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Evaluation of the Relationship Between Factor IX Inhibitor in Hemophilia B Patients and Different Types of Therapy in the North-eastern Part of Iran

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Abstract

Background: Hemophilia B is a bleeding disorder with a recessive X-linked inheritance pattern, in which the infected individuals have low levels of factor IX in their plasma. Affected individuals may have bleeding episodes after trauma or spontaneously considering the plasma level of factor IX. In order to prevent these episodes and to control bleeding, they should use coagulation factor concentrates that may be associated with the formation of inhibitors.

Methods: This study was conducted in the northeast of Iran in 2006. Among 48 individuals who agreed to participate in our survey, 3 individuals (6.25%) had used FFP, 38 s (79.16%) factor IX concentrate and 7 (14.58 both FFP and factor IX concentrate in the 6 months prior to the study. Of them, three participants (6.3%) had factor IX inhibitor which was assayed using Bethesda method.

Results: Three hemophilia B (6.3%) patients had factor IX inhibitor, but no correlation was found between the existence of the inhibitor and the type of coagulation therapy.

Conclusion: Our findings did not show any correlation between factor IX inhibitor and type of coagulation therapy used in the 6 month period (p=0.65). None of the hemophiliacs had used coagulation factor as a prophylaxis regimen and most of them (83.33%) had injected coagulation factor on demand.

Keywords: hemophilia B, coagulation factor concentrates, inhibitor of factor IX.

Brief Report

Hemophilia B is a lifetime hemorrhagic disorder (1). The gene encoding coagulation factor IX is located on chromosome X. This bleeding disorder is inherited in a recessive X-linked pattern.[2,3] It is classified into severe, moderate, and mild according to the level of factor IX in plasma. Although hemorrhage in individuals with the mild form occurs after trauma or surgery, individuals with the severe form of the disease may experience various bleeding episodes spontaneously.[4,5]

To control bleeding episodes in these individuals and also for prophylaxis, appropriate volumes of factor IX concentrates (FIXC) should be injected to them.[6,7] In developing countries where fresh frozen plasma (FFP) is cheap, it is infused to affected individuals when there is no access to FIXC.[8,9]

Except for concerns about virus-infected products,[10] a new concern that has emerged is the formation of factor IX inhibitor in hemophiliacs. Individuals with factor IX inhibitor have more severe haemorrhagic episodes and control of bleeding is difficult in them.[11] Our main aim was to address the relationship between factor IX inhibitor antibody and administration of various types of coagulation factors.

Forty eight cases with hemophilia B from various cities of North-eastern Iran agreed to

***Table 1**: The Relationship Between Factor IX Inhibitor and Coagulation Therapy in 48 Individuals with Hemophilia B in North-eastern Iran.*

Type of coagulation therapy	Result for inhibitor		Total
	Negative	Positive	
FFP			
Count	3		3
%Within treatment	100%		100%
FIX Concentrate			
Count	35	3	38
% Within treatment	92.1%	7.9%	100%
FFP+FIX			
Count	7		7
% Within treatment	100%		100%
Total			
Count	45	3	48
% Within treatment	93.8%	6.3%	100%

FFP: fresh frozen plasma; FIX: factor X.

participate in this survey in 2006. These participants were invited to Ghaem hospital to fill out a questionnaire and give blood samples. Their mean age was 21.35 ± 11.8 SD years of age ranging from 4 to 53. They were 22 individuals (48%) with severe, 18 individuals (37.7%) with moderate and 8 individuals (16.5%) with mild haemophilia B.

After mixing blood samples with 3.2gr/dl (0.109 M) trisodium citrate at a ratio of 1:9, blood samples were centrifuged at 2000 rpm for 15 minutes to obtain poor platelet plasma (PPP). Two tests, activated partial thromboplastine time (APTT) mix and Bethesda, were done on PPP according to the procedures described in detail in our previous article.[12]

Then, Obtained results were analyzed using SPSS version 11.5 for windows (SPSS Inc, Chicago, IL).

Our results showed that only 3 individuals (6.25%) had used FFP but none of them had factor IX inhibitor, only 38 individuals (79.16%) had used FIXC with 3 of them having factor IX inhibitor. Finally, 7 individuals (14.58%) had used both FIXC and FFP but none of them had the inhibitor. The status of coagulation therapy in a period of 6 months was studied. Only 38 individuals (79.1%) had used FIXC and others did not have access to FIXC in bleeding episodes.

Three hemophilia B patients (6.3%) had the factor IX inhibitor and their inhibitor titers were 0.88, 1.48 and 1.8 Bethesda Unit (B.U.), respectively.

Chi-square test was done to detect any relationship between the existence of the inhibitor and type of coagulation therapy, but no relationship was found (p=0.656).

It revealed that 1 individual (2.08%) had used coagulation factor every 3 days, 4 individuals (8.33%) had used coagulation factor every other week, 2 individuals (4.16%) every month, 1 individual (2.08%) every 2 months, and 40 (83.33%) had used it only on demand.

Discussion

Although, Modern control of hemophilia was introduced in 1970s with the introduction of coagulation factor concentrates,[13] It seems that preparation of coagulation factor concentrates is one of the many problems in hemophiliacs care in developing countries.[8] In the present survey, only 3 individuals (6.25%) had used FFP in the 6 months period, 38 individuals (79.1%) had used FIXC, 7 individuals (14.5%) had used both FFP and FIXC. This shows that individuals with hemophilia B do not have enough access to coagulation factor concentrates or distribution of coagulation factors among hemophiliacs is not sufficient and more attention should be paid in this regard.

The frequency of factor IX inhibitor has been reported in various ethnic groups it is similar to our results.[14-18] Another issue is the relationship between factor IX inhibitor and FIXC administration that has been reported in the early studies.[19,20] Although this relationship has been reported in some coagulation factor products,[21] more important factors such as Human Leukocyte Antigens (HLA)[22-24] and genetic abnormalities in the factor IX gene are recently argued.[25-27] All 3 participants with haemophilia B who had inhibitor

belonged to the group which had used FIXC but our findings did not reveal any relationship between the type of coagulation factor concentrates and the existence of factor IX inhibitor. This may be due to the number of our cases or the pattern of coagulation factor administration, because none of our individuals had used one single type of coagulation factor products in their life. Also, the frequency of coagulation therapy is an important factor.

Although nowadays prophylaxis is used in hemophilia B patients every 3 days to prevent hemorrhagic episodes, most individuals in our study had used coagulation therapy only after a hemorrhagic event had occurred. This pattern of coagulation therapy supports inadequate coagulation therapy in these individuals. In our region, no one had used prophylaxis regimen to prevent bleeding events.

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References

1. Mannucci PM, Tuddenham E. The hemophilia from Royal genes to gene therapy. N Engl J Med; 2001. 344: 1773-9.

2. Miners A.H., Sabin C.A., Tolley K.H., Batlorn S., Moatawa L. Assessing the relation between productivity levels and severity of hemophilia. Haemophilia; 2001. 7: 459-63.

3. Liras A. Gene therapy for hemophilia: The end of a Royal pathology in the third millennium? Hemophilia. 2001. 7: 441-5

4. Roberts HR, Jenes MR. Hemophilia and related conditions. 4th ed. London: Mc Graw Hill; 1991. 459-63.

5. Rizza C, Lowe G. Hemophilia and other inherited bleeding disorders. Philadelphia: Saunders; 1997. P. 17-20.

6. Rodriguez MEC. Effects of hemophilia on articulations of children and adults. Clin Orth; 1996. 328: 7-13.

7. Yee TT, Beeton K, Griffioen A. Experience of prophylaxis treatment in children with severe hemophilia. Haemophilia; 2002. 8: 76-82.

8. Sirvastava A. Choice of factor concentrates for hemophilia: a developing world perspective. Haemophilia; 2001. 7: 117-22.

9. Mannucci PM, Giangrande PL. Choice of replacement therapy for hemophilia: recombinant products only? The Hemat J.; 2000. 6: 94-6.

10. Minor PD. Are recombinant products really infection risk free? Hemophilia. 2001. 7: 114-17.

11. Fischer K, Van Der Bom JG, Mauser-Bunschoten EP, Roosendall G. Changes in treatment strategies for severe hemophilia over the last 3 decades. Hemophilia; 2001. 7: 446-52.

12. Mansouri Torghabeh H, Pourfathollah AA, Mahmoodian Shooshtari M, Rezaie Yazdi Z. First survey of factor IX inhibitor in North-eastern Iran: Med J. Islam Rep Iran; 2005. 19: 91-2.

13. Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. Ann Pharmaco Ther; 2002. 36: 882-91.

14. Ehrenforth S, Kreuz W, Schrre I, Missori GH, Keith L. Incidence of development of factor VIII and factor IX inhibitors in hemophiliacs. Lancent; 1992. 339: 594-7.

15. Mc Millan CW, Shapiro SS, Whitehurst D, Hoyer LW, Rao AV and Lazerson J. The nature history of factor VIII: C inhibitor in individuals with hemophilia A: A national cooperative study. Blood; 1998. 71: 344-8.

16. Keith HW, Petrini P, Wing Wong R, Lemon R, Oldeng ECD. A retrospective of the frequency and severity of allergic reactions reported with factor IX concentrates. Blood; 2002. 100: 490a.

17. Yoshkatsu S, Midori S, Masakoni Y, Seiki K, Namer PK, Petrini K et al. Measurement of anti factor IX IgG subclasses in hemophilia B individuals who developed inhibitors with episodes of allergic reactions to factor IX concentrates. Thromb Hemost; 1996. 83: 279-86.

18. Kumar SA, Kern MA, Blanchette V. Factor VIII inhibitors in mild hemophiliacs following continues infusion of recombinant factor VIII. Is there a casual association? Blood; 1989. 74: 977-83.

19. Ehrenforth S, Kreuz W, Scharre I, Linde R, Mollison BC. Incidence of development of factor VIII and factor IX inhibitors in hemophilia. Lancet; 1992. 339: 594-7.

20. Jeame M. Inhibitors in young boys with hemophilia. Res Clin Hematol; 2000. 13: 457-68.

21. Tuddenham ECG. Molecular biological aspects of inhibitot development. Vox Sang; 1999. 77: 113-6.

22. Tiwari J, Terasaki PI. HLA and disease association. London Springer; 1985. 423-4.

23. Oldenburg J, Brackman HH, Schwaab R. Risk factor for inhibitor developing in hemophilia. Hematologica; 2000. 85: 7-13.

24. Matsushita T, Tanimoto M, Yamamoto K, Sugiura I. DNA sequence analysis of the three-inhibitor positive hemophilia B individuals without gross gene deletion. J. Lab Clin Med; 1990. 116: 492-7.

25. Roy Chowdhury M, Kabra M, Menon PSN. Factor IX gene polymorphysems in indian population. Am J Hematol; 2001. 68: 246-8.

26. Frazier CC, Smith K, Cheung WF, Ware J, Wolf C, Elmant PA et al. Mapping of monoclonal antibodies to human factor IX. Blood; 1989. 74: 971-7.

27. Astermark J, Oldenberg J, White GC, Dimichele DD. Genetic defects and inhibitor development in sib-pair with severe hemophilia. Blood; 2002. 100: 127-33.