SUCCESSFUL PROPHYLAXIS OF INTRACRANIAL HEMORRHAGE IN INFANTS WITH SEVERE CONGENITAL FACTOR VII DEFICIENCY

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Abstract. During the period 1984-1992, 2 severe cases (1 male, 1 female) of congenital F VII deficiency with intracranial hemorrhage (ICH) were referred to the Department of Pediatrics, Siriraj Hospital Bangkok, Thailand at the ages of 1 and 3 months old. They both responded very well to fresh frozen plasma (FFP) transfusion therapy. Subsequently, both had repeated episodes of ICH (repeated ICH) 5 and 6 times, despite the 10-14 days of replacement therapy for each episode and eventually died at the ages of 11 and 13 months.

Since September 1996, another 2 severe cases (2 females) of congenital F VII deficiency who had ICH within their first month of life were referred to us. In order to prevent repeated ICH, we started a prophylactic regime after the second episode of ICH, by giving FFP 10 ml/kg twice a week. The average duration of follow up was 21 months (at 8 and 34 months). All of them (aged 14 , and 38 months old) are doing well at this time and free from repeated ICH. From this observation, if there is FFP available, this regime is an effective way to prevent repeated ICH in infants with severe congenital Factor VII deficiency.

INTRODUCTION

Congenital F VII deficiency is a rare but fatal autosomal recessive inherited bleeding disorder, with an estimated incidence of about 1:500,000. (Grabowski and Corrigan, 1995) It is charac-terized by isolated prolonged prothrombin time and confirmed by the low level of factor VII (F VII) by specific factor assay. The role of F VII in hemostasis is very important, since it has now been considered to be a key regulator in the initiation of blood coagulation. After the vessel wall ruptures, the circulating F VII will interact with its cofactor, tissue factors (TF), to become F VIIa. The F VIIa/TF complex will activate FX to FXa and generate some amounts of thrombin. This thrombin is responsible for platelet activation and also for activation of F VIII, and FIX as well. The FIXa/VIIIa complex provides a continuous supply of surface associated FXa for prothrombinase assembly which these perpetuates the generation of an adequate amount of thrombin for hemostasis (Osterud, 1990).

According to the natural course of the disease, we can classify them into two groups, a severe and non-severe group. The severe group cases are usually manifested with life-threatening bleedings such as intracranial hemorrhage (ICH), massive gastrointestinal bleeding, generalized ecchymosis or large hematoma from birth, or in their first few weeks of life. Their specific F VII levels are varied but low, all below 5% (Roberts and Lefkowitz, 1994). Cases with milder or non-severe forms, may have only mild bleeding symptoms or never bleed abnormally, and usually have an F VII level around 5-10%. In the severe group, despite good response to replacement therapy in each bleeding episode, they usually suffer from frequent bleeding problems during their lifetime, especially repeated ICH, which can lead to severe morbidity and death. Most of them usually die within their first year of life (Hassen *et al*, 1984)

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MATERIALS AND METHODS

Case definition

Severe congenital F VII deficiency is defined as a patient who was diagnosed as congenital F VII deficiency by isolated prolonged prothrombin time and/or a low level of F VII by specific factor assay (F VII level of less than 5%), and/or had severe clinical manifestation within their first few months of life. The severe bleeding symptoms included intracranial hemorrhage (ICH), gastro-intestinal bleeding, massive cephalhematoma, large

Table 1
The initial bleeding symptoms and their age of onset.

Case	Initial symptoms	Age of onset (days)
1	Multiple ecchymosis at trunk	6
2	Massive hematoma at back	2
3	Multiple ecchymosis, umbilical bleeding and right adrenal hemorrhage	3
4	GI and umbilical bleeding	2
	Mean	3.2

Table 2
Prothrombin time (PT) and level of F VII.

Case	Prothrombin time (seconds)	F VII level (%)
1	prolonged	ND*
2	32	ND*
3	36.6	8
4	50.7	6

ND*: not done due to lack of laboratory facilities or they were treated with replacement therapy at the time of referral.

intramuscular bleeding, etc.

Intracranial hemorrhage was clinically diagnosed by acute alteration of consciousness, abnormal neurological deficits, bulging of anterior fontanel, and confirmed by the imaging study (CT scan).

The prophylactic treatment is defined as the transfusion of fresh frozen plasma (FFP), or cryo-removed plasma 10 ml/kg body weight of each patient twice a week (every Monday and Thursday).

Determination of outcomes

The aim of the prophylactic regime was to prevent the occurrence of repeated ICH. The success of the regime is determined by the reduction of frequency of repeated ICH in the prophylactic group.

RESULTS

From 1984 to 1999 there were 4 cases of severe congenital Factor VII deficiency diagnosed to the Department of Pediatrics, Siriraj Hospital, Mahidol University. There were 3 females and 1 male. All of them presented bleeding symptoms within their first week of life. Their average age of onset of bleeding symptoms was 3.2 days (range 2-6 days) after birth. Their initial bleeding symptoms were GI bleeding, umbilical bleeding, multiple ecchymosis, and large hematoma (Table 1).

All of them were diagnosed as having congenital Factor VII deficiency by isolated prolonged prothrombin time, low level of Factor VII by specific factor assay in Case 3, and 4. The prothrombin time ranged between 32 and 50.5 second and their Factor VII levels were 6 and 8 % (Table 2).

Cases 1 and 2 were diagnosed during the period of 1984-1996. During the follow up period, both of them suffered from multiple episodes of severe and life-threatening bleeding. Case 1 had his first ICH at the age of 3 months with a subsequent 6 episodes of repeated ICH and including 1 episode of oral mucosal bleeding. Case 2 had her first massive ICH at the age of 2 weeks which required the surgical removal of a clot and insertion of ventriculo- peritoneal shunt. After that, she suffered from an intractable clinical course complicated with multiple episodes of bleeding during her short life, which included 2 gastrointestinal bleeding, 2 oral mucosal bleeding, 1 intramuscular bleeding and a subsequent 4 episodes of repeated ICH. At every episode of bleeding, an adequate amount of fresh frozen plasma was given to both cases as replacement therapy, with an optimal period of replacement, (5-7 days for minor bleeding, and 14 days for ICH). Both of them responded very well to replacement therapy. The bleeding was stopped in every episode. But finally, they eventually died at age of 13 and 11 months respectively, as a result of multiple episodes of ICH. Moreover, during their lives, they were severely morbid, had delayed developmental milestones and were frequently admitted to the hospital for replacement therapy, about 7-14 days for each episode of bleeding (Table 3).

Since 1996, we have had another 2 cases (cases 3,4) of congenital F VII deficiency, who

Table 3
Clinical course of all 5 severe congenital F VII deficiency cases.

	Non-prophylactic group		Prophylactic group	
Clinical	Case 1	Case 2	Case 3	Case 4
Sex	M	F	F	F
Age at onset (days)	6	2	3	2
Initial bleeding symptoms	Gen ecchymosis	Massive hematoma at back	Gen ecchymosis Umbilical bleeding Rt adrenal hemorrhage	GI bleeding Umbilical bleeding
PT (sec)	Prolong	32	36.6	50.7
F VII level (%)	ND	ND	8	6
Age (month)				
0				
2 wks		ICH (Sx,VP shunt)		ICH and IVH
1			ICH (Sx)	gum bleeding
2		ICH		
3	ICH	Mucosal bleeding	ICH	
4			**Prophylaxis**	
		ICH	GI bleeding	
5	Mucosal bleeding	Mucosal bleeding	.	
			.	ICH
6	ICH	Intramusc bleeding	.	**Prophylaxis**
			.	.
7	ICH		.	.
			GI bleeding	.
8	ICH		.	.
			.	.
9		GI bleeding	.	.
		GI bleeding	.	.
10			.	.
		ICH	.	.
11	ICH	**ICH (rebleed), dead**	.	.
12			.	.
			.	.
13	**ICH, dead**		.	.
			.	.
14			Gum bleeding	**Last F/U**
			Gum bleeding	
19			Gum bleeding	
20			Intramusc bleeding	
21			Intramusc bleeding	
22			Nasal bleeding	
			Nasal bleeding	
28			Nasal bleeding	
			.	
			.	
38			**Last F/U**	
Duration of prophylactic treatment	-	-	34 Mo	8 Mo

Table 4
Level of specific F VII assay, pre- and post-FFP transfusion.

Case	Level of specific F VII assay (%)	
	Pre-transfusion	Post-transfusion
3	6.5	64
4	3	66

were also classified as severe cases by their clinical presentation and age of onset as in the previous 2 cases. They had abnormal bleeding symptoms such as umbilical bleeding (cases 3 and 4) and multiple ecchymoses (case 3) within their first week of life, followed by their first ICH at the ages of 17 days (case 4) and 1 month (cases 3). These 2 cases had massive ICH which required surgical intervention and insertion of a ventriculo-peritoneal shunt. After treating their second episodes of ICH, we aimed to prevent them from repeated ICH for their better outcome. So, we started a prophylactic regime by giving FFP 10 mg/kg twice a week.

Both of them had very good compliance, they regularly attended the clinic and received regular FFP transfusion. During the follow up periods of 8, and 34 months, case 4 was freed from all types of hemorrhage. Case number 3 had 5 breakthrough bleedings (2 GI, 1 gum, 1 nasal, and 1 intramuscular bleeding) which were mild and successfully treated with FFP replacement for a duration of 5-7 days. Fortunately, both of them were freed from repeated ICH and are doing well both in their growth and development at the present time.

During the prophylactic period, their blood was drawn for specific F VII assay before and after FFP transfusion. The pretransfusion or trough level were 3-6.5 % and the post-transfusion or peak level were around 65% (64,66 %) (Table 4).

DISCUSSION

Congenital F VII deficiency is one of the most serious and fatal bleeding disorders, especially in a group of severe manifestation. The patients who tend to have severe clinical courses, seem to have serious bleeding symptoms earlier in their life than the non-severe group (Roberts and Lefkowitz, 1994). Most of them are manifested with evidence of abnormal hemostasis such as generalized and multiple ecchymosis, massive subgaleal hematoma in the neonatal period, or presented with ICH in their early months (Chen *et al* 1993; Ucsel *et al*, 1996). The level of specific F VII assay does not correlate well with the severity of the disease (Roberts and Lefkowitz, 1994). In the 4 presented cases, their F VII level average around 6 % whereas we now have another 2 cases of congenital F VII deficiency, who are clinically milder. Their F VII level are 6.4 % and 12 %. Both of them are now aged 11 and 13 years old, they are diagnosed at the age of 2 and a half and 8 years old respectively. They have only mild and infrequent bleeding episodes such as recurrent epistaxis in one case, hematuria and tendency of easily bruising in the another one. They never have ICH and live with normal life and activity. As in the previous literature reviewed, patients with congenital F VII deficiency they are classified into 2 groups, patients who usually have ICH which is fatal within their first 3 months and another group who can live normally and are diagnosed only by the preoperative evaluation or manifest later (Montgomery *et al*, 1993). In this article, we emphasized on the patients who were classified as severe according to their age of onset and clinical manifestation (especially early ICH). All 4 cases fit our criteria of severe categories, eventhough their initial factor VII specific assay is not lower than 5%. This may be a kind of variant whose genetic mutation result in more severe form of non-functioning factor. The heterogeneity of genetic mutation of F VII gene might explain the wide variation of clinical manifestation among congenital F VII deficiency patients.

After treating and following the 2 previous cases (Cases 1 and 2) we realized that we could treat them in every episode of bleeding, but we could not prevent them from handicap and death. They always suffered from recurrent bleeding problems and multiple repeated ICH all their lifetime period. They were severely morbid and eventually died. That is why we try to prevent them from bleeding by giving long term prophylaxis as is acceptably done in severe cases of hemophilia (Leisner *et al*, 1996; Kavakli, 1999).

We started to give FFP 10 ml/kg twice a week in Cases 3, and 4 for their convenience and good compliance even though we know that the half life of F VII is very short (4-6 hours) and the hemostatic level is around 10-15 % (Zimmermann *et al*, 1979) for mild bleeding and higher for severe events.

We chose to transfuse them with fresh frozen plasma (FFP) or cryo-removed plasma because of its lower costs and its availability in our hospital.

Despite the many other reports of higher efficacy of F IX concentrate, prothrombin concentrate, rF VIIa concentrate in increasing the level of F VII (Cohen, 1995), we could not use them in our developing country, mainly due to its cost. We were also concerned about the risk of blood-borne infection such as HIV, HBV, HCV, CMV, syphilis and etc. Our blood bank has routinely screened all units of blood before processing for HBSAg, anti HIV, HIVAg, anti HCV, and VDRL. The rate of positive serological markers for each screened infectious agents was found to be 6.2, 0.7, 0.02, 1.6 and 2.3 % respectively (Bejrachandra, 1998). All units with positive results will be discarded. Moreover, we routinely immunized them with hepatitis B vaccine since birth, and at 2 and 6 months old and regularly checked their blood for evidence of HBV and HIV infection every 6 months during treatment. From the study based on 60,483 donors at a public university hospital blood bank in Bangkok during 1990-1993, the probability of window period donations was 38 in 100,000 donation (Kitayaporn *et al*, 1996). But after screening for both antigen and antibody and also predonation cancelling, the risk of HIV transmission should be lower. The risk of frequent exposure induced F VII inhibitor development is also in our concern. But the causal association between frequent exposure and inhibitor development in other diseases such as in hemophilia is still debated and inconclusive (Rizza and Mathews, 1982; Nilsson *et al*, 1990). So we have to follow our patients to see whether they will develop inhibitor to F VII or not.

After follow up the prophylactic group for a period of 8 and 34 months in both cases we found that we could prevent them from repeated ICH which was the most serious complication that can cause a lot of morbidity and mortality in this group of patients. Their quality of life, growth and development, including survival, are much improved compared to the previous non-prophylactic group.

We tried to check the level of F VII pre- and post-transfusion to measure the peak and trough levels of F VII. As we know that the half life of F VII is very short, we want to know whether the transfusion interval is adequate or not. The peak level was about 65%, which was sufficient for its hemostatic level, but the trough level was as low as their own F VII level, initially screened at the time of diagnosis. But this regime can demonstrate clinically its effectiveness in preventing the occurrence of ICH in severe cases. There is also one reported case of congenital F VII deficiency who was treated with prothrombin complex concentrates on a regular basis, mucocutaneous bleedings was controlled for 3 to 4 days after a single infusion, eventhough factor VII was not measurable after 24 hours (Ragni and Lewis, 1981). Whether this was due to surface binding of factor VII to endothelial cells or platelets, removing it from plasma, or some nonspecific effect from the concentrate infusion is not clear (Montgomery and Scott, 1993).

Since the availability of FFP in every general hospital in our country, patients can choose to receive their treatment in their comfortable place. The disadvantages of this regime are the time consuming, life-long treatment, risk of blood-borne infection, and questionable risk of inhibitor development. However, from this observation we conclude that this prophylactic regime is an effective way to prevent repeated ICH in infant with severe congenital factor VII deficiency for better outcome in term of growth and development and their quality of life.

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