Version 4.0 with Amendment 1, 2 and 3

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

Research group and principal collaborators:
Nadine Gretenkort Andersson¹, MD, Consultant, Principal Investigator
Rolf Ljung¹, MD, Professor, Senior Consultant
Pia Petrini², MD, Senior Consultant
¹Department of Pediatrics and Coagulation Disorders, Malmö University Hospital, SE-205 02 Malmö.
²Department of Pediatrics and Coagulation Disorders, Karolinska University Hospital, Solna

Participants:
Thirty-three centers belonging to the European Paediatric Network for Haemophilia Management (PedNet) and the International Network of Pediatric Hemophilia (INPH) will participate in the study.
Rolf Ljung is the scientific chairman of those networks.

General aim of the project
The general aim of this project is to improve the quality of care for children with hemophilia by investigating the mortality and morbidity caused by intracranial hemorrhage, and determining whether those aspects can be improved by adjusting the treatment regimen.

Specific objectives
The specific objectives of this project are to test the following hypotheses:
- **Primary hypothesis**: children on prophylactic treatment rarely develop intracranial hemorrhage compared to children with 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**: After intracranial hemorrhage, sequelae are less common in children on prophylaxis than in those without prophylaxis.

Background:
Hemophilia A and B are caused by lack of the blood coagulation factors VIII and IX, respectively. Depending on the blood concentration of the factor in question, the hemophilia is categorized as severe (< 1%), moderate (1–5%), or mild (5–25%). Without treatment, hemophilia leads to internal bleeding, especially in the joints and muscles. Treatment with FVIII and FIX concentrates emerged in the 1960s to 1970s, which has led to dramatic improvement in morbidity and mortality in patients with hemophilia A or B. According to clinical experience, prophylactic replacement of FVIII/IX is the optimal treatment regimen for children with hemophilia, as indicated by several studies published during the
last decades, as well as in consensus statements (1-3). However, the majority of children in most countries are still receiving on-demand treatment. The discussion regarding choice of therapy is focused largely on joint outcomes, even though intracranial hemorrhage (ICH) is a significant cause of death and morbidity in hemophilia patients treated on-demand (4-7).

In Sweden in 1960, the mean age of death for a person with hemophilia was 23 years, and intracranial hemorrhage (ICH) accounted for one-third of all deaths (8). The mortality rate associated with ICH decreased from 70% before 1960 (9) to 20–30% in the mid 1970s (10), and it has remained at around 20% in more recent studies (11-14). The risk of mortality is higher in inhibitor patients.

Most investigations have indicated that spontaneous hemorrhage is more common than trauma-induced hemorrhage, and the former is still responsible for a mortality rate of around 20%. Furthermore, a substantial risk of sequelae has been observed in many recent series of ICH survivors (15, 16). ICH during the neonatal period affects 3.5–4.0% of all hemophilic boys in countries with a good standard of health care, a level that is considerably (40–80 times) higher than expected in the normal population. ICH is also a frequent occurrence after the neonatal period, affecting 3–10% of the hemophilia population treated mainly on-demand. Several recent studies have shown that the risk of ICH (after the neonatal period) in patients receiving on-demand treatment is in the range 290–796 per $10^5$ patient years (4). Corresponding rates for males in the normal, non-hemophilia population were found to be 13.9 and 38.6 ICH events per $10^5$ patient years in two investigations (17, 18) Thus it is apparent that ICH is 20–50 times more common in people with hemophilia than in those who do not have such disease.

Accordingly, there should be a potential to improve the current situation for children receiving on-demand therapy. However, no studies have been published that demonstrate the prevalence of ICH in patients treated with a prophylactic regimen. Therefore, research is needed to show that prophylactic therapy in children with hemophilia not only improves joint outcome, but also offers protection against serious bleeding such as ICH, which is indeed the purpose of the proposed project.

**Methods**

**Study group:** The participants will be children (born between the 1st of January 1993 and the 31st of December 2012; n = 1,000) suffering from severe hemophilia A or B (FVIII/IX < 1%), who have been without inhibitors over the last five years and are receiving continuous prophylactic treatment (defined as >20 U/kg, ≥ 2 times/week or ≥ 3 times/week), other prophylactic treatment (regularly at least once a week) or on-demand therapy. Participating centers will be recruited from PedNet (the European Paediatric Network for Haemophilia Management) and INPH (the International Network of Pediatric Hemophilia). PedNet comprises 21 pediatricians in 15 European countries with a long tradition of performing studies together. INPH includes 15 centers that are responsible for treating a large pediatric population and also have a certain amount of experience in scientific research. The
proposed study has been presented to the two networks, and several centers have expressed interest in participating and have also suggested the names of a number of prospective members of a steering committee. The PedNet and INPH organizations provide an excellent existing infrastructure that will greatly facilitate the project.

At some of the centers, treatment of the children is exclusively prophylactic. However, it will be possible to recruit children treated on-demand at several of the other facilities, where, if feasible, control group will be selected using the same entry criteria but with on-demand treatment.

**Methodology:** The proposed study is planned to be a three-year prospective survey of the cohorts. Ten recent investigations have provided rather uniform data regarding on-demand treatment of hemophilia, suggesting that there is approximately one ICH per 200 patient years. Thus, if 1,000 children were to be included, it could be expected that there would be 15 ICHs during the three-year study period.

Using the same cohort of children, it should be possible to extend the study to include a five-year retrospective part in order to investigate the relationship between ICH and treatment during that period. An ICH is such a dramatic event that it is not likely to be ‘overseen’ or ‘forgotten’ in a retrospective survey, and hence the data obtained should be almost as reliable as the information provided by the prospective part of the study. Statistically, this is expected to add about 20 cases of ICH, based on the approximation indicating one ICH per 200 patient years in children receiving on-demand therapy (although some of the children will still be < 5 years old).

For each patient, only minimal data will be entered annually into a web-based case report form (CRF). The most important information will concern the following: mode of treatment (as defined above), ICH or ICH-free period, technique for ICH imaging, preceding trauma, estimation of FVIII/IX concentrations at the time of ICH and sequelae after ICH. Requesting only a limited amount of data should facilitate a sufficiently large cohort of patients. If a patient changes from on-demand to prophylaxis or vice versa during the study period, events will be calculated for the respective period.

**Timelines:** According to the plan, the study will be started in 2010 and will continue to 2014 as a three-year prospective survey of the cohorts. After this period, the data will be evaluated, and the results will be published. The entry of the baseline CRF will be closed 31st August 2011.

**Data:** The data will be collected by the treating physicians and sent anonymously, then stored in accordance with the Swedish Personal Data Act (PDA, designated PUL in Swedish) at Children’s Hospital, Malmö University Hospital.

**Ethics:** There are no risks or complications associated with collection of the data, and all data will be handled in accordance with the PDA. In short, this means that there will be neither risks nor benefits
for the individual patients participating in the study, but, if the research does lead to new guidelines, it will be beneficial for the patient group as a whole.

All of the participating centers are responsible for ensuring that the work done within the project is conducted in accordance with the ethics rules that are applicable in the respective countries.

**Clinical relevance:**

If the findings of the proposed study can provide convincing results to validate the stated hypotheses, it will add new and strong support for using a prophylactic approach in children with hemophilia. This is definitely needed in the on-going discussion about choice of an optimal treatment regimen for this patient group. Furthermore, the outcome of the study can help us obtain additional scientific evidence concerning appropriate treatment that can be used in discussions with the patients.

3. Foundation. NH. MASAC recommendations concerning prophylaxis (regular administration of clotting factor concentrate to prevent bleeding). (Chapter Advisory 197)2007.

Malmö, 16th of June 2011
Version 2.0

Amendment 1 to Research program: “Intracranial hemorrhage in children with hemophilia A or B”, Version 2.0

Timelines: The study started in 2010 and will continue to 2015 as a three-year prospective survey of the cohorts. The entry of the baseline CRF will be prolonged and closed on 31st January 2013.

Malmö, 12th of October 2011
Amendment 1
Version 1

Amendment 2 to Research program: “Intracranial hemorrhage in children with hemophilia A or B”, Version 3.0

Study group: The participants will be children (born between the 1st of January 1993 and the 1st of January 2010; n = 1,000) suffering from severe hemophilia A or B (FVIII/IX < 1%), who have been without inhibitors over the last five years and are receiving continuous prophylactic treatment (defined as >20 U/kg, ≥ 2 times/week or ≥ 3 times/week), other prophylactic treatment (regularly at least once a week) or on-demand therapy.

Malmö, 17th of September 2012
Amendment 2
Version 1

Amendment 3 to Research program: “Intracranial hemorrhage in children with hemophilia A or B”, Version 4.0

Study group: The participants will be children (born between the 1st of January 1993 and the 31st of December 2012; n = 1,000) suffering from severe hemophilia A or B (FVIII/IX < 1%), who have been without inhibitors over the last five years and are receiving continuous prophylactic treatment (defined as >20 U/kg, ≥ 2 times/week or ≥ 3 times/week), other prophylactic treatment (regularly at least once a week) or on-demand therapy.
**Timelines:** The study started in 2010 and will continue to 2016 as a three-year prospective survey of the cohorts. The entry of the baseline CRF will be prolonged and closed on **31st January 2014**.

Malmö, 4th of April 2013

Nadine Gretenkort Andersson  
MD, PHD, Consultant, Principal Investigator

Rolf Ljung  
MD, Professor, Senior Consultant

Department of Pediatrics and Coagulation Disorders  
Skåne University Hospital Malmö, Sweden