



Pre-operative autologous blood donation and transfusion-related adverse reactions: A 14-year experience at a university hospital

Yoshiaki Furuta^a, Yuki Nakamura^a, Miho Tokida^a, Kayoko Ichikawa^a, Toshiya Ohsawa^a, Mitsuo Ohkubo^{b,c}, Akimichi Ohsaka^{a,c,*}

^a Department of Transfusion Service, Juntendo University Hospital, Tokyo, Japan

^b Department of Transfusion Service, Juntendo University Urayasu Hospital, Chiba, Japan

^c Department of Transfusion Medicine and Stem Cell Regulation, Juntendo University Graduate School of Medicine, Tokyo, Japan

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ABSTRACT

Objective: The objective of this study was to determine the rate of adverse reactions to pre-operative autologous blood donation (PAD) transfusion in a single institution over a 14-year period.

Study design and methods: Between January 2003 and December 2016, we investigated adverse reactions to PAD transfusion and compared them with those to allogeneic blood transfusion in Juntendo University Hospital. Adverse reactions were categorized according to the definition proposed by the International Society of Blood Transfusion (ISBT) Working Party on Haemovigilance.

Results: A total of 178,014 blood components were transfused during the study period, of which PAD transfusions were 13,653 (8%), whereas allogeneic blood transfusions were 164,361 (92%). The number and rate of adverse reactions to PAD transfusion were 16 and 0.1%, whereas those of allogeneic blood transfusion were 1075 and 0.7%, respectively. The rate of adverse reactions to allogeneic blood transfusions excluding platelet transfusion was 0.3%, being significant ($p < 0.01$) against PAD transfusion. Among 16 adverse reactions to PAD transfusion, the most common was febrile non-hemolytic transfusion reaction (FNHTR) at 12 (75%), followed by allergic reaction at 4 (25%). The severity of adverse reactions to PAD transfusion was Grade 1 (non-severe) in all cases. With regard to blood component types, 16 adverse reactions involved: 12 cases of whole blood PAD, 2 of frozen PAD, and 2 of autologous fresh-frozen plasma.

Conclusions: Non-severe adverse reactions were observed on PAD transfusion at a rate of 0.1% at our institution.

1. Introduction

Autologous blood conservation techniques include perioperative autologous cell salvage (PACS), acute normovolemic hemodilution (ANH), and pre-operative autologous blood donation (PAD). PAD involves collecting and storing the patient's own blood prior to surgery in order to administer it, if necessary, post-operatively. PAD has been advocated to reduce the risks related to allogeneic blood transfusion, including transfusion-transmitted infectious disease, alloimmunization, transfusion-associated graft-versus-host disease (TA-GVHD), and transfusion-related acute lung injury (TRALI). However, PAD transfusion does not eliminate the risk of some immunologic complications, bacterial contamination, or mistransfusion [1]. In a meta-analysis of randomized trials and controlled observational studies, autologous

transfusion techniques consistently reduced the frequency of allogeneic transfusions but increased the overall transfusion rates [2]. However, adverse reactions to autologous transfusion were not reported in these studies. There have been few studies examining the frequency of adverse reactions to PAD transfusion [3,4].

In this study, we investigated adverse reactions to PAD transfusion and compared them with those of allogeneic blood transfusion, excluding platelet (PLT) transfusion, in our hospital over a 14-year period. Our observations suggest that non-severe adverse reactions were observed following PAD transfusion, although the rate of adverse reactions to PAD transfusion was lower than those to allogeneic blood transfusion.

* Corresponding author at: Department of Transfusion Medicine and Stem Cell Regulation, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan.

E-mail addresses: yfuruta@juntendo.ac.jp (Y. Furuta), yunakamu@juntendo.ac.jp (Y. Nakamura), mtokida@juntendo.ac.jp (M. Tokida), kyichika@juntendo.ac.jp (K. Ichikawa), toosawa@juntendo.ac.jp (T. Ohsawa), mi-okubo@juntendo.ac.jp (M. Ohkubo), ohsaka@juntendo.ac.jp (A. Ohsaka).

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2. Materials and methods

2.1. Study design

This was a retrospective study conducted over a 14-year period in Juntendo University Hospital, Tokyo, Japan. Between January 2003 and December 2016, we investigated adverse reactions to PAD transfusion and compared them with those to allogeneic blood transfusion. All adverse transfusion reactions were clinically evaluated by the treating physician and reported to the transfusion service. Grade 1 (non-severe) adverse reactions were typically reported using a paper-based system, where a duplicated compatibility report form was returned to the transfusion service the day after the completion of blood transfusion, as described previously [5]. In the case of Grade 2 or 3 adverse reactions, the treating physician or nurse reported immediately at onset via a telephone, and then the staff member of the transfusion service visited the issuing section (i.e., inpatient wards, outpatient units, and operating rooms) and determined the precise details of the adverse reaction.

2.2. Collection and processing of PAD units

In Japan, autologous blood transfusion has been encouraged in the Guidance on the implementation of blood transfusion therapy, issued by the Ministry of Health, Labour and Welfare in Japan (September 2005, partially updated in November 2014) (available at <https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000065580.html>, in Japanese). Collection and processing of PAD units were described previously [6]. In brief, PAD units were scheduled for patients awaiting operations, where intraoperative bleeding was predicted more than 15% of circulating blood volume, in accordance with the PAD program in our hospital, including the scheduled date of operation, type of surgery, body weight, number of units to be collected, blood volume per donation (usually 400 mL), intervals of donation (usually once a week), and type of blood components. The PAD components included red blood cells (RBCs): liquid (whole blood [WB] or mannitol-adenine-phosphate [MAP] additive solution-preserved) or frozen storage, fresh-frozen plasma (FFP), and cryoprecipitates (CPs). The following criteria had to be met to donate: a hemoglobin (Hb) concentration greater than or equal to 11 g/dL for initial donation, and absence of fever or infection. The Hb concentration of the patient for subsequent donation was acceptable at greater than 10 g/dL, being dependent on the decision on the appropriateness of donation by the responsible physician. After the completion of donation, replacement intravenous fluids were administered to the patient. The patients received iron supplementation or erythropoietin if needed. In the case of the liquid storage of RBC components, the collected WB was left untreated and stored at 2–6 °C (WB-PAD) or separated into RBC concentrate, preserved in MAP additive solution, and stored at 2–6 °C (MAP-PAD). Frozen RBC components (frozen PAD) were prepared by the Huggins method [7] with slight modifications, which used glycerol in a low-ionic medium to achieve a final glycerol concentration of 45% (w/v), and stored at –80 °C for up to one year. Autologous CPs were prepared from autologous frozen FFP, with final volume of 10 mL in autologous plasma, and stored at –20 °C until use. The intended use of autologous CPs was the resource of autologous fibrin glue in the operation of esophageal and gastric surgery. The expiration date of PAD components were as follows: WB-PAD, 35 days after donation; MAP-PAD, 42 days; frozen PAD, one year; autologous FFP, one year; and autologous CPs, one year. PAD components were available until the expiration date, even if they were not transfused intraoperatively.

2.3. Categorization of adverse transfusion reactions

Adverse reactions were categorized according to the definition proposed by the International Society of Blood Transfusion (ISBT)

Working Party on Haemovigilance (http://www.isbtweb.org/fileadmin/user_upload/Proposed_definitions_2011_surveillance_non_infectious_adverse_reactions_haemovigilance_incl_TRALI_correction_2013.pdf). Febrile non-hemolytic transfusion reaction (FNHTR) was defined as fever with a change of > 1 °C from the pre-transfusion value, with or without chills/rigors, including headache, nausea, and/or vomiting. Cases of chills/rigors but without fever were included in FNHTR. Allergic reactions (Grade 1, non-severe) were as follows: morbilliform rash with pruritus; urticaria; localized angioedema; edema of lips, tongue, and uvula; periorbital pruritus, erythema, and edema; and conjunctival edema, occurring during or within 4 h of transfusion. Anaphylactic reactions with systemic symptoms were categorized as allergic reactions (Grade 2 [severe] or 3 [life-threatening]). Transfusion-associated dyspnea (TAD) is characterized by respiratory distress within 24 h of transfusion that does not meet the criteria of TRALI, transfusion-associated circulatory overload (TACO), or allergic reaction. Hypotensive transfusion reaction is characterized by hypotension defined as a drop in systolic blood pressure of ≥ 30 mmHg and a systolic blood pressure ≤ 80 mmHg, including facial flushing and gastrointestinal symptoms.

2.4. Statistical analysis

To determine the significance of differences in the rate of adverse reactions between PAD and allogeneic transfusions, paired-sample *t*-tests were performed using the StatFlex 5.0 program (Artech Inc., Osaka, Japan). Significance was defined as $p < 0.05$.

3. Results

3.1. Trends in PAD transfusion over a 14-year period

A total of 178,014 blood components, including 88,390 RBCs, 36,164 PLTs, and 53,460 FFP, were transfused during the study period, of which PAD transfusions were 13,653 (8%) for 5434 patients, whereas allogeneic blood transfusions were 164,361 (92%) for 14,994 patients. Of the 13,653 PAD transfusions, WB-PAD was 4099 (30%), frozen PAD 3421 (25%), MAP-PAD 813 (6%), autologous FFP 4618 (34%; 3640 were derived from frozen PAD, 767 from MAP-PAD, and 211 from plasma apheresis), and autologous CP 702 (5%). PAD components transfused intraoperatively were 10,192 (75%), whereas those transfused postoperatively were 3461 (25%). Of the 5434 patients who received PAD transfusions, 305 (5.6%) patients were received allogeneic blood components simultaneously, including 115 (2.1%) patients with RBCs and 187 (3.4%) patients with PLTs. During the study period, a total of 16,785 PAD were collected, of which 13,590 (81%) were transfused, whereas 3195 (19%) were discarded. Because the number of PAD components transfused during the study period was included those collected in late 2002, the number of PAD transfusions was different in the case of calculating the discard rate.

Among the specialties, the most frequent in PAD transfusions was orthopedic surgery at 5452 (40%), followed by cardiovascular surgery at 3649 (27%), esophageal and gastric surgery at 1620 (12%), neurosurgery at 1201 (9%), urology at 834 (6%), obstetrics and gynecology at 421 (3%), hepato-biliary-pancreatic surgery at 302 (2%), and others. As shown in Fig. 1, the number of PAD collections annually declined, and there was a trend of a slow decline in PAD transfusions over a 14-year period. With regard to the rate of PAD transfusion (WB-PAD, frozen PAD, and MAP-PAD) among all RBC transfusions, there was a trend toward a slow decline during the study period, with an overall mean annual rate of 9.4% (Fig. 2). Although the overall rate of esophageal and gastric surgery in PAD transfusions was 12% during the study period, the rates of esophageal and gastric surgery and autologous CPs annually declined and were zero after 2014 (Fig. 3). The reason of this was that the director of esophageal and gastric surgery retired in 2008 and the operative technique was changed.

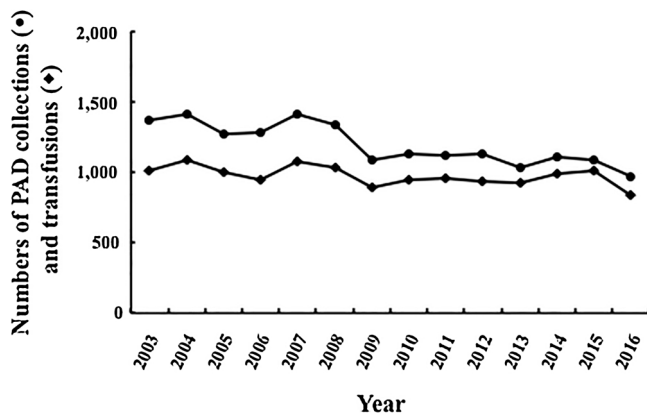


Fig. 1. Changes in the numbers of PAD collections (●) and transfusions (◆) over a 14-year period. Each data entry is for a year. The number of PAD collections annually declined.

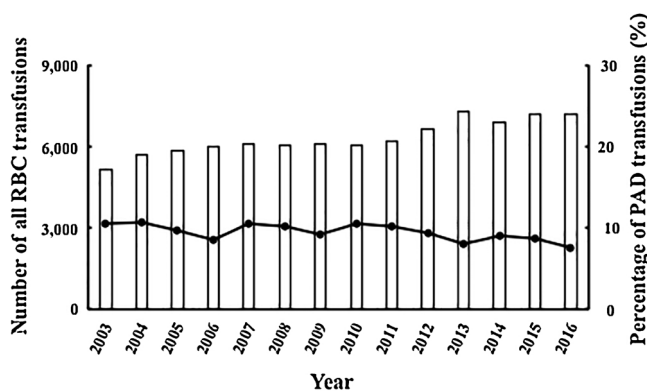


Fig. 2. Changes in the number of all RBC components transfused (column) and rate with PAD transfusion (line) over a 14-year period. Each data entry is for a year. There was a trend toward a slow decline in PAD transfusions.

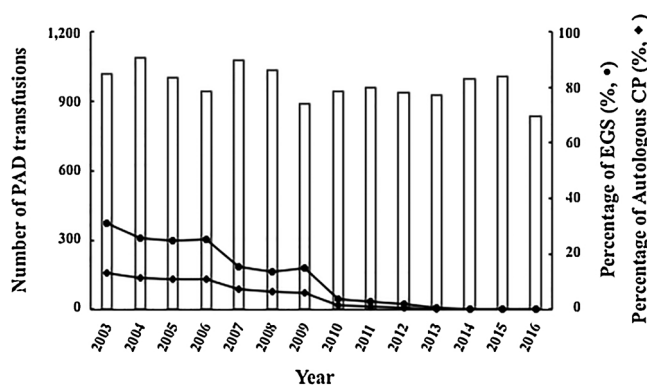


Fig. 3. Changes in the number of PAD transfusions (column) and rates with esophageal and gastric surgery (EGS) and autologous CP (line) over a 14-year period. Each data entry is for a year. There was a decline in EGS and autologous CP transfusion.

3.2. Adverse reactions to PAD transfusion over a 14-year period

The number and rate of adverse reactions to PAD transfusion were 16 and 0.1%, whereas those to allogeneic blood transfusions were 1075 and 0.7%, respectively. Precise data on 16 adverse reactions to PAD transfusion are shown in Table 1. Among the 16 adverse reactions, the most common was FNHTR at 12 (75%), followed by allergic reactions at 4 (25%). One case each of tachycardia and pallor was observed as an overlapping symptom. The severity of adverse reactions to PAD

transfusion was Grade 1 (non-severe) in all cases, and no serious adverse reactions were observed. With regard to blood component types, 16 adverse reactions were caused by 12 WB-PAD (0.29% as the rate of the component), 2 frozen PAD (0.06%), and 2 autologous FFP (0.04%). There was no interrelationship between adverse reactions and the PAD storage duration.

3.3. Adverse reactions to allogeneic blood transfusion over a 14-year period

A total of 164,361 allogeneic blood components were transfused during the study period, of which 1075 (0.7%) adverse reactions were observed. The most common was allergic reaction at 808 (75.2%), followed by FNHTR at 165 (15.4%), hypotensive transfusion reaction at 48 (4.5%), TAD at 38 (3.5%), others, including hypertension and tachycardia that did not meet the criteria of TACO, at 13 (1.2%), TRALI at 2 (0.2%), and delayed hemolytic transfusion reaction (DHTR) at 1 (0.1%). In this study, acute hemolytic transfusion reaction (AHTR) was not observed. With regard to the severity of adverse reactions, the most common was Grade 1 (non-severe) at 1055 (98.1%), followed by Grade 2 (severe) at 15 (1.4%), including 10 cases with hypotensive transfusion reaction, 4 cases with TAD, and one case with DHTR, and Grade 3 (life-threatening) at 5 (0.5%), including 3 cases with anaphylactic reaction due to 2 IgA deficiency and one haptoglobin deficiency, and 2 cases with TRALI. To compare the rate of adverse reactions to PAD and allogeneic blood transfusions, the number of PLT transfusion was excluded from allogeneic blood transfusions. As shown in Table 2, the number and rate of adverse reactions to allogeneic blood transfusions were 383 and 0.3% in 128,197 blood components, with the latter being significant ($p < 0.01$) against PAD transfusion. These findings indicated that approximately 2% of adverse reactions to allogeneic blood transfusion were severe or life-threatening, whereas adverse reactions to PAD were non-severe in all cases.

4. Discussion

There have been few studies examining the frequency of adverse reactions to PAD transfusion [3,4]. Ohto and colleague [4] reported a nationwide survey in Japan regarding the frequency of autologous blood donation and transfusion. They identified 117 errors or problems (0.47%) in 24,929 PAD transfusions, of which 2 (0.008%) cases involved fever, one (0.004%) case involved eruption, and one (0.004%) case involved mistransfusion. Dömen [3] reported a total of 20 (0.072%) adverse reactions in 27,859 autologous blood transfusions, of which 5 cases of FNHTR and 4 cases of allergic transfusion reactions were observed. In addition, one in 18,506 intra-operatively salvaged blood products was transfused to the wrong patient, resulting in an AHTR secondary to ABO blood group incompatibility. In this study, we identified 16 (0.1%) adverse reactions in 13,653 PAD transfusions, of which 12 were FNHTR and 4 were allergic reactions.

PAD transfusion involves many of the same complications as the transfusion of allogeneic blood components, such as the risk of administrative errors [2,3]. Patients may receive another patient's autologous blood as a result of clerical errors or may receive allogeneic blood when autologous blood is available [4]. We reported previously that a bar code-based electronic identification system (EIS) was successfully applied to the pre-transfusion checking procedure in the setting of PAD transfusion [5], as well as allogeneic blood transfusion [8], and no mistransfusion has been observed to date. Although the frequency of mistransfusion may be low in autologous blood transfusion, we may have to approach it with the same level of care and consideration as allogeneic blood transfusion.

FNHTR is one of the most frequently occurring adverse transfusion reactions [9,10]. The mechanisms of FNHTR occurrence include an antileukocyte antibody-mediated mechanism and/or accumulation of pro-inflammatory cytokines during the storage of blood components [10,11]. In the former situation, antileukocyte antibodies present in the

Table 1
Summary of 16 patients with adverse reactions to PAD transfusions.

Patient no.	Age/ Gender	Year	Adverse reaction	Severity	Specialty	Component types	Duration of PAD storage (days)	History of transfusion/ pregnancy
1	60/M	2003	Allergic reaction ^a	Grade 1	EGS ^b	Frozen PAD	131	Yes/-
2	69/M	2003	FNHTR ^c	Grade 1	Urology	WB-PAD	14	No/-
3	75/M	2003	FNHTR	Grade 1	Urology	WB-PAD	13	No/-
4	68/M	2004	FNHTR	Grade 1	Urology	WB-PAD	31	No/-
5	64/M	2005	FNHTR	Grade 1	Urology	WB-PAD	24	No/-
6	67/F	2005	Allergic reaction ^a	Grade 1	OS	Autologous FFP	21	No/Yes
7	72/F	2009	FNHTR	Grade 1	OS	Frozen PAD	28	No/Yes
8	26/F	2009	Allergic reaction	Grade 1	HBPS	Autologous FFP	88	No/Yes
9	72/F	2009	FNHTR	Grade 1	OS	WB-PAD	19	No/Yes
10	54/F	2010	FNHTR	Grade 1	OS	WB-PAD	11	No/No
11	37/M	2013	FNHTR	Grade 1	OS	WB-PAD	15	No/-
12	40/F	2013	Allergic reaction	Grade 1	OG	WB-PAD	22	No/Yes
13	63/F	2014	FNHTR	Grade 1	OS	WB-PAD	26	No/Yes
14	73/F	2015	FNHTR	Grade 1	OS	WB-PAD	25	No/Yes
15	33/M	2015	FNHTR	Grade 1	OS	WB-PAD	21	No/
16	52/F	2016	FNHTR	Grade 1	OS	WB-PAD	18	No/Yes

^a Other symptoms were present in Patient 1 with tachycardia and in Patient 6 with pallor.

^b EGS, esophageal and gastric surgery; OS, orthopedic surgery; HBPS, hepato-biliary-pancreatic surgery; OG, obstetrics and gynecology.

^c FNHTR, febrile non-hemolytic transfusion reaction.

Table 2
Comparison of adverse reactions between PAD and allogeneic transfusions during the study period.

Adverse reactions	Allogeneic transfusions ^a (n = 383)		PAD transfusions (n = 16)	
	Number (%)	Severity	Number (%)	Severity
AHTR ^b	0		0	
DHTR	1 (0.3)	Grade 2	0	
FNHTR	104 (27.2)	Grade 1	12 (75)	Grade 1
Allergic reaction	216 (56.4)	Grade 1	4 (25)	Grade 1
	215	Grade 3		
	1 ^c			
TRALI	2 (0.5)	Grade 3	0	
TACO	0		0	
Hypotensive transfusion reaction	38 (9.9)	Grade 1	0	
	31	Grade 2		
	7			
TAD	14 (3.7)	Grade 1	0	
	12	Grade 2		
	2			
PTP	0		0	
TA-GVHD	0 ^d		0	
Others ^e	8 (2.0)	Grade 1	0	

^a The number of adverse reactions to PLT transfusion was excluded from those to allogeneic blood transfusions in this comparative study.

^b AHTR, acute hemolytic transfusion reaction; DHTR, delayed hemolytic transfusion reaction; FNHTR, febrile non-hemolytic transfusion reaction; TRALI, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload; TAD, transfusion-associated dyspnea; PTP, post-transfusion purpura; and TA-GVHD, transfusion-associated graft-versus-host disease.

^c One patient with IgA deficiency was included.

^d Since the year 2000, irradiated allogeneic blood components excluding fresh frozen plasma have been recommended for all patients in Japan.

^e Others included 6 cases of hypertension and 2 cases of tachycardia, which did not meet the TACO criteria.

patients due to prior alloimmunization (e.g., transfusion, pregnancy) interact with leukocytes of transfused blood components, resulting in the release of endogenous pyrogens. Although FNHTR is not considered to be life-threatening, it is uncomfortable for the patient and can exacerbate underlying health conditions and interrupt a needed blood transfusion [10,12]. In this study, the most common adverse reaction to PAD transfusion was FNHTR, involving 12 (75%) cases, of which 11 cases were caused by WB-PAD components. None of the 12 patients with FNHTR had a prior transfusion history, and one of 6 female

patients with FNHTR had no history of pregnancy. These findings suggest that FNHTR in our patients was likely to have been caused by the accumulation of pro-inflammatory cytokines during the storage of WB-PAD components. It has been shown that universal leukoreduction decreases the frequency of FNHTR in the setting of allogeneic blood transfusion [13–15]. In Japan, the Japanese Red Cross Blood Center implemented universal leukoreduction for allogeneic blood components in 2006. Apart from the situation of allogeneic blood transfusion, we did not perform prestorage leukocyte reduction for WB-PAD components in our hospital. Prestorage leukoreduction for autologous blood has been reported to suppress cytokine accumulation, without demonstration of clinical benefits [16]. Further studies are needed to determine whether such prestorage leukoreduction actually reduces the frequency of FNHTR in the setting of WB-PAD component transfusion.

Downward trends in PAD collection and transfusion have been reported in Europe and the Americas, resulting from the decreasing residual risks of transfusion-transmitted infection and the declining need for blood transfusion due to patient blood management programs [1,17]. In Japan, PAD transfusion still plays a role in eliminating risks related to allogeneic blood transfusion, especially TA-GVHD. ‘HLA one-way match’ results in the inability to reject donor lymphocytes even if the recipient is immunocompetent, and it occurs at a high frequency: one in several hundred blood transfusions from unrelated donors in Japan [18]. The Japanese Red Cross Blood Center disseminated transfusion information regarding TA-GVHD to most Japanese hospitals in December 1999, in which the administration of irradiated blood components except for FFP is recommended for preventing TA-GVHD. In the present study, the number of PAD collections showed an annual decline, there was a trend toward a slow decline in PAD transfusion over a 14-year period at our institution, and the overall mean annual rate of PAD transfusion was 9.4% of all RBC transfusions.

The main limitation of the present study is that it was conducted in a single university hospital. So, the frequency and characteristics of adverse reactions to PAD transfusion may be different by institutions. Multi-institutional joint studies are needed to clarify the frequency of adverse reactions and differences with allogeneic blood transfusion in autologous blood transfusion.

In conclusion, this retrospective study over a 14-year period revealed the presence of non-severe adverse reactions to PAD transfusion, with a rate of 0.1% at our institution.

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Conflict of interest

The authors declare that there is no conflict of interest associated with this publication.

Authors contributions

A.O. designed the experiments, analyzed the data, and prepared and edited the manuscript; T.O. designed the experiments, and collected and analyzed the data; Y.N. collected and analyzed the data; M.T. collected the data; K.I. collected the data; and Y.F. collected and analyzed the data.

This manuscript was approved by all authors, and has not been published previously nor is under consideration for publication elsewhere.

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