Clin. Lab. 2025;71:XXX-XXX

CASE REPORT

A Rare Case of Intraoperative Transfusion-associated Hypotension in a Chinese Pregnant Patient

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SUMMARY

Background: **Transfusion-associated hypotension (TAH) is characterized by the abrupt onset of hypotension immediately after the start of transfusion and usually resolves when transfusion ceases. The pathogenesis of TAH is not yet fully understood.**
Methods: **A 36-year-old woman underwent exploratory laparotomy and cesarean section due to cervical squamous cell carcinoma. During surgery, the patients experienced acute, profound intraoperative hypotension within 5 minutes after the initiation of the prestorage leukocyte-reduced suspension red blood cells (RBC) transfusion. A series of laboratory tests confirmed TAH. The patient then underwent a successful blood transfusion and operation. TAH can occur in all types of blood components under various conditions. The literature surrounding the incidence of TAH differs widely from 0.03 to 2.13 in 10,000.**
Conclusions: **This is the first case report of TAH in an intraoperative pregnant woman in China, neither associated with prestorage leukocyte-reduced RBC nor irrelevant to ACE inhibitors. Some biological response mediators (BRMs) and acute phase reactive proteins might play a role in this case. Understanding the etiology and the pathophysiology of TAH facilitates proper management, leading to improved transfusion safety.**
(Clin. Lab. 2025;71:xx-xx. DOI: 10.7754/Clin.Lab.2024.240745)

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KEYWORDS

transfusion-associated hypotension (TAH), prestorage leukocyte-reduced suspension red blood cells, angiotensin-converting enzyme (ACE) inhibitors, biological response mediators (BRMs), acute phase reactive proteins

CASE REPORT

A 36-year-old woman had stopped menses for 19 weeks and had intermittent vaginal bleeding for two more months. At five weeks of pregnancy, the patient set up an antenatal examination file at a local hospital, and there was no abnormality by regular antenatal examination. At the 17th week of pregnancy, a color Doppler ultrasound examined by the local hospital found a low echo mass in the posterior wall of the cervix. For further consultation, she came to our hospital's outpatient clinic.

Case Report accepted August 5, 2024

The patient was diagnosed with syphilis in the local hospital when she was five weeks pregnant, and she was then treated with a course of standard treatment for syphilis (injections of benzylpenicillin 2.4 million units, three times once a week). A recent reexamination result of TRUST was 1:16. Two months ago, she had symptoms of intermittent vaginal bleeding without obvious inducement, but the bleeding volume was small and without abdominal pain, dizziness, vaginal discharge, and other discomfort. She did not take it seriously at the time. In addition, she had a history of abdominal operation and multiple vaccinations, without other infectious diseases, allergies, trauma, blood transfusion, or other unique medical history. Finally, she was diagnosed as G4P1, 19 weeks of intrauterine pregnancy, single live fetus, pregnant with cervical squamous cell carcinoma at IB2 stage, human papillomavirus infection (HPV16 positive), syphilis, and obesity. The patient and her family requested to terminate the pregnancy after careful consideration. An exploratory laparotomy and cesarean section were planned.

During surgery, the patient's blood loss reached 1,800 mL, and a prestorage leukocyte-reduced suspension red blood cell (RBC) transfusion was initiated. Five minutes later, the patient's blood pressure dropped sharply from 110/60 mmHg to 66/44 mmHg, there was no skin rash. The surgeon suspected an allergic reaction, and the blood transfusion was stopped immediately. Hemodynamic support was given with intravenous injection of dexamethasone 20 mg and calcium gluconate 1 g. After intermittent epinephrine injection, the blood pressure returned to 95/60 mmHg within a few minutes. The surgical team communicated with the Blood Bank since the patient experienced acute profound intraoperative hypotension, and the blood bank immediately launched an investigation to find out the potential causes.

Laboratory role in diagnosis

Intraoperative hypotension is often a critical event, and hemodynamically unstable patients will be at high risk of further complications associated with hypotension. A precise diagnosis needs to be made quickly to guide further management and to decide whether to terminate surgery immediately or if it is safe to continue with surgery.

Transfusion reactions are adverse events associated with the transfusion. Several severe transfusion reactions are accompanied by hypotension, such as acute hemolytic transfusion reactions, anaphylactic transfusion reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, transfusion-related sepsis, etc. It must be managed with caution. Meanwhile, hypotension is usually the sole manifestation of transfusion-associated hypotension (TAH). TAH is also called a hypotensive transfusion reaction, which is rare and characterized by the abrupt onset of hypotension immediately after the initiation of transfusion and resolves rapidly after the cessation of transfusion. It is essential to recognize the TAH and be able to manage TAH rapidly, especially in the intraoperative setting.

Intraoperative transfused blood unit along with the patient's freshly drawn post-transfusion blood samples, were sent to the transfusion reaction workup. The technologists rechecked the blood type of the RBC unit and the patient's specimen. The patient's O Rh (D) was positive. No clerical errors were found. Its direct anti-globulin test (DAT) and indirect anti-globulin test (IAT) were negative in pre- and post-transfusion specimens. Therefore, the possibility of an acute onset immune-mediated hemolytic transfusion reaction was categorically ruled out. She did not develop any rise in body temperature, cough, breathlessness, or fall in oxygen saturation. The absence of any flushing and or urticaria helped us rule out any allergies and anaphylactic reaction to the blood product. Following, the transfusion-related acute lung injury was excluded, as this typically takes place within 1 to 6 hours after the beginning of the transfusion, which chiefly manifests as a sudden onset of severe dyspnea, hypoxia, and the development of diffuse pulmonary infiltrates. The patient had no other symptoms except hypotension. Postoperative cardiac workup showed no evidence of ischemia or infarction. Ongoing surgical bleeding and impaired fluid balance were excluded. Then the transfusion-associated circulatory overload was eliminated, and the blood unit was sent for culture immediately, getting a negative result two days later. Up to now, a TAH transfusion reaction has been highly suspected.

Once an episode of TAH occurs, the most critical measure is to stop the transfusion immediately. Symptoms usually subside quickly as the transfusion is discontinued. The patient should not be rechallenged with that same product because symptoms are expected to recur as a result of activation substances presumed to be present in the blood product. In most instances, no other treatment is required, although in some cases, when the hypotension does not immediately correct with the interruption of the transfusion, the use of a bolus of intravenous fluids may be helpful. Vasoactive drugs are rarely indicated. However, most patients with TAH were treated with medications for active intervention, the same as our case. Whether it is because the patient is in a severe condition or because the clinicians are not familiar with the characteristics of TAH, they are not sure.

Close monitoring of the patient showed that she became hemodynamically stable over the next 20 minutes. Another prestorage 1.5-unit leukocyte-reduced RBC transfusion was initiated after being evaluated by the surgical team and blood bank, and she did not have any adverse reactions. After that, 800 mL fresh frozen plasma (FFP) was transfused with no adverse reactions. Intraoperative infusion volume was 6,500 mL, and urine volume was 400 mL. The urine color was light yellow, clear, and without blood clots. After surgery, she was transferred to the intensive care unit (ICU). Three days later, a prestorage 1.5-unit of leukocyte-reduced RBC was issued without adverse reactions. Then, she was discharged af-

Table 1. Reported incidence rate of TAH during the last decade.

No.	Authors	Year	Country	Organization	Period	Incidence rate of ATRs (‰)	Incidence rate of TAH (‰)				TAH in ATRs (%)	Severe TAH in TAHs (%)
							Overall	RBC	FFP	PLT		
1	Tian [9]	2022	China	Chinese Haemovigilance Network (CHN)	2018 - 2020	6.96 (2,348/ 3,375,301)	0.03 (11/ 3,375,301)	0.018 (6/ 3,375,301)	0.012 (4/ 3,375,301)	0.003 (1/ 3,375,301)	0.36 (11/ 3,033)	81.8 (9/ 11)
2	Politis [10]	2022	Interna-tional	International Haemovigilance Network (IHN)	2012 - 2016	8.77 (94,503/ 107,778,290)	0.15 (1,565/ 107,778,290)	NA	NA	NA	1.7 (1,565/ 94,503)	50.16 (785/ 1,565)
3	Kwon [11]	2022	Korea	a tertiary hospital	2013 - 2022	NA	0.5 (37/ 741,955)	0.46 (21/ 451,817)	0.28 (2/ 70,712)	0.64 (14/ 219,426)	NA	NA
4	Yeter [12]	2021	Turkey	a tertiary hospital	2018 - 2019	8.60 (53/ 61,636)	0.65 (4/ 61,636)	0.16 (1/ 61,636)	0.16 (1/61,636)	0.32 (2/ 61,636)	7.55 (4/ 53)	NA
5	Savinkina [13]	2020	United States	National Blood Collection and Utilization Survey	2017	28.18 (45,165/ 16,029,000)	0.91 (1,462/ 16,029,000)	NA	NA	NA	3.24 (1,462/ 45,165)	NA
6	Savinkina [13]	2020	United States	National Blood Collection and Utilization Survey	2015	27.46 (47,297/ 17,227,000)	0.91 (1,565/ 17,227,000)	NA	NA	NA	3.31 (1,565/ 47,297)	NA
7	Vossoughi [14]	2018	United States	44 hospitals	2009 - 2015	31.75 (3,822/ 1,222,869)	0.43 (52/ 1,222,869)	0.21 (26/ 1,222,869)	0.07 (8/ 1,222,869)	0.11 (14/ 1,222,869)	1.36 (52/ 3,822)	NA
8	TTISS [1]	2018	Canada	Transfusion Transmitted Injuries Surveillance System (TTISS)	2011 - 2015	4.15 (2,479/ 5,973,827)	0.39 (230/ 5,973,827)	NA	NA	NA	9.28 (230/ 2,479)	24.35 (56/ 230)

1. ‰ - indicate per 10,000. 2. ATRs = acute transfusion reactions.

ter four days.
Eventually, according to the Guideline for Haemovigilance from the Chinese Society of Blood Transfusion (CSBT), a definite TAH was identified in this case. TAH is defined as a decrease in blood pressure during blood transfusion or within 1 hour after the termination of blood transfusion, excluding all other adverse reactions, which is in accordance with The U.S. National Healthcare Safety Network (NHSN) Hemovigilance criteria [1]. The patient's systolic blood pressure dropped sharply from 110/60 mmHg to 66/44 mmHg within 10 minutes, accompanied by no other symptoms.

DISCUSSION

Owing to the rare occurrence of TAH, the incidence and clinical characteristics of TAH have been reported in only a few studies, and the pathophysiology has not been fully established. TAH can occur in all types of blood components under various conditions. The incidence of TAH in literature varies widely, from 0.03 to 2.13 in 10,000, as summarized in Table 1. The incidence rate of TAH during the last decade is reported. TAH is thought to occur with activation of the intrinsic contact activation pathway of the coagulation cascade and generation of bradykinin and its active metabolite des-Arg9-bradykinin [2]. Two known factors, angiotensin-converting enzyme (ACE) inhibitors [3] and negatively charged leukoreduction filters [4], may result in subsequent hypotension by affecting the bradykinin metabolism. Bradykinin is released by the breakdown of a high-molecular-weight kininogen by kallikrein and inactivated by peptidases such as ACE. In patients receiving ACE inhibitors, bradykinin in the transfused blood component cannot be inactivated, causing hypotension [3]. Similarly, kinin-mediated pathways can be activated by negatively charged surfaces of filters, leading to the production of bradykinin and hypotension [4]. Although bedside leukoreduction is no longer commonplace, TAHs still occur and are insufficiently characterized.
There might be some other unknown factors related to TAH. Hume et al. [5] have suggested that a few biological response mediators (BRMs), such as interleukin-1, TNF-alpha, and histamine accumulated in the platelet concentrate, could be involved in causing isolated TAH. These BRMs and cytokines get released from the leukocytes that accumulate in the plasma during storage. IL-1 at sufficient concentrations in the blood will lead to circulatory collapse, shock, and death. Tumor necrosis factor can stimulate the release of IL-1 [6]. Hui Y et al. [7] studied the polymorphisms of the aminopeptidase P (APP) gene, another essential enzyme responsible for bradykinin degradation, which might be associated with TAH. Raturi et al. [8] reported a TAH in an Indian female patient and hypothesized two reasons, one possibly due to higher factor XII levels because of the ongoing regular dialysis, and another cause might be the accumulated BRMs in the stored PRBC unit. The exact reason is still unclear.
The patient in this case, who was not on any ACE inhibitors, had the TAH accidentally after receiving a prestorage leukoreduced RBC during operation. This RBC unit, issued on the 8th day from the date of whole blood collection, was prepared by a disposable de-leucocyte plastic blood bag with a hard filter (Shandong Wegao Group Medical Polymer Co. LTD, China). Through retrospective tracking, the platelets and fresh frozen plasma units prepared from the same donor unit did not cause any adverse event in their respective recipients. What is puzzling is that there were no adverse reactions with the following transfusion: intraoperative transfusion with a new 1.5 unit prestorage leukoreduced RBC on the 8th day from the collection and another new 1.5 unit prestorage leukoreduced RBC on the 25th day from the collection after the operation. Unfortunately, the donor or the patient did not assess the serum concentration of B.K. and factor XII due to certain constraints. The causes of the negatively charged filters and ACE inhibitors can definitely be excluded in our case. Therefore, we speculate that some BRMs related to the patient may play a role in this TAH. In addition, we guess some acute phase reactive protein might play a role in this case. Those acute phase reactive proteins might be associated with infection and stress state, and they were consumed in the TAH and cannot be replenished in time. A professional transfusion reaction workup is crucial to initiate the investigation and analyze the root cause. The TAH incidence in China is 10 - 50 times lower than in other countries, according to Table 1. The incidence rate of ATRs was 1.03% for the past five years in all types of blood components, and this TAH was the first diagnosed case. Whether the low incidence is related to ethnic differences or the omission of reports in the surveillance system needs more effort to confirm.
To sum up, our understanding of the etiology and the pathophysiology of TAH remains inadequate. There could be many more causal elements, including the accumulation of BRMs and cytokines in blood components, which merits further research.

Declaration of Interest:
None.

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