Research program: “Intracranial hemorrhage in children with hemophilia A and B”

Research group and principal collaborators:
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General aim of the project
The general aim of this project is to improve the quality of care of children with hemophilia by investigation of the mortality and morbidity caused by intracranial hemorrhage and if it can be improved by the treatment regimen.

Specific aims of the project.
The specific aims of this project are to test the hypothesis:

- **Primary hypothesis:** children on prophylactic treatment rarely develop intracranial hemorrhage in comparison with children on-demand therapy
- **Secondary hypothesis:** intracranial hemorrhage in children on prophylaxis is caused by a combination of trauma and low factor VIII/IX concentrations
- **Secondary hypothesis:** intracranial hemorrhage in children on prophylaxis cause less sequele compared to hemorrhages in children without prophylaxis

Background:
Hemophilia A and B is caused by the lack of coagulation factor VIII respectively factor IX in the blood. Depending on the coagulation factor concentrate in the blood hemophilia is categorized in severe (<1%), moderate (1-5%) and mild (5-25%) hemophilia. Without treatment hemophilia will cause bleedings especially in the joints and muscle. Treatment with FVIII or FIX concentrates that was started in the 1960-70 has dramatically improved morbidity and mortality in hemophilia A and B. Prophylactic replacement of FVIII/IX is the optimal treatment regimen for children with hemophilia according to clinical experience, several published studies during the last decades and consensus statements (Nilsson, Berntorp et al. 1992; Berntorp, Astermark et al. 2003; Foundation. 2007). However, in most countries the majority of children are still on-demand treatment.

In Sweden, 1960, the mean age of death for a person with hemophilia was 23 years and intracranial hemorrhages (ICH) accounted for one-third of all deaths (Larsson and Wiechel 1983). The mortality rate from ICH decreased from 70% before 1960 (Silverstein 1960) to 20-30% in the mid-70s (deTezanos Pinto, Fernandez et al. 1992) but is still around 20% in more recent studies (Chorba, Holman et al. 1994; Triemstra, Rosendaal et al. 1995; Quinones-Hinojosa, Gulati et al. 2003; Stieltjes, Calvez et al. 2005). The risk is higher in inhibitor patients.

Spontaneous hemorrhage is reported more frequently than trauma-induced hemorrhage in most studies. The mortality is still around 20% and in survivors of ICH, the risk of sequele is considerable in many recent series (Klinge, Aubergier et al. 1999; Kulkami and Lusher 1999). ICH during the neonatal period affects 3.5-4.0% of all haemophilia boys, in countries with a good standard of health care, which is considerably (40-80 times) higher than expected in the normal population. Intracranial hemorrhages are frequent also after the neonatal period affecting 3-10% of the hemophilia population who are mainly treated on demand. In several recent studies the risk of ICH (after the neonatal period) in patients treated on-demand is in the range of 290-796 per 10⁵ patient years (Ljung 2008). For the normal, non-haemophilia population, the frequency for ICH in males has been found to be 13.9 and 38.6 per 10⁵ patient-years, respectively, in two studies, i.e. ICH is 20-50 times more frequent in a person with haemophilia compared to a non-haemophiliac (Nilsson, Lindgren et al. 2000; Giroud, Milan et al. 2001).
This means there should be a potential to improve the current situation when children have on-demand therapy. The discussion on choice of treatment is very much focused on the joint outcome although intracranial hemorrhage is a significant cause of death and morbidity in hemophilia treated on-demand (Aledort, Haschmeyer et al. 1994; Ljung 1998; Manco-Johnson 2007; Ljung 2008). However, there are no studies on record demonstrating the prevalence of ICH in patients treated with a prophylactic regimen. It needs to be documented that prophylactic therapy not only improves joint outcome in children with hemophilia but also offers protection against serious hemorrhages such as ICH. i.e. the basis of this proposed project.

**Methods**

**Study group:** Children (n=1000), age <18 years, with severe hemophilia A or B (FVIII/IX <1%), without inhibitors who are on continuous prophylactic treatment (defined as >20 U/kg, 2 or more times/week). Participating centres will be recruited from PedNet (European Paediatric Network for Haemophilia Management) and INPH (International Network of Pediatric Hemophilia). PedNet is comprised of 21 pediatricians from 15 European countries and has a long tradition of performing studies together. INPH consists of 15 centres treating a large pediatric population and, in addition, a certain competence and experience of scientific work. RL is the scientific chairperson of these two networks. The study has been proposed in the two networks and several centres have expressed interest to participate and persons have been suggested as steering committee members. The PedNet and INPH provide excellent existing infrastructure that will considerably facilitate a project like the suggested.

Some of the centres exclusively treat children prophylactically. However, in several centres it will be possible to enrol also children treated on-demand. If possible in these centres, an age-matched control will be selected using the same entry criteria but with on-demand treatment. Since the frequency of ICH is expected to be higher in this group it is acceptable that it will not be able to get 1000 controls on-demand therapy.

**Methodology:** The study is planned to be a 3-year prospective survey of the cohorts. Available data from on-demand treatment are rather uniform in 10 recent studies, suggesting approx. 1 ICH/200 patient years. The expected frequency of ICH is at least 15 in this prospective part during three years if 1000 children are included and treated on-demand.

Using the same cohort of children, it should be possible to add a retrospective part of 5-years and investigate for ICH and treatment during this period. An ICH is such a dramatic event that it is not ‘overseen’ or ‘forgotten’ in a retrospective survey and the obtained data should thus be almost as reliable as the prospective part. This will statistically add about 20 expected cases of ICH using the approximation of 1 ICH/200 patient years on-demand (although some children will still be <5 years old).

Only minimal data will be entered annually on each patient on a web-based CRF. Mode of treatment as defined above, ICH or ICH event free period, imaging technique of ICH, preceding trauma, estimation of FVIII/IX concentrations when hemorrhage occurred and sequelae after ICH being the most important. If the amount of data requested is low it will facilitate to sample a large enough cohort of patients. If a patient during the study changes from on-demand to prophylaxis or vice versa, events will be calculated for the respective period.

**Timelines**

The study is planned to be started in 2010/11 and will continue as a 3-year prospective survey of the cohorts, until 2014. After this period the data will be evaluated and is planned to be published in a scientific journal.

**Data:**
The data is collected by the treating physicians and will be sent anonymous. The data will be saved in accordance to the PUL at Pediatric Clinic, Skåne University Hospital
Ethics:
There are no risks or complications by collecting data. All data will be handled in accordance to PUL. If the research will show less ICH in the group on prophylactic treatment this will have an impact on the indications for prophylactic treatment for children with haemophilia.

Clinical relevance:
If the hypothesis of this proposed study can be validated with convincing figures, new strong arguments for a prophylactic approach will be added to the on-going discussion on choice of optimal treatment regimen for children with hemophilia. The outcome of the study has a potential to have a significant impact on the treatment of children and thus be an aid in overcoming some of the present obstacles to regular replacement therapy.

References


