# Home Treatment for Patients with Congenital Bleeding Disorders in a Developing Country

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**Abstract**

Ninety-six patients with congenital bleeding disorders were enrolled in a home treatment program from 1979 to 1997. The diagnosis included severe and moderate hemophilia A and B (n = 63), mild hemophilia A (n = 18), von Willebrand disease (vWD) (n = 12) and congenital factor VII deficiency (n = 3). The median age was 9 years and the median duration of follow-up was 4 3/12 years. The home treatment was modified 4 ways: (1) Using locally-prepared single units of fresh dry plasma in the majority of the patients while mild hemophilia A and vWD patients received 1-deamino 8D-arginine vasopressin. (2) Recruiting local health personnel as the primary care providers. (3) Teaching and training patients and parents intensively. (4) Maintaining an effective control system. The heartful effort of the health personnel was not in vain; the patients learned to take good care of themselves. Twenty patients and 20 parents or relatives were able to perform venipuncture properly and no adverse effect was observed. Since the hemorrhage was treated very early, the severity and sequelae of bleeding were decreased. The utilized blood components and days of hospitalization were reduced. Impressively, the absenteeism from work or school was minimized so that the patients could enjoy a near normal life in their family, school and society.

**Key word :** Home Treatment, Bleeding Disorders

Patients with congenital bleeding disorders such as hemophilia, von Willebrand disease (vWD) and congenital factor VII deficiency commonly present life-long bleeding. The bleeding symptoms vary from mild to severe. Moderate to severe hemophiliacs will have frequent hemarthrosis and hematoma while patients with vWD will have troublesome epistaxis. However, patients with mild

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hemophilia or vWD are also prone to iatrogenic bleeding from surgery or dental procedures if the deficient factors are not adequately raised. Moreover, patients with congenital factor VII deficiency risk serious bleeding in the vital organs especially the central nervous system during their first year of life. In order to control these bleeding episodes properly, the home treatment for early bleeding episodes or prophylaxis treatment is obviously desirable. However, giving blood components or medicine intravenously is a strong barrier for the achievement of home treatment. It should be modified to serve low-educated and low-economic patients and parents.

This paper presents over 18 years of modified home treatment for patients with various bleeding disorders in Thailand.

## MATERIAL AND METHOD

**Patients** Ninety-six patients with various congenital bleeding disorders who regularly attended the Hematology Clinic at the Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Bangkok from 1979 to 1997 were enrolled in the study.

**1) Education** The patients and parents directly learned the following aspects from the physicians: signs and symptoms of bleeding sites, dose and frequency of the blood component, 1-deamino 8D-arginine vasopressin (DDAVP) to be given, transfusion reactions and simple medications such as paracetamol and chlorpheniramine. Additionally, in serious bleeding episodes, the patients understood that they should immediately receive blood components or DDAVP and see the physicians at the university, regional or provincial hospital.

A package of educational materials related to the bleeding disorders was provided. It was informative, easy to understand and in the native language. The action plan for the procedures was also provided. Under the supervision of a physician or a nurse, the patients and parents learned how to dissolve the blood component or factor concentrate by using sterile technique. They also learned how to perform venipuncture. The simple model for practicing venipuncture consisted of a 5 mm rubber tube which was struck to a plastic plate and subsequently covered by a thin gauze layer. The rubber tube imitated the human vein beneath the skin.

**2) Patient's home treatment level** The people who dissolved the blood components and performed venipuncture could be classified into 3 groups: group I, the health personnel (n = 56); group II, the parents or relatives (n = 20); and group III, the patients themselves (n = 20).

**3) Patient's assistants** The physicians or health personnel in the village health stations or district hospitals were the patients' major assistants. They served as primary care providers who participated in the home treatment process.

**4) Patient's medical record** The patients and/or parents learned how to write medical records reporting the bleeding sites, cause, severity, blood components, medications, venipuncture, adverse reactions and response to the treatment.

**5) Patient's follow-up** The patients or parents came to see their physicians every 3 to 6 months for physical examination; blood testings for anti-HIV, anti-HCV, a liver profile and an inhibitor to the deficient factor; and a medical record review of home treatment. Then, blood components or DDAVP to be used at home were prescribed.

**Blood components** In 1979, cryoprecipitate was initially used in the home treatment. Each bag contained approximately 100 units of factor VIII[1]. The parents transported the cryoprecipitate in dry ice and kept it in a -20°C locally-made refrigerator. Then, fresh dry plasma (FDP), which is the lyophilized form of fresh frozen plasma (FFP), has been produced by the National Blood Center, Thai Red Cross Society since 1984. Each bottle of FDP was dissolved in 220 ml of sterile water to obtain a clear yellowish plasma containing approximately 250 units of coagulation factors[2]. It was infused by a blood transfusion set within one hour. FDP was transported in an ice box and kept in a 4°C home refrigerator or a shared refrigerator at the village health station. FDP has been commonly used in home treatment since 1984. The cryoprecipitate and FDP could be purchased from the National Blood Center, Thai Red Cross Society in Bangkok with a physician's prescription. The desired level of factor VII, VIII or IX was 10-20 per cent.

In 1991, the virus-inactivated factor concentrates with intermediate purity (Profilate, Profilnine) were available at Ramathibodi Hospital Pharmacy. A few hemophiliacs, who could afford the high price, used factor concentrate. The factor VIII or IX concentrate could be purchased with a physician's prescription and reconstituted in 10 ml of sterile water.

**DDAVP** The intravenous form of DDAVP was first introduced in Thailand in 1985. It was shown to increase the factor VIII levels two to threefold in patients with mild hemophilia A[3]. The dosage was 0.3-0.4 μg/kg. It was dissolved in 15-20 ml of normal saline and given *via* intravenous route within 10-15 minutes exclusively by the health personnel.

**Indicators for home treatment** The indications for giving blood components or DDAVP to patients with hemophilia or vWD included early bleeding episodes, preparation for simple surgery or dental procedures. Repeated doses depended upon the severity of the bleeding episodes and the half-life of the raised factor. For example, in cases of accident without any swollen joint, one dose of FDP or factor concentrate was given and for swollen joints, 1 to 4 blood components were given. In addition, cold compression was applied in the first 24 hours followed by warm compression. On the contrary, patients with congenital factor VII deficiency received 10 ml/kg of dissolved FDP every 3 to 5 days as prophylaxis treatment.

**Statistics** The difference between the 2 groups was calculated by paired *t* test or chi-square test. The p value of less than 0.05 was considered significant.

## RESULTS

Patients who enrolled in the study had congenital bleeding disorders comprising severe and moderate hemophilia A and B (A = 57, B = 6), mild hemophilia A (n = 18), vWD (n = 12) and congenital factor VII deficiency (n = 3). The median age was 9 years with quartile ranges from 4 7/12 years to 12 years. The median duration of follow-up was 4 3/12 years with quartile ranges of 1 to 8 years.

**Severe and moderate hemophilia A and B** Three patients used cryoprecipitate initially and switched to FDP or factor concentrate. Two of them used the cryoprecipitate prepared from the plasmapheresis of their fathers or relatives. Eventually, 45 patients used FDP and 18 patients used factor concentrate. From 1984 to 1997, a total of 8,893 bottles of FDP were infused. The utilized FDP ranged from 6 to 211 bottles per person per year with a mean of 40 bottles per person per year. Additionally, the utilized FDP could be expressed in the range of 0.2 to 2.5 bottles per kg per year with a mean of 0.95 bottle per kg per year.

Regarding venipuncture, 6 patients could perform it successfully after the first lesson, 48 required the assistance from health personnel and 9 from their parents (6 fathers, 3 mothers). After the duration of 1 to 9 years with a mean of 4 2/12 years, 14 patients could take over the venipuncture from the health personnel or parents and 11 parents or relatives could also take over the venipuncture from the health personnel. Eventually, 20 patients who attended formal education in school or college could perform venipuncture properly. Their ages ranged from 11 to 31 years with a mean age of 17 years. However, 20 parents or relatives (8 fathers, 4 mothers, 6 brothers, 2 sisters) who could perform venipuncture, had variable education levels as follows: grade 4 (n = 4), grade 9 (n = 7), vocational training (n = 6) and college (n = 3).

The common indications for FDP or factor concentrate infusion included hemarthrosis or large hematoma as shown in Table 1. Significantly, the occurrence of joint bleeding in the patients receiving FDP was higher than in those receiving factor concentrate ($p < 0.0001$). The response to FDP was categorized as fair to good while the response to factor concentrate was categorized as excellent. Fifteen out of 63 patients (23.8%), who received only FDP, had already developed chronic hemarthrosis before enrolling in the home treatment program. All of them had limitations of movement in the knee, ankle or elbow. They did not require crutches or wheelchair except one patient who developed paraplegia requiring a wheelchair as a result of not receiving replacement therapy for hematoma at the spinal cord.

**Table 1. The indication for FDP and factor concentrate infusion in home treatment.**

| | FDP 1,697 episodes | Factor concentrate 136 episodes |
|---|---|---|
| Hemarthrosis* | 80.6% | 47.8% |
| Hematoma | 12.3% | 50.7% |
| Bleeding of gum & teeth | 4.8% | - |
| Bleeding at other sites | 2.3% | 1.5% |

* The sites of hemarthrosis included: knee 38.6%, elbow 23%, ankle 17%, shoulder 7.6%, hip 5.2%, toe 3.4%, finger 2.5%, wrist 1.6%, metatarsal 0.6, and metacarpal 0.5%.

The complication of home treatment was closely monitored. Two patients were anti-HIV seropositive after enrolling in the home treatment program. They received more than 1,000 bags of cryoprecipitate unscreened for anti-HIV for an orthopedic corrective surgery in 1986 and bleeding in the central nervous system due to a motorcycle accident in 1989. Another 2 patients were anti-HIV seropositive before enrolling in the home treatment program. They also contracted HIV infection from blood unscreened for anti-HIV in their hometown. However, 25 out of 35 patients (71%) were positive for the hepatitis C virus. The liver profiles were consistently checked and revealed that 19.5 per cent (17/87) of the patients had a transient elevation of alanine aminotransferase. Lastly, the inhibitor to factor VIII or factor IX was regularly performed. Forty-one out of 243 samples (16.9%) revealed inhibitor, most of which (85%) were low titer to factor VIII ranging from 0.5 to 5 Bethesda units. The durations of inhibitor ranged from 2 weeks to 12 months with a mean of 6 months. Only 4 patients developed high titer levels of 9.7, 10.8, 24 and 1,900 Bethesda units. The first three patients, who were 8, 15 and 5 years old, developed inhibitor after receiving a large dose of factor VIII concentrate for their orthopedic corrective surgeries. The inhibitor spontaneously disappeared after one year follow-up. The fourth patient was a 2-year-old boy, who regularly received factor VIII concentrate for his frequent bleeding episodes and was kept under close observation.

The mean duration of hospitalization before receiving the home treatment was 19 days per person per year, which was markedly decreased to 7.9 days per person per year after enrollment ($p = 0.001$). Moreover, absenteeism from school or work was markedly decreased. Excluding 7 patients in the toddler period and 3 patients with severe mental retardation, 31 patients attended regular school, 12 patients worked with their family business or were self-employed, 4 patients stayed home without jobs and 6 patients died. Two patients succumbed to AIDS, 3 patients had severe bleeding episodes from traffic accident and one patient had uncontrolled spontaneous bleeding in the chin and neck while hospitalized. No adverse effect such as infection, excessive bleeding or severe transfusion reaction was noted during the home treatment. Neither patients nor parents were involved in intravenous drug addiction.

**Mild hemophilia A** Thirty episodes of DDAVP infusion were recorded which included trauma-related hemarthrosis (n = 13), trauma related hematoma (n = 6), preparation for dental procedures (n = 9) and cut wounds (n = 2). The response to DDAVP was classified as excellent. The patients were in good health and no chronic hemarthrosis was observed. None of them received any blood component after enrolling in the DDAVP home treatment.

**von Willebrand disease** Twenty-five episodes of DDAVP infusions were recorded which included epistaxis (n = 16), preparation for dental procedures (n = 5) and bleeding of gums and teeth (n = 4). The response to DDAVP was classified as excellent in all but the latter. They required dental procedures of filling, scaling or tooth extractions. None of the patients received any blood component except one patient with type II vWD, who received factor VIII concentrate. His von Willebrand factor activity scarcely increased after the DDAVP administration.

**Congenital factor VII deficiency** Three patients whose ages were 9/12, 1 and 1 3/12 years started to receive 10-15 ml per kg of dissolved FDP every 3 to 5 days as prophylaxis treatment. The duration of follow-up was 6/12, 7 and 7 7/12 years respectively. All of them were negative for anti-HIV and one patient had anti-HCV seropositive. Since these patients experienced intracranial hemorrhage prior to the prophylaxis treatment, their development was delayed. Two patients had hydrocephalus and one patient had microcephaly. However, no serious bleeding episodes occurred after commencing the prophylaxis treatment.

## DISCUSSION

The home treatment for patients with lifelong bleeding has proven to be an effective management in western countries[4] and in a small group of patients in Thailand[5]. Since health care resources in Thailand are limited, home treatment is essential for patients with various congenital bleeding disorders. Patients and parents in rural areas mostly have low education and low incomes; therefore, the home treatment should be modified to serve them.

The achievement of home treatment requires 4 elements. First is the appropriate preparation of blood components. The imported factor concentrate is too expensive for most patients. The

locally-prepared blood component is obviously desirable. Cryoprecipitate is not suitable because it needs dry ice during transportation and it has to be kept in a -20°C refrigerator. FDP seems to be an appropriate alternative to cryoprecipitate. It can be conveniently transported in an ice box and kept in a 4°C refrigerator. The disadvantages of FDP are its large volume of 220 ml and the fact that it is not a virus-inactivated blood component. Although most of the patients did not contract HIV infection, they contracted HCV infection. The anti-HCV positive among the hemophiliacs was similar to other study[6]. The elevation in alanine aminotransferase among these patients was transient and inconsistent[7]. Therefore, the virus-inactivated processing of blood component should be established.

Second is the recruitment of local health personnel as the primary care providers in the home treatment program. Before commencing the home treatment program, good communication between the physicians in charge and the local health personnel was a fundamental requirement. They principally provided assistance and support to the patients and parents.

Third is the intensive teaching and training of patients and parents. Actually, they were already familiar with various bleeding episodes and replacement therapy. Even young boys could find a proper vein for venipuncture and keep it patent during the transfusion period. They knew the symptoms and signs of early bleeding episodes well such as a tinkling sensation and discomfort. They could tutor their parent accurately and gradually learned how to perform self-venipuncture properly. Importantly, easily understood educational materials and a simple model for practicing venipuncture were emphasized. This model could replace the costly artificial vein model. The heartful effort of the physicians and health personnel were not in vain; the patients and parents could successfully perform the home treatment and take good care of themselves.

Fourth is the maintenance of an effective control system. The good patient-doctor relationship and the proper system of purchasing blood components or medicine should be ascertained. Unintentionally, the patients receiving home treatment were seen less frequently by the treating physicians[8]. In this study, the occurrence of joint bleeding episodes in the patients with severe and moderate hemophilia receiving FDP was higher than those receiving factor concentrate. Since 15 patients in the FDP group had already developed chronic hemarthrosis before enrolling in the home treatment program, the chance of bleeding in the previously defective joints was more frequent. Another explanation is the factor VIII level raised by giving FDP is lower than that of the factor concentrate. FDP is crude concentrate with a specific activity of 0.1 to 1 unit/mg as compared to the factor concentrate which is an intermediate purity with the specific activity of 1-10 unit/mg[9]. Inadequate replacement therapy will lead to frequent bleeding episodes.

In general, most of the hemophiliacs showed good response to the home treatment which did not increase the risk of developing inhibitor. The best result was shown in patients with mild hemophilia A and vWD. Since the hemorrhage can be prevented or treated very early, the severity of bleeding and late sequelae are decreased. The utilized blood component and the duration of hospitalization are reduced. Impressively, the attendance at work or school increases. The patients can enjoy a near normal life in their family, school and society. They are independent and have good self-esteem. A less satisfactory outcome is for the patients with congenital factor VII deficiency. Although the prophylaxis treatment was comprehensively given, they had delayed development due to previous intracranial hemorrhage. Therefore, the early diagnosis and initiation of prophylaxis treatment before the occurrence of serious bleeding episodes in the central nervous system is essential so that the prophylaxis treatment will be cost-effective.

In conclusion, the home treatment for patients with various congenital bleeding disorders in a developing country with limited resources is possible to achieve. The low-educated and low-economic patients and parents were not a barrier to the accomplishment of home treatment. Modified home treatment can be adopted for other chronically ill patients.

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# การรักษาผู้ป่วยโรคเลือดออกง่ายแต่กำเนิดที่บ้านในประเทศกำลังพัฒนา

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ผู้ป่วยโรคเลือดออกง่ายแต่กำเนิด จำนวน 96 ราย ได้แก่ โรคฮีโมฟีเลีย เอและบี ชนิดรุนแรงมากและปานกลาง 63 ราย โรคฮีโมฟีเลีย เอ ชนิดรุนแรงน้อย 18 ราย โรควอนวิลลิแบรน 12 ราย และภาวะพร่องแฟคเตอร์ VII 3 ราย ได้รับการรักษาที่บ้านตั้งแต่ พ.ศ. 2522 ถึง 2540 อายุเฉลี่ย (median) 9 ปี และติดตามการรักษาเฉลี่ย 4 ปี 3 เดือน ได้ดัดแปลงการรักษาที่บ้านให้เหมาะสมกับประเทศกำลังพัฒนาดังนี้ (1) ใช้พลาสม่าสดผง (fresh dry plasma) ที่ผลิตในประเทศเป็นส่วนประกอบของเลือดสำหรับการรักษาที่บ้าน หรือให้ยา DDAVP แก่ผู้ป่วย (2) ให้บุคลากรทางการแพทย์เป็นผู้ช่วยเหลือผู้ป่วยเกี่ยวกับการให้พลาสม่าหรือยา (3) สอนหรือฝึกฝนผู้ป่วยและพ่อแม่อย่างใกล้ชิด (4) มีระบบควบคุมการรักษาที่บ้านอย่างมีประสิทธิภาพ ความพยายามของบุคลากรทางการแพทย์ไม่สูญเปล่า ผู้ป่วยเรียนรู้การดูแลตนเองได้อย่างดี ผู้ป่วย 20 ราย และพ่อแม่หรือญาติจำนวน 20 ราย สามารถแทงเส้นให้พลาสม่าได้เองอย่างถูกต้อง ไม่มีข้อแทรกซ้อนเกิดขึ้น และเนื่องจากภาวะเลือดออกได้รับการรักษาตั้งแต่เริ่มแสดงอาการ ดังนั้นความรุนแรงและข้อแทรกซ้อนจากภาวะเลือดออกจึงลดลง ใช้ส่วนประกอบของเลือดน้อยลง และระยะพักรักษาตัวในโรงพยาบาลก็ลดลงด้วย การขาดเรียนของผู้ป่วยและขาดงานของพ่อแม่ก็ลดลงอย่างมาก ผู้ป่วยสามารถใช้ชีวิตใกล้เคียงกับคนปกติในครอบครัว ในโรงเรียน และในสังคม

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