

Storage of thawed fresh frozen plasma in an active transport refrigerator for prehospital use

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1. Background

Plasma resuscitation improves mortality and neurological function in patients with severe multiple trauma and severe isolated traumatic brain injury^{1–3}. Early transfusion and prehospital transfusion of plasma also contribute to improved outcomes in patients with severe multiple trauma^{4,5}. Sperry et al.⁶ recently reported that prehospital thawed plasma transfusion was safe and resulted in lower 30-day mortality than standard-care resuscitation. In Japan, prehospital transfusion is uncommon due to the lack of an adequate method for transporting blood products from the hospital to the accident site. A recent study reported the use of an active transport refrigerator (ATR)⁷ to store and preserve red blood cell (RBC) solutions under adequate temperature conditions during transport^{8)–10)}. We previously reported the use of an ATR in the Ogasawara blood rotation, which involves long distance transport of RBCs to the Ogasawara Islands located 1,000 km from Tokyo; the transport time from Tokyo is approximately 11 hours 43 minutes⁷⁾¹¹⁾. Taguchi¹¹⁾ reported emergency transportation over a 6-year period in which 1,418 patients were transported from the remote Izu Islands; transport times ranged from approximately 2 hours 51 minutes (Ohshima Island) to 4 hours 59 minutes (Aogashima Island). Taguchi did not transport thawed fresh frozen plasma (FFP) because an ATR was not available. Moreover, there is currently no report concerning the use of ATR in the transport of thawed FFP for prehospital transfusion.

Here, we studied the effects of ATR storage on clot-

ting factor activity in thawed FFP to determine the usefulness of ATR-stored FFP for prehospital plasma transfusion in Tokyo Metropolitan hospitals for emergency medicine in remote islands.

2. Materials and methods

2.1 Blood products

Bags containing 240 ml of FFP were obtained from the Japan Red Cross Society (Tokyo, Japan) and thawed using a recirculating water bath thawing system at 37°C (FF-40, Kawasumi Laboratories Incorporated, Oita, Japan). After thawing, the 240 ml of thawed FFP was separated into two bags of 120 ml each using a modified version of a previously reported method¹²⁾. In Japan, thawed FFP must be dissolved and stored at 4–6°C, and used within 24 hours. Six bags of FFP were used in this experiment: three bags, two of which contained blood type A and the other blood type B, were each divided in two and stored for three hours in an ATR or blood product refrigerator; the other three bags, all of which contained blood type AB, were each divided in two and stored for 24 hours in an ATR or blood product refrigerator (Table 1).

2.2 Storage

Each 120-ml bag of thawed FFP was stored for 3 or 24 hours in an ATR (ATR-700, FUJIFILM Toyama Chemical Co., Ltd., Tokyo, Japan) or blood product refrigerator (MBR-506T, Sanyo Co., Ltd., Tokyo, Japan), which is typically used for storage of blood products in hospitals. The ATR-700 (400 × 250 × 320 mm, 6.6 kg) maintains an internal temperature of 2–6°C regardless

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Table 1 Effects of storage in the active transport refrigerator or blood product refrigerator on clotting factor activity in thawed plasma

	hour	Active transport refrigerator		Blood product refrigerator	
		Pre-storage	Post-storage	Pre-storage	Post-storage
Activated thromboplastin time	3	100.0 ± 1.4	99.7 ± 1.3	100.0 ± 0.9	98.6 ± 0.9
	24	100.1 ± 1.3	107.8 ± 1.6*	99.9 ± 0.7	106.4 ± 1.8*
% Prothrombin time	3	100.1 ± 6.6	99.8 ± 7.9	100.0 ± 7.1	102.6 ± 7.6
	24	100.0 ± 0.8	93.6 ± 2.5	100.0 ± 1.8	94.0 ± 3.0
Fibrinogen	3	99.9 ± 19.6	100.0 ± 19.2	100.2 ± 17.7	100.3 ± 18.0
	24	99.9 ± 21.3	96.8 ± 18.0	99.9 ± 22.5	95.3 ± 17.5
Factor II	3	100.1 ± 2.8	101.1 ± 3.2	100.6 ± 5.1	99.4 ± 5.7
	24	100.0 ± 6.1	99.5 ± 5.6	100.3 ± 4.2	100.9 ± 2.5
Factor V	3	100.1 ± 5.0	102.1 ± 5.9	99.9 ± 10.0	99.9 ± 10.0
	24	100.0 ± 7.8	91.6 ± 1.4	99.7 ± 12.4	100.9 ± 13.6
Factor VII	3	100.9 ± 10.6	100.3 ± 9.9	99.9 ± 10.0	99.9 ± 10.0
	24	99.6 ± 0.7	93.5 ± 2.9	99.8 ± 4.3	98.1 ± 4.7
Factor VIII	3	99.9 ± 21.7	104.6 ± 24.2	100.5 ± 19.6	101.9 ± 21.8
	24	100.0 ± 17.0	99.9 ± 6.5	99.8 ± 24.7	87.3 ± 11.3
Factor IX	3	100.4 ± 11.5	100.3 ± 11.2	100.4 ± 11.4	101.3 ± 10.7
	24	100.3 ± 2.9	93.5 ± 7.7	100.4 ± 1.3	96.7 ± 2.8
Factor XI	3	99.8 ± 4.5	99.0 ± 5.3	100.1 ± 3.8	102.6 ± 3.8
	24	100.3 ± 9.3	90.7 ± 12.4	100.3 ± 8.8	98.6 ± 9.4
von Willebrand factor	3	99.5 ± 13.1	101.0 ± 14.3	100.0 ± 15.2	99.0 ± 16.5
	24	99.7 ± 9.4	94.2 ± 8.9	99.7 ± 5.3	100.3 ± 9.7

Data are expressed as group means (% of control) ± standard error of the mean.

* : $p < 0.05$ vs. pre-storage group

of the ambient temperature, which ranges from -10 to $+35^{\circ}\text{C}$ along the route from Tokyo to the Ogasawara Islands⁷⁾. Transport of blood products is possible over a long period (up to 7 hours) with the internal lithium-ion battery. The refrigerator has a capacity of 3.8 l, and up to five bags of RBCs (280-ml bags) or five bags of thawed FFP (240-ml bags) can be stored in the upright position⁷⁾⁸⁾.

2.3 Evaluation of clotting test results and clotting factor activity

Clotting factor activity (factors II, V, VII, VIII, IX, and XI and von Willebrand factor, tested for each bag pre- and post-storage), and clotting test results (tested for each bag pre- and post-storage) including activated partial thromboplastin time (aPTT), % prothrombin time (%PT), and fibrinogen level in plasma were evaluated by Biomedical Laboratories Company (Tokyo, Japan). Results are expressed as percentages, calculated using the formula $A/B \times 100$ (%), where A is the pre- or post (3-14 hours) -storage value, and B is the mean pre-storage value.

2.4 Statistical analysis

Data are expressed as the group mean ± standard error of the mean. All statistical calculations were performed using JMP version 8.0 software (SAS Institute, Inc., Cary, NC). We analyzed differences in laboratory

values between pre- and post-storage conditions using a paired t test. A P -value < 0.05 was considered significant.

2.5 Ethical approval

This study was approved by the institutional review board of Tokyo Metropolitan Bokutoh Hospital.

3. Results

3.1 Effects of storage of thawed plasma in the ATR or blood product refrigerator on clotting test results

As shown in Table 1, three-hour storage in the ATR-700 and blood product refrigerator had no effect on the clotting test results. In experiments using the ATR and blood product refrigerator for 24-hour storage, aPTT was significantly increased and %PT and fibrinogen levels were slightly but not significantly decreased compared to pre-storage.

3.2 Effects of storage of thawed plasma in the ATR or blood product refrigerator on clotting factor activity

As shown in Table 1, three-hour storage in the ATR-700 and blood product refrigerator had no effect on clotting factor activity. While 24-hour storage in the ATR-700 and blood product refrigerator similarly had no effect on the activity of clotting factor II, VIII, and XI, the activity of clotting factor V, VII and IX and von Willebrand factor tended to be lower than that at pre-

storage.

4. Discussion

In Japan, FFP is usually frozen at -20°C and, when thawed, must be used within 24 hours, with adequate storage at $4-6^{\circ}\text{C}$. Tokyo Metropolitan Bokutoh Hospital is located in the eastern region of the Tokyo metropolitan area, and injured patients at accident sites are typically within a reasonable distance. Therefore, when thawed plasma is transported by official vehicle or helicopter, it is typically used within 24 hours for prehospital transfusion. This is important because prehospital transfusion improves the outcomes of patients with severe trauma who are transported by helicopter^{(6)(13)~(15)}.

A number of methods can be used for storage in the transport of FFP from the hospital to the accident site. As reported by Zielinski et al.⁽¹⁶⁾, one approach is to transport thawed FFP after dissolving it at the hospital. Another approach, as reported by Moore et al.⁽¹⁾, is to transport unthawed FFP and an FFP thawing machine. However, we expect that it is likely difficult to manage a thawing machine and dissolving the FFP during transport in an emergency setting.

Compared with saline infusion in experimental settings⁽¹⁷⁾, early plasma transfusion inhibits hyperfibrinolysis⁽²⁾ and reduces platelet dysfunction in trauma-induced coagulopathy. As a result, early plasma transfusion may protect neurological function after traumatic brain injury⁽³⁾. Therefore, transport of plasma as well as RBC solution by official vehicle or helicopter is necessary for prehospital transfusion.

Early use of lyophilized plasma improves the neurological outcomes of patients with severe traumatic brain injury⁽¹⁸⁾. In addition, lyophilized plasma and FFP are beneficial in trauma-induced coagulopathy⁽¹⁹⁾. Therefore, lyophilized plasma will likely be used in the future for prehospital infusion. However, in Japan, data regarding the stability of lyophilized plasma at ambient temperatures are not currently available.

Based on clotting factor activity, the current study showed that storage of FFP in the ATR-700 and blood product refrigerator had no effect on the quality of the thawed plasma (Table 1). Therefore, ATR-700 can be used for the transport of thawed plasma for prehospital transfusion within the Tokyo metropolitan area and between Tokyo and remote islands.

Several limitations of this study warrant mention. First, Mori et al.⁽²⁰⁾ previously reported the clotting fac-

tor activity in thawed FFP stored in a blood product refrigerator for preservation, while this paper reported the clotting factor activity in thawed FFP stored during transport. Second, we have no clinical data regarding the pre-hospital use of thawed FFP. Therefore, further research in a clinical setting is warranted.

5. Conclusion

We conclude that thawed plasma stored and transported in an ATR can be used in prehospital plasma transfusion in Tokyo Metropolitan hospitals for emergency medicine in remote islands.

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Author contributions

HF performed the study and wrote the manuscript. SN designed the study. YH, MN, and MT analyzed the data. HA managed the active transport refrigerator.

Disclosure of conflicts of interest

The authors declare that they have no conflicts of interest.

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病院前使用のための可搬式血液冷蔵庫での融解新鮮凍結漿の保管

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