literature search was conducted using four electronic databases (MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials) up to June 29, 2021, with no language restriction. The search strategy is shown in Table 1. The review protocol was prospectively registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN: 000044787). Ethical approval and consent for analysis and publication were waived because of the nature of systematic review and meta-analysis studies.

Case screening and selection

After removing duplicates, titles and abstracts of all publications were reviewed independently by two pairs of review authors (YA and TF, TT and TH). Articles that could potentially contain relevant information were selected for full-text review and examined in-depth to assess eligibility. Translation software was used for articles not written in English (http://translate.google.co.jp/). Any disagreement was resolved by consensus or discussion with a third reviewer (KN).

Inclusion criteria

Inclusion criteria were as follows: (1) diagnosed as anaphylaxis by the author (including anaphylactic shock, anaphylactic/anaphylactoid reaction, or Kounis syndrome), (2) the causative agent was blood product (blood transfusion, blood component, whole blood, red blood cell, erythrocyte, plasma, fresh frozen plasma, cryoprecipitate, platelet), (3) anaphylaxis occurred intraoperatively (during surgery or anesthesia in the operating room), and (4) the timing of onset of anaphylaxis to start of transfusion (onset delay) was clearly noted. Animal studies were excluded.

Data extraction

The selected articles were collected and reviewed by two pairs of review authors (YA and TF, TT and TH) in their portable document format. Data from each article were collated and

Table 1 Literature search strategy

Electronic databases	Search	Search strategy	Results
MEDLINE	#1	MH "Anaphylaxis"	21,582
	#2	MH "Kounis Syndrome"	115
	#3	#1 OR #2	21,660
	#4	MH "Surgical Procedures, Operative+"	3,275,229
	#5	MH "Intraoperative Complications+"	54,461
	#6	MH "Anesthesia+"	195,900
	#7	#4 OR #5 OR #6	3,387,733
	#8	#3 AND #7	2,184
	#9	(MH "animals") NOT (MH "humans")	4,816,059
	#10	#8 NOT #9	**1,993**
Embase	#1	'anaphylaxis'/exp	55,872
	#2	'Kounis syndrome'/exp	721
	#3	#1 OR #2	56,326
	#4	'surgery'/exp	5,397,230
	#5	'perioperative complication'/exp	53,769
	#6	'anesthesia'/exp	380,600
	#7	#4 OR #5 OR #6	5,584,576
	#8	#3 AND #7	8,307
	#9	'animal'/exp NOT 'human'/exp	5,629,713
	#10	#8 NOT #9	**7,912**
Cochrane CENTRAL/CDSR	#1	anaphylaxis	1,779
	#2	Kounis syndrome	1
	#3	#1 OR #2	1,779
	#4	surgery or operation or surgical procedure	284,051
	#5	intraoperative complications	3,692
	#6	perioperative complications	2,390
	#7	anesthesia	101,042
	#8	#4 OR #5 OR #6 OR #7	325,295
	#9	#3 AND #8	**273**

CENTRAL: Central Register of Controlled Trials
CDSR: Cochrane Database of Systematic Reviews
exp: explosion
MH: Medical Subject Headings (MeSH) terms

entered into Microsoft Excel (Microsoft, Washington, USA). The following data were recorded from each selected study: year of publication, patient characteristics (age, sex), diagnosis, onset delay, and causative agents of intraoperative transfusion anaphylaxis. No attempt was made to contact the authors of articles that provided limited data or information. Any disagreement was resolved by consensus or discussion with a third reviewer (KN).

RESULTS

We identified 10,178 references from our searches (Figure 1). After removing 1,260 duplicates, we screened the titles and abstracts of 8,918 articles, and 8,732 were excluded. The full texts of 186 articles were reviewed, and we identified 11 articles[13-23] containing 20 intraoperative transfusion anaphylaxis cases with a clearly noted onset delay (Table 2). The mean age was 55.2 (4–80) years, and male patients accounted for 60% of all patients. One patient died after transfusion anaphylaxis. Intraoperative transfusion anaphylaxis mostly occurred in cardiovascular surgery (n=9, 45%), followed by gynecological surgery (n=3, 15%) and urological surgery (n=2, 10%). The causative blood components varied in the 20 intraoperative transfusion anaphylaxis cases. Japan had the highest number of publications (seven articles), followed by the USA (two articles), Spain (one article), and Denmark (one article). Three articles used translation software, as mentioned above. Of the 20 intraoperative transfusion anaphylaxis cases, 15 cases included timing of onset in minutes, and of those, 14 had timeframes within 30 minutes, and one was recorded as 180 minutes (Figure 2).

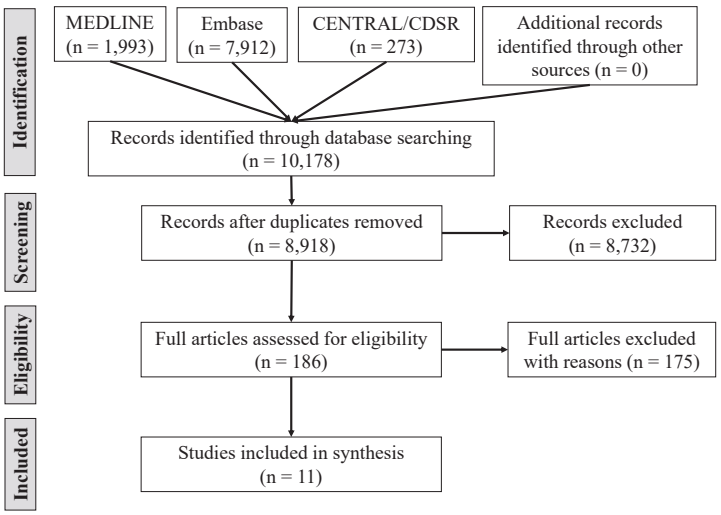

Fig. 1 Flowchart for article selection for intraoperative transfusion anaphylaxis cases
CENTRAL: Central Register of Controlled Trials
CDSR: Cochrane Database of Systematic Reviews

Table 2 Intraoperative transfusion anaphylaxis cases with clearly written onset delay

Ref	Year	Country	Age	Sex	Diagnosis	Cause	Onset delay
13	1983	Japan	59	F	Anaphylactoid reaction	Blood transfusion	30 min
14	1984	USA	44	F	Anaphylactic reaction	FFP	While the patient was receiving FFP
15	1984	Japan	59	M	Anaphylactic shock	Blood transfusion	*When the sixth preserved blood was started*[a]
16	1985	Spain	77	M	Anaphylactic reaction	Whole blood	*Once*[b]
17	1987	Japan	53	F	Anaphylactoid reaction	RBC, FFP	30 min
18	1989	USA	NA	NA	Anaphylactic/anaphylactoid reactions	Whole blood	17 min
19	1993	Japan	80	M	Anaphylactoid reaction	Whole blood	A few minutes later
20	2002	Japan	4	F	Anaphylactic reaction	Whole blood	20 min
21	2008	Japan	75	M	Anaphylaxis	RBCs	30 min
22	2010	Japan	32	M	Anaphylactic shock	FFP	*Immediately after*[a]
23	2014	Denmark	60	M	Anaphylaxis	FFP	5 min
23	2014	Denmark	58	M	Anaphylaxis	PC, RBC, FFP	5 min
23	2014	Denmark	66	M	Anaphylaxis	RBCs, FFP	5 min
23	2014	Denmark	75	M	Anaphylaxis	RBCs, PC, FFP	5 min
23	2014	Denmark	46	F	Anaphylaxis	RBCs, FFP	5 min
23	2014	Denmark	56	M	Anaphylaxis	RBCs	10 min
23	2014	Denmark	43	F	Anaphylaxis	RBCs, FFP	10 min
23	2014	Denmark	69	M	Anaphylaxis	FFP, RBCs	20 min
23	2014	Denmark	54	M	Anaphylaxis	RBCs, PC, FFP	25 min
23	2014	Denmark	38	F	Anaphylaxis	RBCs	180 min

M: male
F: female
NA: not available
RBC: red blood cell
FFP: fresh frozen plasma
PC: platelet concentrate
[a] Original sentence was written in Japanese.
[b] Original sentence was written in Spanish.

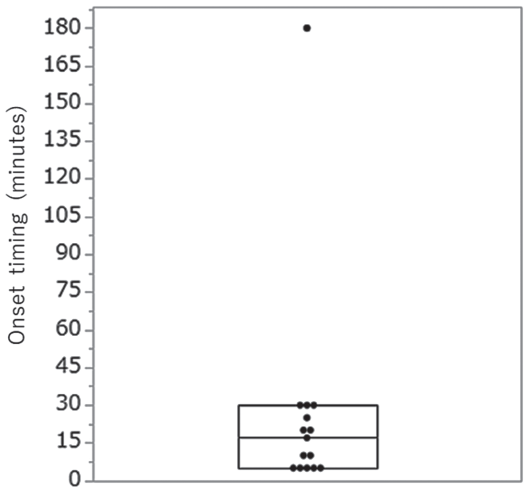

Fig. 2 Dot plot with box plot of timing of onset of intraoperative transfusion anaphylaxis

DISCUSSION

This literature review found that in almost all cases, intraoperative transfusion anaphylaxis occurred within 30 minutes after the start of transfusion. In the perioperative period, the timing of onset of anaphylaxis tends to differ according to the causative agent type and exposure. For example, neuromuscular blocking agents or antibiotics have a rapid onset (≤15 min), colloids have a more delayed onset (15–30 min), and non-intravenous agents, such as disinfectants, dyes, or latex, have a slower onset (≤60 min) than intravenous drugs.[24-33] Our results show that the timing of the onset of transfusion anaphylaxis was 5–30 minutes, consistent with that of intravenous drugs in most cases.

Diagnosing perioperative anaphylaxis is challenging. The timing of the appearance of clinical signs is a valuable tool in diagnosis.[12] We believe that a timeframe of 30 minutes can be applied to diagnose intraoperative transfusion anaphylaxis. Therefore, clinical signs suggesting anaphylaxis and occurring within 30 minutes of the start of transfusion are more likely to be due to transfusion anaphylaxis. In contrast, clinical signs suggestive of anaphylaxis occurring more than 30 minutes after the start of transfusion are less likely to be due to transfusion anaphylaxis, and it may not be necessary to stop the transfusion. Another diagnostic tool for perioperative anaphylaxis is a clinical perioperative anaphylaxis scoring system.[34] This scoring system comprises assessments of symptoms in three organ systems (cardiovascular, respiratory, and dermal/mucosal), the timing of symptom onsets and changes in mast cell tryptase, and it rates the probability of perioperative anaphylaxis on a 5-point scale. Therefore, combining a 30-minute timeframe and a clinical scoring system would improve diagnostic accuracy.

Following the clinical diagnosis of anaphylaxis, patients should be investigated to identify the immune mechanism and the causative agent to prevent recurrences.[35-37] Multiple causative agents exist in the perioperative period and the most common causes were neuromuscular blocking agents and antibiotics.[38] Therefore, a careful assessment, including diagnostic skin prick tests following a 4–6-week delay, is required.[27,36,37] A clinical diagnosis alone cannot accurately assess the underlying cause.[26,39,40] However, since the shelf life of residual suspected causative blood products is shorter than 4–6 weeks,[3] blood products can cause infection 21 days after production, even if they are safely stored.[41,42] No other blood products identical to the suspected causative blood products exist; therefore, it is difficult to perform skin tests for blood products. Although tryptase or plasma protein deficiency measurement is recommended in transfusion anaphylaxis cases,[5,6] the results of those tests often fail to confirm a causative relationship between the reaction and the suspected blood products.[43,44] Recently, the basophil activation test has been applied to transfusion medicine and may help analyze the causative relationship between transfusion and allergic transfusion reaction.[44-51] However, since the utility or the sensitivity and specificity of the basophil activation test to transfusion medicine remains unknown,[44,45] it may be difficult or inappropriate to perform basophil activation tests comprehensively for the dozens of blood products transfused before anaphylaxis. In cases with dozens of suspected causative blood products, such as in massive transfusions, the "within 30 minutes" timeframe might be useful to narrow down the suspected candidates and may increase the pre-test probability of the basophil activation test.

We included all reported cases of intraoperative transfusion anaphylaxis after screening approximately 9,000 articles with no language restriction. However, only 20 cases (11 articles) were finally included. Because of the small number of cases with time of onset precisely described with numbers, we were unable to statistically analyze the onset time. Furthermore, the diagnosis of transfusion anaphylaxis strongly depends on the author's clinical interpretation in most articles because of limited confirmative diagnostic tests for blood products. However, even if there is a lack of diagnostic tests for transfusion anaphylaxis, this does not mean clinicians should not

diagnose transfusion anaphylaxis. It is reasonable to make a clinical diagnosis of transfusion anaphylaxis after the possibilities of other diseases have been properly ruled out. The basophil activation test may aid the clinical diagnosis of transfusion anaphylaxis. However, it is still critical to investigate and review clinical symptoms of transfusion anaphylaxis to create more refined diagnostic criteria: in that way, more studies could be published, allowing statistical analysis.

CONCLUSION

Almost all intraoperative transfusion anaphylaxis occurred within 30 minutes after the start of transfusion in this literature review. This timeframe may be helpful in clinically diagnosing intraoperative transfusion anaphylaxis. This timeframe might also be useful to narrow down the number of suspected blood products and increase the pre-test probability of diagnostic tests in cases of dozens of transfusions.

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YA designed the study, performed the research, analyzed the data, and wrote the first draft of the manuscript. TF performed the research and analyzed the data. TT designed the study, performed the research, reviewed, and edited the manuscript. TH performed the research. KN supervised the research, reviewed, and edited the manuscript. All authors read and approved the final manuscript. The authors thank all anesthesiology medical staff of the Nagoya University Hospital for their assistance.

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PREVIOUS PRESENTATIONS

None.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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