Cross sectional study to investigate the influence of treatment regimes on the development of haemophilic arthropathy
The HemArthro-Project

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Arthropathy, prophylaxis, demand, joint

Summary
Haemophilic arthropathy is often present in patients with severe haemophilia. New studies demonstrate that only a small amount and a short exposure of blood in vitro are able to induce an impairment of the joint cartilage. Free blood in the joint leads to different mechanisms and includes cartilage and bone damage induced by a release of macrophages and monocytes followed by activated cytokines and inflammatory processes. Another mechanism is mediated by free iron resulting in synovitis and synovial hyperplasia and a neoangiogenesis on the base of VEGF release is common. At worst, these processes result in a complete picture of haemophilic arthropathy reducing quality of life. Few studies are available about the influence of factor treatment regime, e.g. prophylaxis or on-demand therapy, on the development of haemophilic arthropathy. However these studies investigated in most cases children. Therefore, it is still impossible to give recommendations for the right treatment in adult haemophilic patients because data are still lacking. For that reason, we attempt to initiate the HemArthro-Project to investigate the influence of treatment therapy on the development of arthropathy in adult haemophilic patients. This study includes the investigation of functional musculoskeletal parameters for the description of joint function in maximal 500 severe haemophilic patients parted into two groups of treatment regime (prophylaxis vs. on-demand). The investigators are seeking further assistance from the haemophilic treatment centers for the support of this study.

Schlüsselwörter
Arthropathie, Prophylaxe, Bedarf, Gelenk

Zusammenfassung

Haemophilic arthropathy is a heavy burden for patients with haemophilia. The early development of haemophilic arthropathy is initiated by few bleedings only. But a small amount of blood in the joint may start the destruction process within the joint. Jansen et al. demonstrated that only a small amount of blood of 10% (volume/volume) and an exposure for only two days lead to prolonged impairment of joint cartilage in an in vitro experiment (6). This destruction of the joint cartilage comes along with synovitis and synovial hyperplasia. Valentino et al. have studied the processes in the early stages of blood induced joint disease in animal models, because basic investigations in humans are very difficult (9). These animal studies, however, are able to shed light on these early
processes and are definitely helpful in increasing our knowledge about the early phases of haemophilic arthropathy.

Blood in the joint leads to several processes in the joint, as demonstrated by Valentino et al. (9). On the one hand iron of free blood may be able to initiate synovial cell proliferation by dysregulating critical genes including an up regulation of c-myc, a proto-oncogene which controls cell proliferation, as well as mdm2 (murine double minute), which reduces synovial cell apoptosis. Both mechanisms result in an enhanced synovial hyperplasia and increase the vulnerability of the joint.

On the other hand free blood includes the release of monocytes and macrophages and the release of such blood cells leads to an increase of inflammatory cytokines such as IL-1a, IL-6 as well as TNFα, which accompany changes of inflammatory cells and mediators followed by the destruction of joint cartilage and bone. The third reaction after free blood exposure to the joint includes neoangiogenesis on a base of VEGF release and activation of endothelial cells.

These mechanisms initiate and perpetuate the destruction processes and cause the haemophilic arthropathy. After undergoing this process, the complete picture of haemophilic arthropathy (Fig 1) includes

- enhanced vulnerability of the joint,
- followed by additional joint bleedings and accompanied by
- pain, immobility and deficiency in muscle function and coordination,
- frequently ending in a conspicuous reduction of quality of life.

**Factors influencing the development of arthropathy**

Several influential factors on haemophilic arthropathy such as age, body weight, BMI, severity of haemophilia, time point of the first joint bleeding as well as the time of the first factor treatment and many others are well known (8). However, less is known about the influence of different specific treatment regimes on haemophilic arthropathy.

Only few studies are available which deal with investigations of relationships between treatment regime and haemophilic arthropathy and in most cases these studies analyze children or adolescents. Aledort et al. investigated the direct relationship between the increasing factor dosage and the orthopaedic outcome in severe haemophilia A, in patients under the age of 25 and confirmed that higher factor doses per se did not necessarily produce improved orthopaedic outcomes, but that full time prophylaxis did so (1). Fischer et al. showed that children primarily treated with prophylaxis experienced fewer joint bleeds per year and less arthropathy measured by Petterson score (2-4).

A randomized controlled trial was published in 2007 in the *New England Journal of Medicine* by Manco-Johnson et al. to confirm other results by a RCT (7). In this study, young boys with severe haemophilia A were randomly treated with a recombinant factor VIII prophylaxis in one group in comparison with the second group, treated with an enhanced episodic infusion schedule of at least three doses totaling a minimum of 80 IU of factor VIII per kilogram of body weight at the time of a joint hemorrhage.

This study revealed that a prophylaxis with a recombinant factor VIII can prevent joint damage and reduces the frequency of joint as well as other haemorrhages in young boys with severe hemophilia A.

The authors demonstrated a reduction of joint bleeds of 0.63 ± 1.35 during prophylaxis in contrast to 4.89 ± 3.57/year under enhanced episodic treatment (EET). The joint damages measured by MRI were reduced to 7% in the prophylactic, compared to 45% in the EET group. A close relationship, however, between bone or joint damages and joint bleeds could not be confirmed.

This study shows that the balance between prophylaxis and on-demand therapy concerning haemophilic arthropathy tilts in favor of the benefit of prophylaxis regime in children.

**HemArthro-Project**

In contrast to the situation in children, studies in adult patients with severe haemophilia are still lacking. Therefore, in the authors’ opinion it is necessary to investigate the influence of treatment regime at the further developmental stages of haemophilic arthropathy in adult patients with severe haemophilia as well. To this end, we attempted to initiate the HemArthro-Project to focus on the influence of prophylaxis versus on-demand therapy on

1. clinical joint score and muscle strength of the femoral extensor,
2. functional joint mobility, sensorimotor qualities, subjective physical fitness, quality of life, bleeding frequency.

For this investigation we intend to include a maximum of 500 severe haemophilic A and B patients during a maximal period of three years. In group A, maximum of 250 patients with severe haemophilia A or B and an age between 18 and 50 years treated with a prophylactic therapy regime shall be included. Pro-
A phylactic therapy regime is defined as a factor treatment ≥2 times per week, > 45 weeks per year (> 80%). A maximum of 250 on-demand (> 80%, > 45 weeks per year) treated patients with severe haemophilia A or B and an age between 18 and 50 years shall be enclosed in group B. All participants have to fulfill another inclusion criterion, namely an unchanged therapy ≥5 years or lifelong before the start of the study (Fig. 2).

In addition, an age dependent subgroup analysis should be carried out if possible, depending on data. In this case, six age specific subgroups should be tested:
- group I: 18–24 years;
- group II: 25–30 years;
- group III: 31–35 years;
- group IV: 36–40 years;
- group V: 41–45 years;
- group VI: 46–50 years.

**Test parameters**

The study design mainly focuses on functional parameters of the musculoskeletal apparatus (Fig. 3). To analyze joint function, the clinical orthopaedic score of Gilbert shall be used as recommended by the World Federation of Hemophilia (5). The m3 diagnosis Schnell test system will be employed for isometric muscle strength testing as second test parameter with top priority.

In addition, motion analysis, one leg stand testing, surface EMG testing as well as different questionnaires to investigate subjective fitness and quality of life shall be utilized for the investigation of additional parameters. Moreover, the study includes a comprehensive documentation of bleeding events, factor treatment, daily living activities as well as additional parameters.

The hypothesis suggests that a prophylactic treatment results in a better outcome in joint function also in haemophilic adults. However, this conception should be examined sufficiently.

**Precondition for realization**

In this type of studies, confounders are a great problem during the data management and analysis process. Many confounders (e.g. age, body weight, BMI, time point of the first bleeding, age of the first factor treatment, surgical procedures, other diseases, medication, extent of physical activity) should be controlled by specific statistical programs. To realize this comprehensive study it is imperative that the haemophilic treatment centers are willing to support this study.

The study cooperation partners Dr. Axel Seuser and Prof. Dr. Thomas Hilberg and their teams are seeking further assistance from the haemophilic treatment centers in Germany to carry out this study, because the results will turn out as helpful in the difficult decision for right therapy regime in the future treatment of adult haemophilic patients.

**Conclusion**

For the first time, the HemArthro-Project will investigate the influence of different therapy regimes on the development of haemophilic arthropathy in adult patients by measuring functional musculoskeletal parameters. To realize this study, intense support by the haemophilic treatment centers in Germany is absolutely necessary.

**Interessenkonflikt**

Alle Autoren erklären, dass kein Interessenkonflikt besteht.

**References**