General discussion
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Hemophilia is a hereditary bleeding disorder affecting both mortality and morbidity. Since the discovery by Judith Poole of cryoprecipitate and the introduction of clotting factor preparations in the 1970s the prospects for patients with hemophilia have improved considerably\(^1\). This was offset by disease due to blood borne viruses, such as the human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Since 1985 clotting factor preparations have been safe for HIV and since 1992 also for transmission of hepatitis C.

The aim of this thesis was to describe temporal changes in the medical and social situation of patients with hemophilia. In addition we examined the hemorrhagic tendency of female relatives of hemophilia patients. In the present chapter we discuss our considerations regarding the methods we used and the validity of our findings. In addition we discuss potential implications for the care of patients with hemophilia and we make suggestions for future research.

Study design

We performed two cross-sectional surveys. The first survey was the fifth of a national cross-sectional study that periodically collected information on the medical and social situation of patients with hemophilia in the Netherlands, the Hemophilia in the Netherlands (HiN) study. Patients' ascertainment was through the membership of the Netherlands Hemophilia Society, the hemophilia centers and by updated mailing lists from previous surveys. Comparison over time was made possible by the repeated use of similar pre-structured questionnaires that included items on treatment, the annual number of bleeding episodes, the use of inpatient hospital care and hepatitis C and HIV infections. The number of participating patients increased over the years from 540 in 1972 to 1066 in the latest survey; the introduction
of specialized hemophilia treatment centers and an increasing interest for treatment of all patients with hemophilia, including patients with mild hemophilia, contributed to this growth. The cooperation in this project between the Netherlands Hemophilia Society, hemophilia treatment centers and the Netherlands Society of hemophilia treating physicians added to the national character of the HiN study. It is likely that we have been able to address all Dutch patients with hemophilia. The extensive time period of 30-years covered by the project and its national character make the Hemophilia in the Netherlands an unique project. Because of the HiN surveys hemophilia has become one of the best-described rare diseases in the Netherlands. The second survey was performed among all women who underwent carrier testing of hemophilia between 1985 and 2003.

**Validity**

**Selection**

The biggest threat to the validity of studies of a descriptive nature is non-participation. Subjects who participate differ, by definition, from those who do not respond, although not necessarily on aspects relevant to the research question of the study. In virtually every survey, only a proportion of those who are eligible to participate do so. The result of the difference between these groups affects the generalizability of the study results. In the HiN-5 study response was 70%. Non-responders to the questionnaire may have been less severely affected, failing to see the need for a survey in this population. However in the non-responders the distribution of severity was similar to the participants. As age and type of hemophilia were also comparable therefore we consider the results of the HiN-5 study to be generalizable to all Dutch hemophilia patients. Mortality of patients with hemophilia was studied among those who had participated in the Hemophilia in the Netherlands-4 survey in 1992. In the HiN-4, it was estimated that 93% of all Dutch hemophilia patients had been sent a questionnaire, of whom 74% were willing to
participate. As again no differences in the distribution of severity and age were observed between the responding and the non-responding individuals we considered our data to be generalizable to the Dutch hemophilia population.

Response in the cross-sectional study among women who had been tested for carriership of hemophilia A or B between before 1985 and 2001 in the Leiden University Medical Center and the University Medical Center Utrecht was 80%. In this period, these were the two centres where carrier testing was offered, and therefore they performed virtually all carrier tests for hemophilia in the country. We included 519 women, which made our study currently the largest survey into the hemorrhagic risk in female relatives of men with hemophilia. In the non-response group the average age was slightly higher than in the response group. Since clotting factor levels increase with age we may have somewhat overestimated the bleeding frequency in our study population. This however has no effect on the comparison between bleeding frequency in carriers and non-carriers. Selection bias might have been introduced when carrier testing was done because of bleeding problems. As this was reported by a limited number of women we do not think this will affect the comparison between women included in our study and women from the general population eligible for carrier testing for hemophilia. To counter the problem of the possible incomparability of carriers from hemophilia families to women with the general population, we only included women from families with hemophilia. The carriers and non-carriers in our study had grown up in the same environment and had not been aware of their carrier status until testing. As these women are confronted with hemophilia and the related bleeding problems during life they may report bleeding more often or may find this less important and report it less often.
**Misclassification**

As in every study using questionnaires the value of self-reported data may not be as precise as information from the laboratory or a medical chart. Although this may be a disadvantage, self-reported data offer the opportunity to get an insight into the patient's own perception of his situation. Moreover, many relevant data are not reported in medical charts, or not even known to the physician. To avoid errors in the severity and type of hemophilia these data were verified with the treating physicians. In the study regarding hepatitis C (chapter 2.4) a validation study was performed for a group of patients from two large treatment centers showing a high correspondence between self-reported hepatitis C status and the hepatitis C status reported by the treating physician. As patients with hemophilia, especially those with severe forms, are confronted with their disease every day, they are well informed of their treatment and medical situation. They are undoubtedly better able to respond to questions on social participation, education, and absence from work and school, bleeding frequency and quality of life than their physicians. We therefore consider our data to be a reliable overview of the situation of hemophilia patients in the Netherlands.

In the study on mortality the vital status of patients was determined either by the response to the questionnaire in 2001, or from the treating physicians, or from the municipal registries. It is unlikely that any distortion could have occurred with regard to overall mortality data. Theoretically, because the treating hematologist or the general practitioner reported the causes of death there may have been discrepancies on causes of death with the general population data gathered through the Central Bureau of Statistics. We do not expect this to be of large influence. In the study examining bleeding in female relatives of hemophilia patients in a cross sectional design the bleeding symptoms were ascertained in women who were aware of their carrier status. This may have implications for the interpretation of the results. One could argue that the reporting on bleeding could have been influenced by the knowledge about the carrier
status, and that ideally women should have been questioned prior to carrier testing. Carriers may have overreported bleeding symptoms because they are more aware of their status. Yet, a previous study suggested little influence of awareness of carriership of hemophilia on responses to questions on bleeding \(^2\). Yet, our findings may in part reflect the association between awareness of carrier status and an expected tendency to bleed. However, many women and physicians are unaware of the relationship between bleeding and carriers status of hemophilia.

*Implications for care of patients with hemophilia*

Our data give insight in the current situation of patients with hemophilia, which is important for both clinicians and patients. We showed that many improvements have been achieved, a reduction in the annual number of hemorrhages, in the percentage of admitted patients and in absence from both school and work. Besides these improvements we emphasize that the prevalence of perceived joint impairment among young patients did not show the decrease we expected. This group of patients merits extra attention during follow-up of patients in a clinical setting.

In chapter 2.1 we emphasize the persisting influence of viral infections on mortality of hemophilia patients. Treatment of the effects of viral infections, particularly HIV and hepatitis C virus, will result in an improved survival of patients with hemophilia.

In the Netherlands guidelines for the treatment of hemophilia were drawn up during a consensus meeting in 1996. According to these guidelines in patients with severe hemophilia prophylactic treatment is preferable to on demand treatment\(^3\). An international consensus meeting also stated that despite the lack of controlled studies, long-term prophylaxis should be the standard for treating children with severe hemophilia in developed countries. No data are available for forming a consensus on stopping prophylaxis in adult patients. Our findings show that current guidelines are not strictly followed by all patients with severe hemophilia\(^3,4\). This
raises the question whether the guidelines should be reconsidered or adjustments should be made in treatment strategies prescribed by treating physicians. Various aspects should be taken into consideration in answering this question, for instance, the burden of treatment for the patient and his relatives associated with frequent venapunctures and financial constraints. Our data may be a starting point for revision of the guidelines.

Treatment of patients with hemophilia should become more individualized. From a previous study it has become clear that some patients, especially adolescents, tend to interrupt their prophylactic treatment schedule for a short or longer period. Overall these were patients with a milder phenotype. In determining the right treatment schedule the treating physician should consider the personal aspects of the patient; age, daily activities (work, school, sports), existing joint impairments and the patient's opinion on treatment. This may for some patients result in a reduced use of clotting factor preparations while in others there may be a need for a more intense treatment schedule. In chapter 3.1 the association between carriership of hemophilia, clotting factor levels and bleeding after interventions was investigated. An awareness of this risk of bleeding in carriers by physicians may result in a reduction of the frequency of bleeding. Assessment of the clotting factor level of carriers of hemophilia should become a part of the standard measurements performed before a medical intervention in these women. Our study shows that the risk of bleeding is not only increased in women who would be defined as having mild hemophilia, but also in women with clotting factor levels between 0.40 and 0.60 IU/ml. These findings could have implications for the currently used definition of "safe" clotting factor levels.
**Future research**

We have shown that although well treatable, hemophilia is still a disease affecting life and death. We found an excess number of fatal intracranial hemorrhages in patients with hemophilia, which has also been reported in a study performed in the UK\(^6\). Future studies should address whether these deaths can be prevented. Other studies might focus on the risk of death related to different treatment strategies (prophylaxis vs. on demand).

We may also discuss our own raison-d’être: is there a rationale for a sixth Hemophilia in the Netherlands survey? Over the years we have gathered a large amount of data and have shown the improvements related to the changes in treatment. The introduction of the electronic patient file will provide us with the data previously gathered through HiN questionnaires. This will enable us to study more precise aspects of treatment. Another future research project may involve expansion of the study into hemorrhagic risk of carriers of hemophilia. To avoid misclassification of clotting factor levels we should measure these levels in a standardized way and determine factor VIII or IX levels in certified laboratories. By performing a survey prior to the carrier testing we might reduce the effect of recall bias.

Although the medical situation of hemophilia has considerably improved over the last three decades, through an intensive treatment regimen, there are still many aspects that require attention: biological, in medical care and social. The need for continued study of the problems of hemophilia is witnessed by the excess risk of mortality in patients, even those without viral infections. In this thesis, we intended to give an overview of the current medical and social situation of patients with hemophilia. In addition, the results of our study among female carriers of the hemophilia gene may lead to an increased awareness by treating physicians about the problems they face and the importance of the determination of clotting factor levels in these carriers.
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<th>What was already known on this topic?</th>
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<tr>
<td>• Since the introduction of replacement therapy in the early 1960s important changes have occurred for hemophilia patients.</td>
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<tr>
<td>• Since 1985 clotting factor products have been safe for HIV and since 1992 also for the transmission of hepatitis C. Few studies have reported on mortality in the total population of hemophilia patients after the period of risk of viral infections transmission.</td>
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<td>• The uptake of recombinant factor VIII products has been slower in the Netherlands compared to other countries.</td>
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<tr>
<td>• Hepatitis C is a major co-morbidity among patients with hemophilia who received inadequately or non-virus inactivated clotting factor concentrates before 1992.</td>
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<td>• Extensive knowledge is available on bleeding in men with hemophilia; the risk of bleeding in carriers of hemophilia has not often been studied.</td>
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What does this thesis add?

- National and international guidelines describing the use of prophylactic treatment were not strictly followed.

- A steady decrease was observed in the annual number of hemorrhages, of hospital admissions, of duration of stay in hospital and of days absent from school or work.

- Despite intensified treatment limited improvement was observed in self-reported impairment of joint function in patients older than 16 years.

- Hepatitis C and AIDS had a large impact on mortality of hemophilia patients.

- Even without virus infections hemophilia patients live a few years less than the average Dutch male.

- Although hemophilia patients represent one of the most empowered patient groups, physicians' opinions appeared to have been dominant in choosing between pdFVIII and rFVIII.

- In the Netherlands 65% of patients received rVIII, this percentage varied widely among centres.

- In 2002 the prevalence of hepatitis C among patients with hemophilia who received clotting factor products before 1992 was 54%. The majority of patients with a current HCV infection had not been treated with antiviral therapy.

- Social functioning was worse in patients with hemophilia than the general male population, especially among elder patients.

- Carriers of hemophilia experience more bleeding than non-carriers, especially after medical interventions.

- Although in the literature the level of 0.40 IU/ml is used to define mild hemophilia and is related to bleeding, we also found increased risk of bleeding in women with levels between 0.4 and 0.60 IU/ml.
References


