



Mining of mortality-related findings in rare bleeding disorders: a retrospective study from two centers

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Background

Rare bleeding disorders include inherited coagulation disorders except for von Willebrand disease and hemophilia A and B. These disorders affect both men and women worldwide and mainly have an autosomal recessive pattern of inheritance. Given the paucity of cases of rare bleeding disorders, there are limited data regarding some topics among bleeding disorders.

Methods

This retrospective study from 2005–2019 collected demographic data and the causes of death among cases with rare bleeding disorders from 2 provinces of Iran.

Results

Overall, 5 deaths were reported, including 3 cases with factor V deficiency, a case with factor XIII deficiency, and a case with combined factor V and factor VIII deficiencies. The main causes of death were bleeding in the central nervous system (2 cases; 1 with factor V deficiency and 1 with combined factor XIII deficiency). Post-partum hemorrhage was the cause of death in a woman with factor V deficiency while anaphylaxis shock was the cause of death in the case with combined factor V and factor VIII deficiencies. A woman with factor V deficiency died from an internal bleeding episode.

Conclusion

Gathering data on the causes of death in rare bleeding disorders through worldwide registries can be helpful for the management of this rare group of bleeding disorders.

Key Words Anaphylactic shock, Central venous system hemorrhage, Death, Post-partum hemorrhage, rare bleeding disorders, Factor XIII deficiency, Factor V deficiency

INTRODUCTION

The rare bleeding disorders (RBDs) comprise inherited deficiencies of coagulation factors I, II, V, VII, X, XI, XIII, and combined factors V and VIII in the plasma, and combined deficiency of vitamin K-dependent factors. Their prevalence varies from 1 in 500,000 to 1 in 2–3,000,000 population. RBDs comprise approximately 3–5% of all bleeding disorders [1]. According to data released by the World Federation of Hemophilia (WFH), factor XI and FVII deficiencies have the highest prevalence, while factor II deficiency has the lowest prevalence [2]. While 65,000 patients with RBDs

were registered in a European registry through 2010, RBDs disorders are expected to be more prevalent in developing countries [1] due to the high rates of consanguineous marriages in these countries [3, 4]. Hence, national and international data registries have been programmed to gather standardized data [5]. Most RBDs have autosomal recessive patterns of inheritance; thus, except for hemophilia, RBDs occur both in male and female patients [6]. The plasma levels of a deficient coagulation factor do not usually reflect or predict the severity of hemorrhagic symptoms [7]. However, factor XIII, factor X, and fibrinogen deficiencies show an association between the levels of coagulation factor activities in plasma and the clinical picture of bleeding [8, 9]. The

clinical pictures of bleeding are diverse in RBDs and our knowledge of the clinical pictures and therapeutic management of bleeding remains unsatisfactory [10]. Compared to males with RBDs, women with RBDs have more challenges due to more hemorrhagic symptoms secondary to menorrhagia, post-partum bleeding, bleeds of ovarian cysts, polyps, endometriosis, fibroids, and endometrial hyperplasia. Hence, women with RBDs require more care and therapeutic attention [11, 12]. Until now, post-partum bleeding has been considered a leading cause of morbidity and mortality in women worldwide [13].

The treatment of hemorrhagic episodes and bleeding during and after surgeries in patients with RBDs is a challenge due to limited experiences. In the face of classical hemophilia in developing countries, who make use of prophylaxis regimens [14], patients with RBDs are administered on-demand coagulation therapy [15]. Except for coagulation factor VII and X concentrates that are commercially available, there remain no coagulation factor I, II, V, XI concentrates on the market [16]. The mainstay of the treatment in RBDs usually comprises fresh frozen plasma (FFP), cryoprecipitates, and plasma-derived coagulation factor concentrates [5, 17, 18].

The rarity of RBDs has resulted in a paucity of findings regarding many aspects of these current disorders, especially data related to mortality. The analysis of the causes of death of these patients may help to better identify priorities, target allocation of limited resources, and tailor preventive efforts to decrease morbidity and mortality in RBDs [5, 19]. A search for literature available on medical search engines (PubMed and Google Scholar) showed no published studies on deaths directly attributable to RBDs.

MATERIALS AND METHODS

To investigate the numbers and causes of death among patients with RBDs, a retrospective study was performed in two provinces (Hamedan and Khorasan-Razavi) in the northwestern and northeastern areas of Iran in July 2019.

This study approved by the Ethics Committee of Hamadan University of Medical Sciences (Ethics Code: IR.UMSHA.REC.1398.739).

After identifying cases of mortality due to RBD from 2005–2019 from searches of medical records, a prepared questionnaire was completed through interviews with the parents of the dead patients and or reviewing the medical records in the relevant hospitals. The mined data included the patients' date of birth, sex, type of RBD, plasma level of the deficient coagulation factor, cause of death, date of death, place of death, and type of treatment.

RESULTS

The frequencies of factor V, factor XIII, and combined factor V and VIII deficiencies in Khorasan Razavi and Hamedan provinces were 15%, 14%, and 24% and 1%, 8%, and 4% respectively. Overall, 5 dead individuals with RBDs were identified. They comprised 4 females and 1 male. Three cases were from Hamedan province and 2 cases were from Khorasan-Razavi province. They included 3 cases with factor V deficiency (the plasma levels of factor V were 1%, 4%, and 1%), a case with factor XIII deficiency (<5% in plasma), and a case with combined factor V and VIII deficiencies (factor V 7% and factor VIII 10% in plasma). The youngest dead patient was a 2-month-old neonate with factor V deficiency and the oldest was a 23-year-old male with factor XIII deficiency. Their mean and median age was 13.03 and 18 years, respectively. The earliest death occurred in 2005 and the most recent in 2012. Three patients had a history of having another affected member in their families (1 each of factor V deficiency, factor V and VIII deficiencies, and factor XIII deficiency). All of the deaths occurred in hospitals and cause of death was hemorrhage in 4 cases (Table 1). Central nervous system (CNS) hemorrhage was the main cause of mortality, occurring in a case with factor V deficiency and a case with factor XIII deficiency. All of the dead cases received the relevant coagulation therapy as on-demand therapy. The exception was the case with factor XIII deficiency, who had received fibrogammin as a prophylaxis regimen when fibrogammin was available. This patient had received infused cryoprecipitate on-demand when fibrogammin was not available. This case with factor XIII deficiency was also positive for hepatitis C virus (HCV)

Table 1. Main causes of death and therapeutic regimens in 5 patients with RBD.

Cases	Sex	Age (yr)	Factor levels	Cause of death	The last therapeutic regimen	Treatment/province
FVD-1	F	23	1%	Post-hemorrhage	FFP	On-demand/Khorasan-Razavi
FVD-2	F	2	4%	Internal bleeding and hepatomegaly	FFP	On-demand/Khorasan-Razavi
FVD-3	F	2 ^{a)}	1%	CNS bleeding	FFP	On-demand/Hamedan
FXIIID ^{b)}	M	23	<5%	CNS bleeding post HCV eradication	Fibro+Cryo	Pro & On-demand/Hamedan
F58D	F	18	7% ^{c)} , 10% ^{d)}	Anaphylaxis shock post FF	FFP+FVIIC	On-demand/Hamedan

^{a)}Months, ^{b)}case infected with hepatitis C virus (HCV), ^{c)}factor V level in plasma, ^{d)}factor VIII in plasma.

Abbreviations: CNS, central nervous system; Cryo, cryoprecipitate; F58D, factor V and VIII deficiency; FFP, fresh frozen plasma; Fibro, fibrogammin; FXIIID, factor XIII deficiency; FVD, factor V deficiency; FVIIC, factor VIII concentrate; Pro, prophylaxis; RBD, rare bleeding disorder.

infection. He had undergone eradication therapy for HCV infection. The CNS bleeding happened while receiving treatment for HCV eradication.

On-demand coagulation therapy was the common therapeutic regimen used for these patients. Two of the 3 patients with factor V deficiency had severe disorders (factor V plasma levels <1%). None of them were on prophylaxis regimens.

DISCUSSION

The RBDs exist in all ethnic populations and are widely distributed worldwide. They affect both males and females. According to the literature, the prevalence of RBDs is higher in the Iranian population compared to that in developed countries. Consanguinity unions are a common custom in Iran [3, 20]. Nevertheless, RBDs are considered orphan bleeding disorders due to their rarity and dispersion. Moreover, there are limited data on many topics including the types of genetic defects and treatment strategies. Collecting disperse data under the umbrella of a worldwide registry can bridge these gaps. This study collected death-related data in patients with RBDs in 2 centers. It is hoped that by mining such data, health system defects regarding patients with RBDs will be highlighted to allow health system providers to better program to cover these conditions.

The results of this study do not reflect all deaths of cases with RBDs in these 2 regions as other deaths may have been missed in our search. One limitation of this study was the low number of deaths, which made it challenging to interpret the results. Most of the deaths in this study had factor V deficiency; however, this deficiency is not the most common RBD. Palla *et al.* [10] reported factor VII deficiency (with a prevalence of 37.5%) and factor XI deficiency (with a prevalence of 36.5%) to be the most common RBDs worldwide. While author's ancient study showed that factor VII deficiency is the most common RBD in this region, the present study found no reports of death in any cases with factor VII deficiency. This may be due to both low numbers of included cases as well as differences in bleeding severity among RBDs. Moreover, there also was no death report for any case with factor XI deficiency, which, again, may also be due to the low number of cases and differences in bleeding severity among various types of RBDs. These findings need to be addressed in further investigations on death in RBDs.

Overall, CNS hemorrhage was the main cause of death, occurring in 2 cases with factor V deficiency and a case with factor XIII deficiency. These findings show that bleeding in this organ can be dangerous and fatal. Regardless of the type of bleeding disorder, CNS bleeds should be considered an emergency and a vital problem requiring immediate treatment. Our findings are compatible with the results of an evaluation of the causes of death in hemophilia [19]. CNS bleeding can occur spontaneously or as post-trauma. Patients with a severe type of RBD are more susceptible to spontaneous CNS bleeding. Post-trauma CNS bleeding

can occur in patients with severe and mild types of RBDs.

All of the reported deaths received on-demand therapy. There is no specific coagulation factor concentrate for some types of RBDs. These patients usually make use of FFP, without the option of prophylaxis regimens, especially in developing countries. Nevertheless, there is a possibility for prophylaxis for factors VII, X, and XIII deficiencies using relevant recombinant coagulation factor concentrates.

Patients with factor V and combined factor V and VIII deficiencies require FFP infusion as a source of coagulation factor V for replacement therapy. The administration of FFP is associated with disadvantages including volume overload, exposure to unwanted plasma proteins, and risk of blood-borne viruses. Although the occurrence of anaphylactic shock post-FFP infusion is rare, it occurred in a patient with combined factor V and VIII deficiencies in this study and resulted in patient death. Hence, FFP should be administered with caution and under direct physician supervision.

There are currently no commercially available recombinant or plasma-derived factor V concentrates, likely due to the low frequency of individuals with factor V deficiency and subsequent limited commercial market for recombinant factor V concentrate. These limitations have resulted in a challenge in the treatment of patients with factor V deficiency. The manufacturing of recombinant factor V concentrate by a pharmaceutical company will allow faster, better, and more effective management of bleeding episodes in factor V and combined factor V and VIII deficiencies. The cause of death in 1 of the patients with factor V deficiency was post-partum bleeding that was not controlled using an infusion of FFP. This experience underscores that FFP is not a fully satisfactory treatment as the amount of factor V in each bag is not standardized.

The case with factor XIII deficiency was positive for HCV infection. He had a history of multiple fibrogammin and cryoprecipitate infusions. These infusions may be associated with risks of the transmission of blood-borne viruses including HCV. The patient was receiving an HCV eradication regimen using peginterferon when he experienced a fatal hemorrhage in his CNS that was not controlled through fibrogammin infusion.

The collection of related information by hemophilia treatment centers and the sharing of these data with a global RBDs registry are recommended to improve our knowledge about death-related data in RBDs.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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