FREQUENCY AND DEGREE OF CHRONIC ARTHROPATHY IN HEMOPHILIA A PATIENTS ON PROPHYLACTIC AND ON-DEMAND TREATMENT

Miodrag Vučić 1,2, Dragana Drašković 1

Hemophilia A is the most common congenital bleeding disorder caused by a deficiency in coagulation factor VIII activity, characterized by a marked bleeding tendency. It is inherited recessively. The most common complication of the disease is chronic arthropathy.

In the prophylactic treatment regimen, the subjects receive preventative F VIII infusions every second day or three times a week.

In an on-demand regimen, bleeds are treated as they occur.

Analysis of the frequency and degree of chronic hemophilic arthropathy in patients with moderate and severe hemophilia A.

Analysis of involvement of individual joints, and their score values by the treatment regimen (prophylaxis vs. on-demand treatment.)

The study included 23 patients - 15 patients on „on-demand“ regimen and 8 patients who had prophylaxis, all being treated at the Clinic of Hematology and Clinical Immunology, Clinical Center Niš. In the assessment of frequency of complications we used descriptive statistics: the number, proportion and mean. The comparison of arithmetic means of the two samples was performed using the t-test. The comparison of frequency values was performed using the chi-square test or Fisher's test.

In the group without prophylaxis, the knee and hip were the most commonly affected sites (73.33% and 53.33%), and in the group with prophylaxis, the elbow joint was mostly affected (37.50%). The knee was statistically more often affected in patients without prophylaxis compared to those on prophylaxis. The knee score had the highest value in both groups. It was statistically significantly higher in patients without prophylaxis compared to those on prophylaxis. The hip score was the second highest value in the examined groups, the third was the elbow joint score, followed by the ankle score, and the lowest score was observed for the shoulder joint. Elbow and ankle scores were statistically significantly higher in patients without prophylaxis compared to those on prophylaxis.

Chronic arthropathy is the most common complication in patients with severe and moderate Haemophilia A, with maximum involvement of the knee joint in both groups of patients (with or without prophylaxis), but with a statistically significantly higher score in patients without prophylaxis. Acta Medica Medianae 2016;55(1):38-43.

Key words: Hemophilia A, hemophilic arthropathy, prophylaxis, on-demand treatment

Introduction

Hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency in coagulation factor VIII (F VIII) activity. It generally affects males on the maternal side, but in 1/3 of all cases it is the result of spontaneous mutation without any prior family history.

The severity of the disease depends on the factor VIII level (1). Serious forms are characterized by the level of factor VIII lower than 1%, moderate forms have factor VIII level between 2% and 5%, and mild forms of hemophilia have factor VIII level over 6%. Patients with mild hemophilia do not bleed excessively until they experience trauma or surgery. In severe forms, bleedings occur spontaneously.

The diagnosis is made on the basis of patient history data (gender, personal history, family history), clinical examination and laboratory testing (PTT prolonged low serum factor VIII activity).

The predilection bleeding sites are muscles and joints. Repeated bleedings can lead to degenerative diseases and disabilities, and may be life-threatening (e.g., bleeding in the CNS) (2).

In the prophylactic treatment regimen, subjects receive preventative F VIII infusions (20- 50 IU/kg body weight once every second day, or 20-
60 IU/kg BW three times weekly), with additional treatment for breakthrough bleeds. In an on-demand regimen, bleeds are treated as they occur (3).

Complications of the disease include development of factor VIII inhibitors, chronic hemophilic arthropathy and transmissible infections (HBV, HCV and HIV, etc.).

Chronic hemophilic arthropathy is the most common complication in severe and moderately severe hemophilia A. It is caused by frequent and repeated bleedings into joints, although permanent damage can be caused even by a single, but heavier joint bleeding (4).

Objective

The aim of this study was to analyze the prevalence of chronic hemophilic arthropathy in patients with moderate and severe hemophilia A.

Moreover, we analyzed the involvement of individual joints and their score values by the administered treatment regimen (prophylaxis vs. on-demand treatment.)

Material and methods

The data on 23 patients with moderate and severe hemophilia A were obtained from the archives of the Department of Haematology and Clinical Immunology, Clinical Center Niš. The data used were related to age, positive family history, presence of chronic arthropathy, presence of transmissible infections and inhibitor development.

We retrospectively analyzed and compared the data on patients in the period from January 2011 to December 2014. The patients were men aged 20 to 61, with moderate or severe hemophilia A. There were 16 patients with moderately severe hemophilia A, and 7 with severe hemophilia A.

In the assessment of frequency of complications we used descriptive statistics: the number, proportion and mean.

The assessment of the degree of arthropathy was performed according to the criteria set by the Orthopedic Advisory Committee of the World Federation of Hemophilia (Table 1).

Statistical analysis

The data were presented as arithmetic means and standard deviations, or in the form of absolute and relative numbers. The comparison of arithmetic means of the two samples was performed using the t-test. The comparison of frequency values was performed using the chi-square or Fisher’s test. The hypothesis was tested with the significance threshold set at p<0.05. Statistical data analysis was performed using the SPSS 16.0 software package.

Results

The study included 23 patients - 15 patients on „on-demand“ regimen and 8 patients who had prophylaxis. Demographic and clinical characteristics of the studied groups are shown in Table 2.

Patients on prophylaxis were younger than those without prophylaxis, without a statistically significant difference though (p=0.053). In the group of patients who had no prophylaxis (on-demand treatment), 33.33% had a positive family history, and in the group with prophylaxis, a quarter (25.00%) had a positive family history. It was found that there was no statistically significant difference in the frequency of positive family histories with regard to the use of prophylaxis (p=0.950) (Table 2).

The most common complication in both groups was chronic arthropathy (86.67% and 75.00%). One patient (6.67%) in the group with no prophylaxis had HBV. HCV was present in 40.00% of patients without prophylaxis and in 37.50% of patients with prophylaxis. There were 3 patients with prophylaxis (37.50%) and one patient without prophylaxis (6.67%) who had no complications. There was no statistically significant differences in the incidence of chronic arthropathy (p=0.900), HBV infection (p=0.652), HCV infection (p=0.740), and the number of patients without complications (p=0.102) with regard to the use of prophylaxis.

Clinical changes were evidenced in the following joints (Table 3): changes in the shoulder joint in 3 patients (13.04%), changes in the elbow joint in 8 patients (34.78%), changes in the hip joint in 10 patients (43.48%), changes in the knee joint in 13 patients (56.52%), and changes in the ankle joint in 6 patients (26.09%) (Graph 1).

In the group without prophylaxis (receiving on-demand treatment), the knee and hip were most commonly affected (73.33% and 53.33%), and in the group with prophylaxis the elbow joint was the one most commonly affected (37.50%). The knee was statistically significantly more often

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain</td>
<td>0 – 3</td>
</tr>
<tr>
<td>Range of motion</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Flexion contractures</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Swelling</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>0 – 1</td>
</tr>
<tr>
<td>Axial deformities</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Crepitation during motion</td>
<td>0 – 1</td>
</tr>
<tr>
<td>Instability</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Max.score</td>
<td>0 – 15</td>
</tr>
</tbody>
</table>

Table 1: Criteria for clinical evaluation of the score in hemophilic arthropathy
**Table 2:** Demographic and clinical characteristics according to the treatment regimen

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>On-demand treatment N=15</th>
<th>On prophylaxis N=8</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38.1±4.96</td>
<td>42.1±8.92</td>
<td>34.1±8.99</td>
<td>0.053†</td>
</tr>
<tr>
<td>positive family history</td>
<td>7 (30.43%)</td>
<td>5 (33.33%)</td>
<td>2 (25.00%)</td>
<td>0.950#</td>
</tr>
<tr>
<td>Chronic arthropathy</td>
<td>19 (82.61%)</td>
<td>13 (86.67%)</td>
<td>6 (75.00%)</td>
<td>0.900‡</td>
</tr>
<tr>
<td>HBV</td>
<td>1 (4.35%)</td>
<td>1 (6.67%)</td>
<td>0</td>
<td>0.652#</td>
</tr>
<tr>
<td>HCV</td>
<td>9 (39.13%)</td>
<td>6 (40.00%)</td>
<td>3 (37.50%)</td>
<td>0.740</td>
</tr>
<tr>
<td>Inhibitors development</td>
<td>1 (4.35%)</td>
<td>1 (6.67%)</td>
<td>0</td>
<td>0.652#</td>
</tr>
<tr>
<td>Without complications</td>
<td>4 (17.20%)</td>
<td>1 (6.67%)</td>
<td>3 (37.50%)</td>
<td>0.102#</td>
</tr>
</tbody>
</table>

**Table 3:** Involvement of individual joints according to the treatment regimen

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Total</th>
<th>On-demand treatment N=15</th>
<th>On prophylaxis N=8</th>
<th>p#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder joint</td>
<td>3 (13.04%)</td>
<td>2 (13.33%)</td>
<td>1 (12.50%)</td>
<td>0.731</td>
</tr>
<tr>
<td>Elbow joint</td>
<td>8 (34.78%)</td>
<td>5 (33.33%)</td>
<td>3 (37.50%)</td>
<td>0.596</td>
</tr>
<tr>
<td>Hip joint</td>
<td>10 (43.48%)</td>
<td>8 (53.33%)</td>
<td>2 (25.00%)</td>
<td>0.378</td>
</tr>
<tr>
<td>Knee joint</td>
<td>13 (56.58%)</td>
<td>11 (73.33%)</td>
<td>2 (25.00%)</td>
<td>0.039</td>
</tr>
<tr>
<td>Ankle joint</td>
<td>6 (26.09%)</td>
<td>4 (26.67%)</td>
<td>2 (25.00%)</td>
<td>0.666</td>
</tr>
</tbody>
</table>

**Graph 1:** Involvement of individual joints

- The knee score had the highest value of all in both treatment groups. This score was statistically significantly higher in patients without prophylaxis compared to patients with prophylaxis (p=0.031) (Table 4).
- The hip score was the second largest in the examined groups, the third was elbow joint score, then ankle score, and the lowest score was for the shoulder joint. The elbow and ankle joint scores were statistically significantly higher in patients without prophylaxis compared to patients with prophylaxis (p=0.048 and p=0.027). (Graph 2)

**Discussion**

The clinical picture of hemophilia is characterized by a marked tendency of bleeding. The joints and muscles of the extremities are the most common sites of bleeding in patients with hemophilia A (5).

Repeated intraarticular bleedings lead to the onset of chronic synovitis. As a result of development of the inflammatory process, this leads to swelling and disturbed circulation in the joint space, which causes deterioration of the articular surfaces and deformities on the joints themselves (6).

In chronic synovitis, the joint is deformed and swollen; however, the feeling of tension and
### Table 4: Score values of individual joints according to the treatment regimen

<table>
<thead>
<tr>
<th>Score</th>
<th>On-demand treatment N=15</th>
<th>On prophylaxis N=8</th>
<th>p#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder joint</td>
<td>0,72±0,13</td>
<td>0,62±0,09</td>
<td>0,069</td>
</tr>
<tr>
<td>Elbow joint</td>
<td>1,95±0,21</td>
<td>1,76±0,20</td>
<td>0,048</td>
</tr>
<tr>
<td>Hip joint</td>
<td>3,53±0,42</td>
<td>3,23±0,40</td>
<td>0,112</td>
</tr>
<tr>
<td>Knee joint</td>
<td>4,61±0,58</td>
<td>4,11±0,25</td>
<td>0,031</td>
</tr>
<tr>
<td>Ankle joint</td>
<td>1,56±0,29</td>
<td>1,22±0,39</td>
<td>0,027</td>
</tr>
</tbody>
</table>

**Graph 2:** Score values of individual joints according to the treatment regimen

Partial pain do not occur. This is common in the first and second decade of life (7).

As a consequence of the development of inflammatory process, inflammatory cells release proteolytic enzymes that destroy the cartilage and subchondral bone, leading to bone tissue resorption and ossification (8). The progression of cartilage destruction leads to progressive arthritis with secondary soft tissue contractures, muscle atrophy and deformity (9).

Chronic arthropathy eventually leads to fibrosis of the sinovium and joint capsules, and reduced swelling (10). The most significant functional damage of the joint is the complete loss of motion. (11)

Primary prophylaxis has to be considered as the optimal treatment for patients with severe haemophilia (12). Prophylaxis with recombinant factor VIII is effective in preventing hemarthroses and structural joint damage in young boys with Hemophilia A (13). The best time to begin prophylaxis is before the first joint hemorrhage. However, only a fraction of all haemophilia patients worldwide have access to this treatment (medical trials). Instead, most patients are treated either on-demand or not at all, primarily because of the costs (14).

The benefits of prophylaxis versus on-demand approach are huge, and it has been clearly shown that it is important to minimize the amounts of joint bleeds and to start treatment before the development of arthropathy (15). The mean total number of bleeds per patient is significantly lower in the prophylactic regimen, and joint damage is also a rarer occurrence (16).

Joint scores in the assessment of the degree of arthropathy are significantly higher in patients receiving on-demand treatment than in patients on prophylaxis.

In our study, the highest clinical score was found in the knee joint. The knee score had the highest value in both groups. It was statistically significantly higher in patients without prophylaxis compared to pa-
patients with prophylaxis. The hip score had the second largest value, and the lowest score value was for the shoulder joint. The elbow and ankle joint scores were statistically significantly higher in patients without prophylaxis compared to patients with prophylaxis.

Although the ankle involvement was relatively rare, this was associated with most severe joint mobility limitation.

**Conclusion**

In this study, we showed that chronic arthropathy was the most common complication in patients with severe and moderate haemophilia A, with maximum involvement of the knee joint in both groups of patients (with or without prophylaxis), but with a statistically significantly higher score in patients without prophylaxis.

**References**

UČESTALOST I STEPEN HRONIČNE ARTROPATIJE
KOD BOLESNIKA SA HEMOFILIJOM A NA
PROFILAKTIČKOM I “ON-DEMAND” REŽIMU

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Cilj rada bio je analiza učestalosti hronične hemofilične artropatije kod bolesnika sa umereno teškom i teškom hemofilijom. Učestalost javljanja komplikacija korišćena je deskriptivna statistika: broj, proporcija i srednje vrednosti. Poređenje aritmetičkih sredina dva uzorka vršeno je t testom. Upoređivanje učestalosti vrednosti vršeno je H kvadrat testom ili Fišerovim testom.

U grupi bez profilakse najčešće je bilo zahvaćeno koleno i kuk (73,33%, odnosno 53,33%), a u grupi bez profilakse najčešće je bio zahvaćen lakat (37,50%). Koleno je statistički značajno veće kod bolesnika bez profilakse u odnosu na bolesnike sa profilaksom. Skor kolena ima najveću vrednost u obe ispitivane grupe. On je statistički značajno veći kod bolesnika bez profilakse u odnosu na bolesnike sa profilaksom.


Ključne reči: hemofilija A, hemofilična artropatija, profilaksa, “on-demand” terapija