

Perioperative Management of a Patient with Congenital Afibrinogenemia

Toshimitsu KITAJIMA, Kazumasa URABE,
Hiromaru OGATA and Shigeki NAGASHIMA*

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Congenital afibrinogenemia is a rare coagulation disorder with an autosomal recessive inheritance. Its prognosis has recently been improved through the administration of human fibrinogen. But fibrinogen administration rarely induces severely hypersensitive reactions, and death due to anaphylaxis has been reported in some cases^{1,2}. This is a report on a patient with congenital afibrinogenemia with a history of hypersensitive reactions (bronchospasm, hypotension and skin rash) after administration of fibrinogen. The successful treatment of the case with human fibrinogen and fresh frozen plasma, after rapid desensitization to prevent hypersensitive reactions, is described.

Case Report

The patient was a 21 year-old male whose chief complaint was right facial pain and swelling. Plasma fibrinogen levels in his parents, younger sister and brother were normal. He had had some bleeding incidents in the past and was diagnosed in another university hospital as having congenital afibrinogenemia at the age of six. He also experienced anaphylactic shock after administration of fibrinogen at the ages of six and thirteen, and this was relieved with corticosteroids. He

had had hypertension since the age of 14 years. At twenty, he had a burr hole opening for a chronic subdural hematoma under local anesthesia. The present illness started as a severe pain on the right side of the face three days prior to admission and developed into severe swelling and heat on the same side. The pain and swelling became severer, with a fever of 39.8°C, despite antibiotic therapy, and so he was admitted to the Third Department of Internal Medicine of our hospital. The diagnosis was dental maxillary sinusitis, and an elective operation was scheduled for one month later.

The initial results of the examinations of the clotting factors are shown in table 1. The plasma fibrinogen level was less than 27 mg-dl⁻¹ by the thrombin method. The skin test was positive to human fibrinogen (10 × 10/25 × 24 mm). Other laboratory examinations (liver function, serum electrolyte and kidney function tests) gave normal results. EKG and respiratory function were also normal.

Preoperative treatment

The preoperative treatment was started 48 hr before the day of operation. Methyl prednisolone, chlorpheniramine, amino phyllin, stronger neo-minophagen C, azelastin and tranexamic acid were administered, as table 2 shows.

Rapid desensitization

Twelve hours after the first administration of these drugs, the following therapy for rapid desensitization to fibrinogen was performed (table 3): 0.02 ml of human fib-

First Department of Anesthesiology and *Third Department of Internal Medicine, Dokkyo University School of Medicine, Tochigi-ken, Japan

Address reprint requests to Dr. Kitajima: First Department of Anesthesiology, Dokkyo University School of Medicine, 880 Kitakobayashi, Mibu, Tochigi-ken, 321-02 Japan

Table 1. Results of examinations of clotting factors in the preoperative period

HEMOSTATIC TESTS	DATE	2 days preoperatively	1 day preop. after human fibrinogen 5g	Day of operation before platelet-rich plasma 10 units
Plasma fibrinogen level (mg·dl ⁻¹)		< 27	147	90
Bleeding time (mins)		> 10	6	> 10
Coagulation time (mins)		> 30	13	13
Prothrombin time (secs)		> 276	13.7	14.1
Activated partial thromboplastin time (secs)		> 276	36.9	37.3
Platelet agglutination (%)		< 5	23	29
Platelet adhesivity (%)		< 5	48	33

Table 2. Preoperative treatment

MEDICATION	DATE 2 days before operation	1 day before operation	Day of operation
Methylprednisolone (IV)	125 mg OD	250 mg BID	250 mg BID
Chlorpheniramine (DIV)	5 mg OD	15 mg TID	15 mg TID
Aminophyllin (DIV)	375 mg OD	750 mg BID	750 mg BID
Stronger neo-minophagen C (IV)	40 ml OD	40 ml OD	40 ml OD
Azelastine (PO)	4 mg OD	8 mg BID	—
Tranexamic acid (DIV)	2g	2g	2g

Table 3. Rapid desensitization to human fibrinogen

0.02 ml of human fibrinogen (IV) in increasing concentrations (1:100,000 1:10,000 1:1,000 1:100 1:10 1:1)
↓ Skin test (-) to 1:1
1 ml of 1:100 human fibrinogen (IV)
↓
0.3 ml of 1:10 human fibrinogen (IV)
↓
Concentration of fibrinogen increased to 3× that of previously administered does
↓
10 ml of 1:1 human fibrinogen (IV)
↓ No hypersensitivity reaction
Total of 5 gms human fibrinogen (IV)

rinogen was injected intradermally with concentrations increasing from 1:100,000 to 1:1. Since the skin test was negative against 1:1 fibrinogen, the patient received 1 ml

of 1:100 fibrinogen intravenously. No hypersensitive reactions occurred. Then, 0.3 ml of 1:10 fibrinogen was administered intravenously 15 minutes after the first injection. The fibrinogen concentration was thus increased to three times that reached with the first dose. No hypersensitive reactions occurred after the intravenous administration of 10 ml of 1:1 fibrinogen. Eventually, a total of about 5 grams of human fibrinogen was infused. After this fibrinogen administration, the plasma fibrinogen level increased to 147 mg·dl⁻¹ one day before surgery, and the examinations of clotting factors revealed remarkable improvements, as table 1 shows. On the day of the operation, the bleeding time was prolonged to more than 10 min, and so 10 units of platelet-rich plasma were infused. The bleeding time then improved to 4 minutes and 30 seconds.

Anesthetic management

On the day of the operation the patient

Table 4. Postoperative treatment and results of the examinations of clotting factors

Postoperative day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Prednisolone (mg)	60		40		30		20		10		5			
Hydrocortisone (mg)		500	500	500, 500	500			500		500		500		
Fresh frozen plasma (U)		7	7	7		10		10		10		10		
Plasma fibrinogen level (mg·dl ⁻¹)	68		39	46	59	40	72	51	37			34		41
Bleeding time (mins)	3		8°30'	4°30'	4°30'	3°30'	4°30'	3°30'	6°30'			5		2
Coagulation time (mins)	8		12	11	11	10	9	10	16			11°30'		13
Prothrombin time (secs)	14.6		16.2	15.9	15.5	16.2	15.1	15.7	16.6			17.6		16.6
Activated partial thromboplastin time (secs)	37.6		42.0	41.8	39.7	42.4	38.7	38.8	44.3			45.9		44.1
Platelet agglutination (%)	23		22	40	33		31		20			24		24
Platelet adhesivity (%)	19		14	35	17		13		13			12		15

was given 3 mg of bromazepam in suppository form and 0.25 mg of atropine intravenously as premedication. Nitroglycerine 0.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ was infused preoperatively, because the systolic blood pressure was at first 170 mmHg. General anesthesia was induced with 300 mg of thiopental followed by 70 mg of succinylcholine, and the patient was intubated orally. Anesthesia was maintained with 4 $\text{l}\cdot\text{min}^{-1}$ of nitrous oxide, 2 $\text{l}\cdot\text{min}^{-1}$ of oxygen, and 1.5–2% enflurane under controlled ventilation. As nitroglycerine was continuously infused at a rate of 0.8–1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ during the operation, the systolic blood pressure was maintained at about 100 mmHg. There were no incidents of bleeding during the operation. The plasma fibrinogen level was 92 $\text{mg}\cdot\text{dl}^{-1}$, and FDP was less than 10 $\mu\text{g}\cdot\text{ml}^{-1}$. Operation time was 2 hr and 15 minutes; anesthesia time was 3 hr and 45 min; and blood loss was 325 ml.

Postoperative care

The postoperative course is shown in table 4. The plasma fibrinogen level on the day following the operation was 68 $\text{mg}\cdot\text{dl}^{-1}$, revealing that the other clotting factors were normal. On the second postoperative day, 7 units of fresh frozen plasma instead of human fibrinogen were infused intravenously after the administration of hydrocortisone. On the fourth postoperative day, hydrocortisone

was given twice because the patient showed dyspnea and wheezing after the administration of fresh frozen plasma.

Ten units of fresh frozen plasma was administered every other day and the plasma fibrinogen level was maintained at 30–70 $\text{mg}\cdot\text{dl}^{-1}$. On the 13th postoperative day, all stitches were removed. There was no bleeding incident in the postoperative period.

Discussion

Recently, patients with congenital afibrinogenemia have undergone surgical operations with administration of human fibrinogen and fresh frozen plasma^{2–6}. However, there have been a few patients who showed severe hypersensitive reactions to fibrinogen and some deaths have been reported^{1,2}.

This patient had shown hypersensitive reactions only to the skin test, and had fallen into anaphylactic shock immediately after administration of human fibrinogen at the ages of six and thirteen. We thought that it would be impossible for him to receive a sufficient amount of fibrinogen for surgical operation. Therefore, he was infused intravenously with human fibrinogen and fresh frozen plasma after rapid desensitization with pretreatment drugs such as an adrenocorticosteroid, a bronchodilator, an antiallergic drug and an H₁-anti-histamine.

Thus, he was given a total of about five

grams of human fibrinogen without severe hypersensitive reactions. His plasma fibrinogen level increased to 147 mg-dl^{-1} one day before surgery, and there was no bleeding incident during the operation.

It is considered that a plasma fibrinogen level of at least $60\text{--}100 \text{ mg-dl}^{-1}$ was necessary for surgical operation⁷. His plasma fibrinogen level was satisfactory as a result of the rapid desensitization therapy, and no troubles were encountered. We used fresh frozen plasma instead of human fibrinogen in the postoperative period, because the patient experienced headaches at the end of the preoperative administration of fibrinogen. We felt that fresh frozen plasma was more physiological and safe, because human fibrinogen was a manufactured product and would contain some impurities.

Ten units of fresh frozen plasma was administered every other day after operation, and the plasma fibrinogen level was maintained at $30\text{--}70 \text{ mg-dl}^{-1}$. There was no bleeding incident in the postoperative period. The most important problem during the anesthetic management of those patients with congenital afibrinogenemia may be summarized as follows. All medications including anesthetics should be examined in skin tests. Intramuscular administration of premedicants should be avoided. Atropine should be injected intravenously before anesthesia. A thin-walled endotracheal tube should be used to prevent any tracheal injury, and the cuff should not be inflated tightly. Systolic blood pressure should be maintained at about 100 mmHg during surgery to prevent massive bleeding.

In conclusion, a patient with congenital afibrinogenemia who had a history of

hypersensitive reactions to fibrinogen was operated successfully after intravenous infusion of human fibrinogen and fresh frozen plasma following rapid desensitization therapy.

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