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Challenges in the management of hemophilia: An experience from developing country

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Hemophilia is X-linked recessive disorder, characterized by deficiency of factor VIII or factor IX, known as hemophilia-A & hemophilia-B respectively. It is distributed worldwide with equal frequencies in all ethnic groups & geographic areas with an incidence of 1 in 10000 hemophilia-A and 1 in 3000 hemophilia-B. According to this, there would be more than 100,000 people with hemophilia (PwH). But according to the latest data at Hemophilia Federation India, only around 16,000 PwH are registered. Basic diagnostic and treatment facilities are restricted to major cities and majority of district hospitals, even medical colleges do not have basic coagulation screening facilities. The scenario of hemophilia care in developing countries is different, though 80% of PwH reside in this part of the world. Early diagnosis, provision of adequate and safer treatment, proper education and counseling of the families are major challenges. Most of the PwH are not treated or under treated, leading to crippling disabilities, death due to life threatening bleeds and transmission of blood borne infections due to transfusion of wet blood products are common complications. However, the advocacy efforts of Hemophilia Federation India and its chapters are slowly changing the scenario of hemophilia care. Extensive public awareness programs, training of medical/paramedical professionals, resource mobilization and lobbying advocacy with state and union government has resulted in improving the care. However, an effective strategy to involve government in hemophilia care and providing optimized care to all PwH is ongoing effort by Hemophilia Federation India.

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Optimizing lipid nanotechnologies for structural and functional studies of membrane-bound factor VIII and the FVIIIa-FIXa complex

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The processes localized to biological membranes are of great interest for scientific investigation as they are the primary targets for pharmaceutical interventions. Understanding the detailed mechanism and regulation of these processes requires the investigation of the functional structure of the membrane-bound proteins involved in these processes. We are developing lipid nanotechnologies such as lipid nanodiscs (ND) and nanotubes (LNT) that resemble the activated platelet surface during the propagation phase of coagulation and will allow structural and functional studies of membrane-associated blood coagulation factor VIII (FVIII) and its complex with Factor IXa (FIXa). The proposed lipid nanotechnologies will allow investigating how the membrane environment modulates the function of membrane-associated FVIII and the FVIIIa-FIXa complex both *in-vitro* and *in-vivo*. We have resolved an intermediate structure (~2 nm) for both recombinant human (h) and porcine (p) FVIII bound to phosphatidylserine (PS) rich LNT. Our results show that the two proteins both approved as therapeutics for the treatment of Hemophilia A; form dimers when membrane bound suggesting a dimeric organization for the membrane-bound FVIIIa-FIXa complex. We have also resolved an intermediate structure for recombinant pFVIII bound to PS-ND; further testing the pFVIII-ND complexes in FVIII deficient (FVIII-KO) mice showed a notable improvement of the clotting time after tail snip. Developing lipid nanotechnologies suitable for structural and functional studies of membrane-associated coagulation proteins will advance our understanding of the relationship between macromolecular organization and function required for the design of new therapeutics to regulate effectively blood hemostasis at the FVIIIa-FIXa complex level.

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