Climbing therapy under PK-tailored prophylaxis

M. Stemberger1; E. Schmit1; D. Czepa2; K. Kurnik1; M. Spannagl1

1Haemophilia Treatment Centre, University of Munich; 2Institute for Sports Medicine, Bergische University of Wuppertal, Germany

Keywords
Haemophilia A, PK-tailored prophylaxis, climbing therapy

Summary
Climbing has a low risk of injury and strengthens the entire musculature. Due to its benefits in physical and mental health as well as its high fun factor climbing is an established way of therapy. So far, the usefulness of climbing therapy has not been shown for people with haemophilia (PWH). A crucial requirement for physical activity in PWH is regular prophylaxis. As the patient's individual pharmacokinetic (PK) response varies significantly, PK-tailored prophylaxis may decrease bleeding frequency. Case report: We describe a man (age 25 years) with severe haemophilia A who took part in an 8.5-month weekly climbing program under PK-tailored prophylaxis. Bleeding frequency, factor consumption, joint health (Haemophilia Joint Health Score, HJHS), quality of life (Haemo-QoL-A) and climbing performance (UIAA scale) were assessed before and after the training. Prior to the study, the patient was on demand treatment. The patient was started on standard prophylaxis for 2 months period and then observed for 6.5 months under PK-tailored prophylaxis. PK-tailored prophylaxis was targeted to a trough level of 1–3%. For high-impact activities a factor activity >15%, for low-impact activities a factor activity >5% was suggested. Results: Climbing therapy was safe. The bleeding rate decreased from 14 (2012) to 1 (during the study period of 8.5 months). The one bleeding event was due to a missed infusion and was not triggered by physical activity. The elimination half-life using Bayesian statistics was determined to be 16h. Using this half-life for PK-tailored prophylaxis reduced the factor VIII consumption in comparison to standard prophylaxis. Joint health was particularly improved in the categories range of motion and swelling. Quality of life scores stayed at a high level. Climbing performance improved by 1 grade. Conclusion: The combination of PK-tailored prophylaxis with therapeutic climbing improved clinical outcome in this young adult with severe haemophilia. The tailored concept for high- and low-impact activities appeared to be safe.

Schlüsselwörter
Hämophilie A, individualisierte Prophylaxe, therapeutisches Klettern

Zusammenfassung
Numerous, small cohort studies propose that people with haemophilia (PWH) profit physically and psychologically from participation in appropriate sports (8). Injury and bleeding protection has priority in choosing the appropriate sport for PWH. Climbing with qualified safeguards, especially indoor climbing is considered a low injury risk sport (7).

According to German recommendations regarding suitable sports disciplines for PWH, Toprope climbing and Bouldering are classified as low bleeding risk sports (2).

It strengthens the entire musculature and develops flexibility and coordination abilities (▶ Fig. 1 a). Climbing to the top, exceeding personal limits and the social inclusion into a group where you need to trust your belay partner can be very motivating for an individual with a handicap. Due to its benefits in physical and mental health as well as its high fun factor, climbing is nowadays an established way of therapy. Multiple effects of climbing therapy are proven in the fields of physiotherapy, psychotherapy and ergotherapy (3). The German Alpine Club has been running successful programs for patients with multiple sclerosis and movement disorders for years. Moreover, climbing has become increasingly attractive and trendy among young people. In order to guarantee regular physical activity, patients must be motivated by a challenging and attractive sport.

Prophylaxis from an early age has been well established as the gold standard in the treatment of severe haemophilia (4–6). Patients on long-term prophylaxis are even as active as their healthy peers. Active young PWH on consequent prophylaxis do not show an increased bleed rate, even when engaged in high-impact activities (7). Some authors suggest a minimum factor level of 15% for extensive training sessions (2). A recent study concerning the classification of clinical severity of haemophilia showed that the number of joint bleeds decreased to approximately zero in patients with a baseline FVIII activity >12% (8).

In common clinical practice prophylactic regimens are determined on the basis of body weight and age. However, the patient’s PK response to the dosing is not considered by this method. Variation in response between patients is a crucial issue as the half-life of factor VIII ranges between 6 and 25 h. Thus, a wide difference in the factor level is observed even after administration of equivalent doses/kg body weight (9, 10). These aspects taken into account, individual PK determination is desirable for every patient on prophylaxis in order to target an adequate plasma level. Until now, no established concept for the design of PK-tailored prophylaxis for physically active PWH is available.

Conventional PK guidelines recommend blood sampling over 32–48 hours. As this method is very time-consuming PK measurements are only undertaken in exceptional cases. Recently developed methods enable sparse blood sampling at only three time points in the period from 6 to 40 hours after the infusion. Furthermore, a washout phase and hospitalization is not necessary for the patients. Lately invented computer programs compare population data against measured factor VIII levels. The individual half-life is calculated by Bayesian analysis. By this, suitable doses and ideal intervals between the infusions can be exactly estimated. Previous studies showed promising data and equally acceptable results when compared with the standard protocol (11, 12).

Case report

We report about a young adult (age: 25 years) with severe haemophilia A who took part in a climbing therapy program under PK-tailored prophylaxis. The patient had refused regular prophylaxis in the past. Prior to the study, he was mainly on on-demand treatment and only occasionally applied prophylaxis (2000 or 4000 IU in 2 to 3 weekly intervals). He experienced 9 joint and 5 muscle bleedings in the year 2012. Physical examination revealed haemarthropathy in his left elbow joint only. The haemophilia joint health score (HJHS) was
9 on inclusion to the study. The patient stated an excellent quality of life (HaemoQol-A score: 29 = 96.7%). He exercised once to twice weekly. For a long time, he played squash and practiced jogging. A stress test on a bicycle showed a slightly reduced maximum oxygen capacity for his age (VO2 max: 2046 ml/min).

PK determination was performed twice. The PK results were highly reproducible. For each PK series, 3 blood samples were collected approximately 6, 24 and 32 h after the infusion. Factor VIII levels were measured in duplicate by the one stage technique. The individual PK parameters were estimated through Bayesian analysis (kindly provided by Baxter Innovations GmbH Biostatistics). Until the exact calculations were available, the patient was encouraged to standard prophylaxis using 2000 IU/68 kg (30 IU/kg body weight) ADVATE every other day. Standard prophylaxis was practiced consequently for 2 months prior to the start of PK-tailored prophylaxis. As the half-life turned out to be 16 h (blood group: A+, VWF antigen: 203%, VWF activity: 144 %, VWF ristocetin cofactor activity: 146 %, fibrinogen: 245 mg/dl), dosing could be reduced to 2000 IU twice weekly. The patient preferred dosing on specified weekdays to dosing at regular intervals. He found this regimen easier to remember and to coordinate with

**PK-tailored prophylaxis profile**

Name: XXXX XXXX, Date of birth: XX.XX.1988
Date of the examination: 21./22.02.2013
Height: 1 cm, Weight: 67.5 kg
Age: 25 years

PK Results (based on Bayesian statistics):
**Elimination half-life (t 1/2): 16.3 h**
Volume of Distribution (V1): 24.3 dl, Clearance (CL): 1.5 dl/h

**PK-Graph (prior to prophylaxis) after the infusion of 2000 IU of Advate**

![PK-Graph](image)

**Recommended prophylaxis:**
Product: Advate

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Legend: green: safe, yellow: safe for low impact activities, red: not safe

- Trough levels shall never fall <1% and ideally not <3% to avoid inapparent minor bleeds
- Factor levels >15% (>5%) are needed for high (low) impact activities
- Ideally plan sports activities closely to peak levels - otherwise extra infusions may be needed as indicated

**Fig. 1 b) PK-tailored prophylaxis handout for the patient c, d) A mild extension deficit in the left elbow normalized during the study; prior to the study, ca. 10° (c); at the end of study, ca. <2° (d)**
regular sports activities. PK-tailored prophylaxis was targeted to a trough level of 1–3% and adapted to the individual needs of the patient. For high-impact activities a factor activity >15%, for low-impact activities a factor activity >5% was suggested. Climbing was considered high impact. The patient was advised to plan sports activities closely to peak levels and how to manage extra infusions when this was not the case. A handout including the PK parameters, a graph demonstrating factor VIII activity, and a form for the patient’s PK parameters, a factored activity >15%, for low-impact activities >1% and adapted to the individual needs. PK-tailored prophylaxis with therapeutic climbing improved clinical outcome in this young adult with severe haemophilia. The tailored concept was more expensive than on demand treatment (Table 1). The joint status (HJHS: 3) of the affected elbow improved (Fig. 1c). The swelling subsided and the range of motion normalized. The quality of life remained on a high level (Haemo-Qol-A score: 28.9 = 96.3%).

The patient stated that he very much enjoyed the climbing training and appreciated the exchange with other PWH in an informal setting. The regular sports program was the key motivation for consequent prophylaxis for him. By the end of the study, he was convinced that his personal prophylaxis concept will be valuable for his condition in the future.

**Conclusion**

Climbing therapy was safe and suitable for this patient with mild haemarthropathy. The combination of personalized prophylaxis with therapeutic climbing improved clinical outcome in this young adult with severe haemophilia. The tailored concept for high- and low-impact activities appeared to be safe. In this case, PK-tailored prophylaxis considerably decreased factor usage in comparison to standard prophylaxis. Comprehensive patient education on the basis of a personal handout and regular sports with other PWH increased adherence to prophylaxis.

### References


**Conflict of interest**

The climbing study was sponsored by Bayer Health Care. The PK study was sponsored by Baxter, Germany; the Bayesian population PK calculations were provided by Baxter Innovations GmbH, Vienna, Austria.

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