First Reported Case of Hemophilia B with End Stage Renal Disease in United States of America

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Abstract
Hemophilia is an X-linked recessive disorder causing a deficiency in coagulation factor resulting in either mild, moderate or severe bleeding symptoms. The increased life span of hemophiliacs, we can expect to treat more hemophiliac patients with dialysis. However, although there are a few studies that address the treatment of patients with hemophilia (PWH) and end stage renal disease as it is unusual to come across patients with both of these chronic conditions. This review will discuss the increased risks for hemophiliacs as they age and hemodialysis treatment of a 84 year old male with Hemophilia B and end stage renal disease.

INTRODUCTION
Hemophilia is an X-linked recessive disorder causing a deficiency in coagulation factor VIII (hemophilia A), IX (hemophilia B) or XI (hemophilia C) resulting in either mild, moderate or severe bleeding symptoms [1]. Manifestations of the hemophilia disease include spontaneous bleeding or delayed bleeding after trauma that can possible persist for hours, days, or weeks all varying according to severity level. According to the National Hemophilia Foundation, hemophilia occurs in about 1 in 5,000 live births [1]. It is currently unknown how many patients with hemophilia that progress to end stage renal disease.

Hemophilia patients have increased renal risks of loss of renal mass, decreased renal blood flow, decreased creatinine clearance and nephrotic syndrome while co infection with hepatitis, HIV, hypertension and diabetes increase renal risks [2]. A number of studies address the treatment of patients with hemophilia (PWH) and end stage renal disease as it is unusual to come across patients with both of these chronic conditions. However, the increased life span of hemophiliacs, we can expect to treat more hemophiliac patients with dialysis. PWH may have a higher mortality due to their renal disease compared to general population [3].

Treatment of patients with hemophilia and end stage renal disease are particularly significant to discuss due to conflicting clinical management techniques. Specifically modality: hemodialysis or peritoneal dialysis and injection of clotting factor: pre or post treatment.

This review will discuss the increased risks for hemophiliacs as they age and hemodialysis treatment of a 84 year old male hemophiliac with end stage renal disease.

MATERIALS AND METHODS
This review used many sources from PubMed, Wiley, and Elsevier. Ranging from 2000 to 2017. These searches used combinations of the following key words: "Hemophilia", "End Stage Renal Disease", "Factor IX", and "Aging Population".

Aging among hemophiliacs
The World Federation of Hemophilia estimates that the life expectancy of male hemophiliacs is approximately 10 years less than that of the general male population [4]. This life expectancy is an improvement from previous years in the United States due to increased clotting factor replacement products (lack of clotting factor preparations prior to 1970) and improved management by hemophilia treatment centers [5]. The improved life expectancy has resulted in a greater aging population. For unknown reasons, PWH have a significantly higher prevalence of hypertension compared to the general male population and patients with more severe hemophilia have a tendency to be hypertensive than mild hemophilia [6]. Type II Diabetes is the most common cause of kidney failure [7] and the risk of acquiring diabetes increases with age and body mass index [8]. However it is currently whether hemophiliacs have a higher risk for diabetes. As the prevalence of chronic kidney disease as well as the incidence of
dialysis dependent kidney failure increases with age, the aging population can expect to have more CKD and dialysis [9].

History of patient SB

SB is a 84 year old male with a past medical history of severe hemophilia B (factor IX activity < 1% normal), end stage renal disease, chronic obstructive pulmonary disease, peripheral vascular disease, hypertension, Type 2 diabetes mellitus and stroke at age 71. Surgeries include coronary artery bypass at the age of 79. SB was a heavy smoker for 65 years before quitting at the age of 71; no drug use and minimal alcohol use. SB is a retired cement contractor with three female children, all hemophilia carriers. Family history of hemophilia includes two brothers (one deceased, not hemophilia or ESRD related), a grand son diagnosed at birth, and two nephews-one of which passed away at the age of 42 from AIDS. No other family history of hemophilia and renal disease or dialysis.

SB’s hemophilia disease was diagnosed in the military service at the age of twenty-two after having persistent bleeding for 32 days after a tooth extraction. At the time, no clotting factor was available for injections so he was treated with blood plasma infusions. Despite the diagnosis he continued to remain active, participating in football and boxing. Although not associated with a certain hemophilia foundation, he participated in research studies across the country to aid in the research of this rare disease. He was diagnosed with Type 2 diabetes mellitus around 2010 and was under the care of a nephrologist for 6 to 12 months prior to being diagnosed with End Stage Renal Disease needing chronic dialysis in 2013. At the time, he was the only hemophiliac B on dialysis in the United States. He developed hypertension after dialysis but it is currently controlled. He takes oxygen at night. After his initial hemophilia diagnosis his life expectancy was 18 years, however he is currently 84.

Treatment of patient SB

SB’s renal disease has been treated for two years with Hemodialysis-NxStage 3 times a week. Benefix (factor IX) is given at end of treatments, prior to pulling needles, through venous access.

Current medications are calcium acetate, carvedilol, furosemide, Lantus Solostar Pen, pravastatin, augmentin, and Nephro-Vite; with acetaminophen, doNiDine, Epogen, and Venofer during dialysis. SB has no known allergies.

Recent laboratory studies reveal low RBC Count, (3.23x10E12/L), low hemoglobin (9.7g/dL), low hematocrit (28.2%), and high RDW (15.3%), high glucose (107), low calcium (8.4), low ionized calcium (28.2%), and high RDW (15.3%), high BUN (34), high creatinine (3.23x10E12/L), low hemoglobin (9.7g/dL), low hematocrit (28.2%).

Clotting factor: Benefit

Benefix is given to patients to control and prevent bleeding episodes in those with congenital factor IX deficiency as in Hemophilia B. It is a recombinant coagulation factor IX from the serine protease family derived from a genetically engineered Chinese hamster ovary cell line by recombinant DNA technology and processed and purified [11]. Recombinant factor IX contains a Gla domain (4-carboxyglutamic-acid-containing), two EGF like domains (epidermal growth factor like), activation peptide, and a serine protease region [12]. It binds to vitamin K and factor VIIIa and cleaves the Arg-Ile bond in factor X to produce the active factor Xa that is used in normal blood clotting [13*].

The dose of recombinant clotting factor IX depends on the individual patient (age,weight, severity, etc) however the method of calculating the factor as per the BeneFix instructions state “required units= body weight (kg) x desired factor IX increase (% or IU/dL) x reciprocal of observed recovery (IU/kg per IU/dL)” [11].

The mean biological half life of Benefix is 18.8 +/- 5.4 hours and therefore must be administered frequently [11].

Patient SB receives 3678 units of Benefix after reaching a dry weight of 73 kg after dialysis before the needles are pulled. With the exception of after dialysis, SB does not regularly use the Benefix injections, only taking them after having a bleed.

Benefix pre or post treatment

A substance is dialyzable if it is capable of diffusing through the semi permeable membrane of the dialyzer, therefore the molecular size, protein binding, volume of distribution, water solubility, and plasma clearance of recombinant factor IX must be considered to determine if clotting factor should be administered pre or post treatment [14].

SB’s dialyzer is NxStage Chronic 172 Cartridge with purema H membrane. There are about 10,000 semipermeable tubes/fibers in this dialyzer (1.6m2 fiber internal diameter). Smaller molecular weight substances pass through fixed pore sizes of membrane more easily. Dialysis filter pores do not allow albumin (66 300-69 000 Da) to pass through. Factor IX is smaller than albumin (55 000 Da) so it will pass through the dialysis filter [11]. Protein binding affects the concentration gradient across the dialysis membrane. High amounts of protein binding have low plasma concentration of free drug available for dialysis; also the drug protein complex is too large to pass through the fixed pore size of the membrane. The recombinant factor binds to plasma proteins (albumins, globulins, fibrinogens, etc.).

Substances with low volume of distribution (low distribution throughout tissues with high concentrations in the blood) are easily dialyzable as they are not lipid soluble and have high plasma protein binding. Recombinant factor has a high volume distribution, the highest distribution after dosage in the liver [15].
Substances that are highly water solubility are dialyzed more because the dialysate is in an aqueous solution and is more easily distributed throughout the tissues. Recombinant clotting factor is water soluble (glycoprotein 415 amino acids long [11]) with a hydrophobicity of -0.431 [13].

The clearance of recombinant factor IX is 8.0 +/- 0.60 in human adults [16]. The rate of recombinant factor IX clearance is affected by the interaction between the Gla domain on factor and the collage IV on endothelial surfaces [15].

The recombinant factor is dialyzable so it needs to be given post treatment so that it will not be removed from the system through dialysis. Additionally, the main elimination route for recombinant clotting factor is renal and tissue distribution begins to decline one hour post dose [15].

CONCLUSION

As more hemophilia patients are reaching ages susceptible to hypertension and type 2 diabetes mellitus they can be expected to be susceptible to chronic illnesses such as end stage renal disease. It is important to discuss how to treat patients with both end stage renal disease and hemophilia as currently there are minimal guidelines from their low prevalence and as we can expect to treat more of these patients in the future. Through the discussion of the patient SB, the article hopes to illuminate some of the ambiguity associated with treating end stage renal disease with dialysis in patients with Hemophilia B. Multiple studies have reported that peritoneal dialysis is better for hemophiliacs because it minimizes bleeding risks, however Patient SB has had successful hemodialysis for two years with Benefix injections given after treatment. As Benefix is dialyable it is necessary for it to be administered post treatment in order to ensure that the recombinant clotting factor is not removed from the body.

Further investigations involving the clinical treatment of PWH and ESRD is needed to determine the best course of treatment. This is difficult due to the extremely small population of patients with both these diseases, therefore further research into the uses of BeneFix on PWH could possibly aid in creating guidelines for dialysis treatment of PWH.

REFERENCES

1. National Hemophilia Foundation.