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Case Report

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Perioperative Management of Hemophilia A With Recombinant VIII-SingleChain: A Case Series

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Abstract

Patients with hemophilia A often experience non-traumatic spontaneous bleeding and prolonged time to hemostasis following trauma. Those who require surgery must undergo risk assessment for perioperative bleeding, and factor VIII (FVIII) replacement therapy must be administered when coagulation factors are deficient to prevent perioperative bleeding. This case series reports the first four cases in which single-chain recombinant FVIII (rVIII-SingleChain) was used for perioperative hemostasis management in patients with hemophilia A at Hiroshima University Hospital, Hiroshima, Japan. Three male patients, aged 70, 66, and 77 years, with mild hemophilia A underwent four surgical procedures. After surgery, rVIII-SingleChain administration provided adequate increases in factor VIII activity, measured by the one-stage clotting assay (OSA), and hemostatic effectiveness was observed. This case series demonstrates that real-time changes in coagulation factor activity in the perioperative period can be monitored with the OSA after rVIII-SingleChain administration in patients with hemophilia A.

Keywords: Factor VIII activity; Hemophilia A; Perioperative hemostasis management; Recombinant VIII-SingleChain

Introduction

Hemophilia A is a hemostasis disorder characterized by congenital abnormalities in blood coagulation factor VIII (FVIII) levels or function. This condition consequently leads to non-traumatic spontaneous bleeding and prolonged time to hemostasis after trauma [1]. Furthermore, in patients with hemophilia A who require surgery, it is important to assess the risk of perioperative bleeding before surgery and replace the deficient coagulation factors to ensure that the procedure can be performed safely [1].

Single-chain recombinant FVIII (rVIII-SingleChain) is a recombinant FVIII product that was approved for use in patients with hemophilia A in Japan in September 2017 [2]. Clinical trials have demonstrated that rVIII-SingleChain has an improved pharmacokinetic profile compared with other recombinant FVIII products, and is well tolerated and efficacious as on-demand therapy, prophylaxis, and perioperative replacement in patients with hemophilia A [3-5].

The Japanese guideline on perioperative management of hemophilia includes target coagulation factor activity values (80%) and recommends when additional infusions of FVIII products should be provided, depending on the invasiveness of the procedure [6]. However, the guideline also states that coagulation factors may be infused based on expected values, since monitoring in actual clinical practice may be difficult [6]. The characteristics associated with obtaining the expected coagulation factor activity values, including pharmacokinetics, differ for each FVIII product. However, there have been no reports of changes in FVIII activity over time after administration of rVIII-SingleChain, with the exception of one surgical sub-study from a clinical trial in patients with severe hemophilia A [4].

In Japan, the one-stage clotting assay (OSA) is often used to monitor FVIII activity. In this assay, coagulation factor activity is calculated by converting the measured value using a conversion factor that is specific to each recombinant FVIII product (i.e., 2 for rVIII-SingleChain) [7, 8]. More accurate FVIII activity values can be determined if using the chromogenic substrate assay (CSA); however, few medical institutions in Japan are able to perform this assay. OSA conversion factors have been determined by comparing the measured activity values for purified FVIII products in the OSA versus the CSA, and were validated using plasma samples for prophylaxis [8]. Because the coagulation system is activated during surgery by vascular damage, the conversion factor for rVIII-SingleChain that is used by Japanese medical institutions may be different during surgery from that used in regular replacement therapy.

In our case series, perioperative management with rVIII-SingleChain was performed at Hiroshima University Hospital (Hiroshima, Japan) in three patients with hemophilia A who underwent a total of four surgical procedures. We evaluated hemostasis management and calculated changes in FVIII activity over time, using both real-time data and, in three of the cases, measurements from stored plasma samples. Stored plasma was used to compare FVIII activity measured using the OSA and CSA, and to verify the conversion factor used during the perioperative period.

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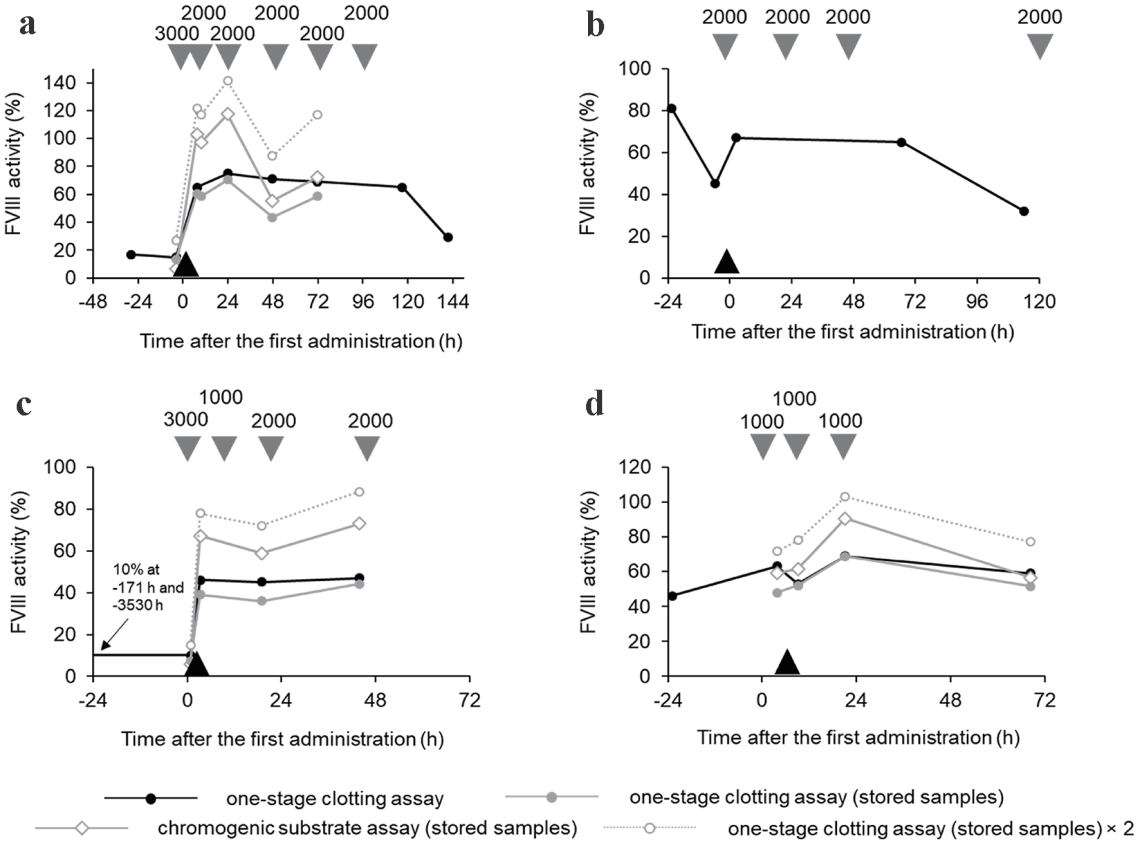

Figure 1. Real-time FVIII activity levels over time for (a) case 1, (b) case 2, (c) case 3, and (d) case 4, measured from the first dose of rVIII-SingleChain. Real-time FVIII activity was measured using the OSA (black circles with solid black lines). Stored plasma samples were used to measure FVIII activity using the OSA (gray circles with solid gray lines) and the CSA (white diamonds with solid gray lines). Converted OSA values (conversion factor = 2) from stored plasma samples are shown (white circles with gray dashed lines). The timing of surgery (black triangles) and the administration of rVIII-SingleChain (gray triangles) are also shown, with the rVIII-SingleChain dose indicated in units. CSA: chromogenic substrate assay; FVIII: factor VIII; OSA: one-stage clotting assay; rVIII: recombinant factor VIII.

Case Reports

Case 1: patient 1, surgery 1

Investigations

A 70-year-old male patient presented with mild hemophilia A without inhibitor. He had been receiving routine prophylaxis therapy with turoctocog alfa (NovoEight®) at a dose of 3,000 units (about 42.9 units/kg), administered twice weekly since 2015. He was scheduled to undergo thoracoscopic surgery in July 2019 for primary lung cancer.

On the day of surgery, coagulation factor activity was 15% (Fig. 1a). rVIII-SingleChain at 42.9 units/kg was administered preoperatively, and 1 h later, his preoperative FVIII activity was 65%. The volume of intraoperative blood loss was 2 mL. Four hours after surgery, the patient received 28.6 units/kg of rVIII-SingleChain. Further doses of rVIII-SingleChain, each of 28.6 units/kg, were administered daily on days 1 - 4 after surgery, and real-time FVIII activity on postoperative days 1, 2, 3, and 5 was 75%, 71%, 69%, and 65%, respectively (Fig. 1a). In addition, FVIII activity was later determined from plasma samples (stored at -80 °C) using OSA and CSAs (Table 1).

Diagnosis

Based on clinical study criteria, the effect of rVIII-SingleChain on perioperative hemostasis was rated as "excellent".

Treatment

No additional doses of rVIII-SingleChain were administered during or after surgery to stop bleeding.

Follow-up and outcomes

Postoperative bleeding was not observed, and the patient was

Table 1. Coagulation Factor Activity in Stored Plasma From Cases 1, 3 and 4

Time from first rVIII-SingleChain dose (h)	rVIII-SingleChain dose (units)	CSA activity (%)	OSA activity (%)	Converted OSA activity (%)[a]	CSA to OSA ratio[b]
Case 1					
-3.7		6.5	13.5	27.0	0.48
0.0	3,000				
Surgery (thoracoscopic surgery for primary lung cancer (partial lung resection))					
7.5		103.1	60.7	121.4	1.70
9.6		97.0	58.5	117	1.66
11.7	2,000				
23.9		117.4	70.6	141.2	1.66
24.7	2,000				
48.7	2,000	55.4	43.7	87.4	1.27
72.7	2,000	72.1	58.5	117	1.23
96.7	2,000				
Case 3					
-0.9		5.8	7.5	15.0	0.77
0.0	3,000				
Surgery (colonic submucosal dissection)					
3.3		67.1	38.9	77.8	1.72
8.0	1,000				
19.0		58.9	36.0	72.0	1.64
20.0	2,000				
43.9		72.9	44.1	88.2	1.65
44.0	2,000				
Case 4					
0.0	1,000				
3.8		58.9	47.8	95.6	1.23
Surgery (endoscopic mucosal resection for early-stage duodenal tumor)					
9.0	1,000				
9.2		61.5	52.0	104.0	1.18
21.0	1,000				
21.1		90.6	68.7	137.4	1.32
68.4		56.6	51.5	103.0	1.10

[a]Coagulation activity from OSA × conversion factor of 2. [b]Ratio between CSA activity/OSA activity values. CSA: chromogenic substrate assay; OSA: one-stage clotting assay; rVIII: recombinant factor VIII.

discharged on postoperative day 5. After discharge, turoctocog alfa was restarted as prophylaxis.

Case 2: patient 1, surgery 2

Investigations

The following year after the surgery described above, the same patient underwent transcatheter arterial chemoembolization for hepatocellular carcinoma.

The patient, now 71 years of age, had been receiving prophylaxis until 48 h before arterial puncture, and 6 h before surgery his FVIII activity was 45%; rVIII-SingleChain 28.6 units/kg was administered (Fig. 1b). The volume of intraoperative bleeding due to arterial puncture was almost 0 mL. Coagulation factor activity at 2.5 h after administration was 67%. On postoperative days 1 and 2, rVIII-SingleChain 28.6 units/kg was administered, and coagulation factor activity on postoperative day 3 and 5 was 75% and 32%, respectively. Subsequently, rVIII-SingleChain at 2,000 units was administered on postoperative day 6.

Diagnosis

Based on clinical study criteria, perioperative hemostasis following rFVII-SingleChain administration was rated as "excellent".

Treatment

No additional doses of rVIII-SingleChain were administered during or after surgery to stop bleeding.

Follow-up and outcomes

Postoperative bleeding was not observed, and the patient was discharged on postoperative day 6. After discharge, turoctocog alfa was again restarted as regular replacement therapy using the same dosage regimen as before.

Case 3: patient 2

Investigations

This patient was a 66-year-old man with mild hemophilia A without inhibitor who underwent colorectal surgery.

One week before colonic submucosal dissection surgery, FVIII activity (OSA) was 10% (Fig. 1c). rVIII-SingleChain at 3,000 units (about 44.8 units/kg; body weight 67 kg) was administered preoperatively. Immediately before surgery, real-time FVIII activity was 46%. Significant bleeding was not reported. rVIII-SingleChain at 14.9 units/kg was administered 7.5 h after the initial dose. In addition, 29.9 units/kg was administered on postoperative days 1 and 2, and FVIII activity was maintained at 47%. In addition to real-time values, FVIII activity was later determined from collected plasma samples using OSA and CSAs (Table 1).

Diagnosis

Perioperative hemostasis following rVIII-SingleChain administration was rated as "excellent".

Treatment

No additional doses of rVIII-SingleChain were administered during or after surgery to stop bleeding.

Follow-up and outcomes

Postoperative bleeding was not observed, and the patient was discharged on postoperative day 5.

Case 4: patient 3

Investigations

This patient was a 77-year-old man with mild hemophilia A without inhibitor who underwent endoscopic mucosal resection for his early-stage duodenal tumor.

One week before surgery, FVIII activity was 44% (Fig. 1d). After preoperative administration of rVIII-SingleChain at 1,000 units (about 16.2 units/kg; body weight 61.6 kg), FVIII activity measured 1.5 h after administration was 63%. No significant bleeding was reported. After surgery, FVIII activity was 53%; an additional 16.2 units/kg was administered after surgery and the following day. FVIII activity on postoperative days 1 and 3 was 69% and 59%, respectively. FVIII activity was later measured from collected plasma samples (Table 1).

Diagnosis

The effect of rVIII-SingleChain on perioperative hemostasis was rated as "excellent".

Treatment

No additional doses of rVIII-SingleChain were required during or after surgery.

Follow-up and outcomes

Postoperative bleeding was not observed, and the patient was discharged on postoperative day 4.

Discussion

We report the first four cases of perioperative hemostasis management with rVIII-SingleChain in three patients with hemophilia A at our institution (Table 2 for a summary of our cases). There were no clinically significant differences in the degree of hemostasis in these patients when compared with patients without FVIII deficiencies. Applying clinical study criteria, the effect of rVIII-SingleChain could be rated as "excellent" in all four cases. Hemostasis was not clinically different from normal (without other hemostatic interventions) and estimated intraoperative blood loss did not exceed predicted blood loss by > 20%. Furthermore, no additional rVIII-SingleChain doses were administered during surgery to stop bleeding. The effectiveness of perioperative hemostasis management with rVIII-SingleChain was, therefore, considered to be comparable with that of other FVIII products.

Although accurate real-time measures of FVIII activity could not be obtained during surgery, we estimated FVIII activity by converting the perioperative OSA measurement. This straightforward approach may assist medical institutions who are managing perioperative hemostasis for the first time.

FVIII activity values obtained using the CSA, which is not generally used, reportedly correlate better with bleeding episodes [9], and the labeled titer on the rVIII-SingleChain vials was determined using the CSA. The OSA conversion

Table 2. Summary of Cases 1, 2, 3 and 4

	Case 1[a]	Case 2[a]	Case 3	Case 4
Patient characteristics				
Age, years	70	71	66	77
Gender	Male	Male	Male	Male
Hemophilia type	Mild hemophilia A without inhibitor	Mild hemophilia A without inhibitor	Mild hemophilia A without inhibitor	Mild hemophilia A without inhibitor
Surgery	Thoracoscopic surgery	Transcatheter arterial chemoembolization for hepatocellular carcinoma	Colonic submucosal dissection	Endoscopic mucosal resection for early-stage duodenal tumor
Real-time coagulation factor activity (measured using OSA), %				
Prior to surgery	15	45	10	44
Post-first dose	65[b]	67[d]	46[f]	63[h]
Post-operatively	75, 71, 69, 65[c]	75, 32[e]	47[g]	53, 69, 59[i]
Dose of rVIII-SingleChain, units				
Pre-operative	3,000	2,000	3,000	1,000
Immediately post-operatively	2,000	N/R	1,000	1,000
Post-operatively	2,000 on days 1-4	2,000 on days 1, 2 and 6	2,000 on days 1 and 2	1,000 on day 1
Bleeding				
During surgery	2 mL	0 mL	No significant bleeding reported	No significant bleeding reported
Post-operatively	Not observed	Not observed	Not observed	Not observed

[a]These cases involve the same individual. [b]1 hour post-dose. [c]Days 1, 2, 3 and 5, respectively. [d]2.5 hours post-dose. [e]Days 3 and 5, respectively. [f]"Immediately" before surgery. [g]Days 1 and 2. [h]1.5 hours post-dose. [i]After surgery and on days 1 and 3, respectively. N/R: not reported; OSA: one-stage clotting assay.

factor is determined by dividing the CSA activity value by the OSA activity value [8]. The conversion factor approved by the United States (US) Food and Drug Administration and European Medicines Agency for rVIII-SingleChain is 2, which is reflected in the Japanese, US, and European package inserts [10-12]. Our institution conducts real-time FVIII activity monitoring using the OSA. As real-time monitoring using the CSA is not feasible, stored plasma samples were used to measure FVIII activity using the CSA and OSA in cases 1, 3, and 4.

Using the conversion factor, converted FVIII activity values for all cases exceeded the guideline-recommended target FVIII activity level of 80% (Table 1) [6]. The ratio of CSA to OSA values tended to decrease from 2 with increasing postoperative time (Table 1). The reason for the decline in CSA to OSA ratio is unclear; however, it is possible that endogenous or replaced FVIII contributed to the changes in FVIII activity during the perioperative period. FVIII activity measured immediately after rVIII-SingleChain administration is considered to reflect activity from rVIII-SingleChain. Since all three patients had mild hemophilia A, endogenous FVIII may have contributed to the measured FVIII activity. In addition, as the patient in cases 1 and 2 was receiving FVIII replacement, recombinant FVIII products administered during this therapy may have been present. Thus, the value obtained by multiplying the measured activity (OSA) by the conversion factor of 2 would deviate from the actual FVIII activity.

Learning points

We report the first cases at our institution of perioperative hemostasis management with rVIII-SingleChain in patients with mild hemophilia A. In all cases, an adequate increase in FVIII activity and hemostatic effectiveness was observed. Comparison of perioperative FVIII activity measurements between the OSA and CSA suggested that a conversion factor of 2 for the OSA may result in overestimation of actual FVIII activity.

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Conflict of Interest

TF participates on a data safety monitoring board or advisory board of KM Biologics Inc. NY has no conflict of interest to be disclosed in relation to this study.

Informed Consent

The patients' informed consent for publication of this report was obtained.

Author Contributions

Both authors were involved in the concept for this manuscript, the acquisition and analysis of the data, and the writing and revising of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

CSA: chromogenic substrate assay; OSA: one-stage clotting assay; rVIII-SingleChain: single-chain recombinant FVIII; FVIII: factor VIII; US: United States

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