

# *Impact of physiotherapy in patients with Hemophilia A*

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## **Abstract**

**Introduction:** Hemophilia is a congenital X-ray disease associated with bleeding in which blood does not clot. It is categorized as a hemostasis problem. Hemostasis, the cessation of blood flow as a result of damage to a blood vessel, is normally divided into two processes, primary hemostasis and secondary hemostasis. In hemophilia, the secondary hemostasis (which results in the formation of a clot in the fibrin) is in this case broken. So, low coagulation is due to an abnormal protein plasma clotting abnormality in factors VIII and IX that are involved. **Aim:** The aim of this study is to show that combined rehabilitation based in exercises is more effective just a simple therapy to improve hemophilia and reducing the symptoms. **Methods:** In this review study 30 studies were obtained which have used different physiotherapeutic methods in the treatment of hemophilia A. The elected studies ranged from 2001-2019. The literature is based on official sources as Cochrane library, Pubmed, MEDLINE, DOAJ, Medscape, Clinical trial.gov and some articles like is Official Journal of WFH , BMJ Open. **Results:** During the study it was observed that the combined physiotherapeutic rehabilitation had more efficiency than a simple treatment method. **Conclusion:** A physiotherapeutic rehabilitation with combined methods based on exercises gives better and positive results in the treatment of hemophilic patients.

**Key words:** hemophilia A, manual therapy, electrical stimul, laser, ultrasound, hematoma, ergo metric bicycle, PNF, arthropathy, yoga, hydrotherapy, kinesio taping.

## Introduction

People in ancient times wrote about blood and bleeding problems. They could see that many people had different bleeding problems. But they knew very little about blood clots. [1]

Patients with mild hemophilia have little spontaneous bleeding and heavy bleeding in cases of severe trauma, patients with moderate hemophilia show severe bleeding after minor trauma, while patients with severe hemophilia are characterized by severe spontaneous bleeding or after a minor trauma. [2]

Although effective treatment has resulted in recent decades, hemophilia has been known since antiquity. A modern description is attributed to Dr John Conrad, who described hemophilia as an inherited tendency of men to bleed. [3]

Hemophilia A and B are recurrent disorders associated with X chromosome. Females carry the mutated gene while the disorders manifest entirely in males. [4]

Hemophilia is a congenital disease of the X chromosome that is associated with bleeding in which the blood does not clot. It is categorized as a problem of homeostasis. Homeostasis, the blockage of blood due to damage to a blood vessel, is normally divided in two processes: primary homeostasis and second homeostasis. In hemophilia, the secondary homeostasis (which results in the formation of a fiber clot) in this case is impaired. So the low coagulation is due to an abnormality of the functional plasma clotting protein of factors VIII and IX that are involved. [5]

Hemophilia A (or classic hemophilia) affects about 80% of cases.

Hemophilia B (or Christmas disease) affects about 15% of cases. [6]

The severity of hemophilia A can be described as:

- Mild hemophilia
- Moderate hemophilia
- Severe hemophilia. [6]

## Epidemiology

The worldwide incidence of hemophilia is approximately 1 case for 5000 men, 1/3 of the affected individuals have no family history. The prevalence of hemophilia A varies by reporting site with a range of 5.4 -14.5 cases for 100000 males. In the USA, the prevalence of hemophilia A is 20,6 cases for 100000 men. In 2016 the number of people with hemophilia in USA was about 20000. [12]

### **Statistical data of Hemophilia A in Albania:**

A total of 200 patients with Hemophilia A have been registered:

- 152 adults patients >14 years old
- 48 pediatric patients < 14 years old

### **Hemophilic A patients grouped by age:**

- 0-4 years old: 7 patients (3.5%)
- 5-13 years old: 41 patients (20.5%)
- 14-18 years old: 28 patients (14%)
- 19-44 years old: 86 patients (43%)
- >44 years old: 38 patients (19%)

### **According to the severity of the disease (factor level) are:**

- 98% adults with severe hemophilia (factor level <1%)
- 30 adults with moderate hemophilia (factor level 1-5%)
- 24 adults with mild hemophilia (factor level 5-40%)

### **48 pediatric patients are registered:**

- 26 patients with severe hemophilia (factor VIII level <1%)
- 19 patients with moderate hemophilia (factor VIII level 1-5%)
- 3 patients with mild hemophilia (factor VIII level 5-40%) [14]

## **Etiology**

Blood coagulation factors VIII and IX are found on the X chromosome causing a disorder on the X chromosome and making hemophilia a rare disease for women. Since women have two chromosomes X they are hemophilic when both X chromosomes are affected. Men will always be affected by hemophilia when they carry an affected chromosome. 2/3 have a prominent family history while 1/3 of cases come from a spontaneous genetic mutation. [7]

Hemophilia A binds to a recessive pattern that binds to the X chromosome. The gene for factor VIII is located on the long arm of the X chromosome in the q28 band. The factor VIII gene is one of the largest genes containing about 0.1% of the DNA on the X chromosome that is 186 kilo base long. The mature protein contains 2332 monoacids and has a molecular weight of 300 kb. It includes 3 domains A, 1

domain B, 2 domains C. The intron 22 of the factor VIII gene contains two other genes. The first gene is transcribed in the opposite direction to that of the factor VIII gene itself. The second gene is transcribed in a direction similar to the factor VIII gene. Homologues recombination of the factor VIII gene by inversion and cross linking results in a division in the factor VIII with two parts directed in opposite direction. This causes an interruption in the normal factor coding sequence with an inability to transcribe the complete protein resulting in loss of function. [8]

Combined factor V and VIII deficiency is an autosomal recessive disorder, with clinical manifestations in both males and females. This disorder is caused by mutations in one or two genes, the LMAN1 binding protein or by the lack of coagulation factor MFCD2 which encodes the proteins involved in the intracellular transport of factor V and VIII the coagulation factors themselves are normal. [10]

## **Study Method**

### *Purpose*

The purpose of this study is to show that combined exercise based rehabilitation is more effective than just a combination therapy in improving the treatment of hemophilia and reducing symptoms.

## **Objectives of the study**

### *General objectives*

The main objective of this study is to show the effectiveness of each method as combined and not combined in reducing symptoms and improving the quality of life in hemophilic patients. To demonstrate the impact of an exercise program on increasing joint ROM and muscle strength on improving the lives of hemophilic patients. To demonstrate the effectiveness of combined kinesio taping therapy with exercises. To find out which combination of modalities is most effective in treating hemophilia. To demonstrate the psychological and physical effects that come from Yoga or other specific methods in improving the activities of daily living. To compare the effectiveness of hydrotherapy and ground exercises with each other. To find the most efficient and least costly method in rehabilitating hemophilia.

## Methodology

To realize this study work the method of reviewing was used the latest literature according to the current guidelines for hemophilia from WFH. 38 studies were reviewed of which 8 of them were eliminated due to small number of subjects, leaving between treatments or not completing the study for various reasons and from these 30 studies were selected. Patients underwent a rehabilitation or combined rehabilitation and the effectiveness of each treatment method was monitored. The literature was obtained from official sources such as: Cochrane library, Pubmed, MEDLINE, DOAJ, Medscape, Clinical trial.gov and much information was obtained from various journals such as Official Journal of WFH, BMJ Open. The studies obtained are from the years 2001-2019. Keywords used are: hemophilia A, manual therapy, electrical stimulation, laser, ultrasound, acupuncture, hematoma, PNF, ergo metric bike, arthropathy, yoga, hydrotherapy. These studies can not be conducted here due to small samples taken in the study and conditions not applicable in Albania, lack of qualified staff and intervention methods.

## Criteria

Inclusive criteria	Exclusive criteria
Men Mild, moderate, severe hemophilia With or without factor and prophylactic treatment Age 6-65 Hemophilic arthropathy Pain Literacy skills	Von Hillenbrand disease History of fracture or trauma of the limbs Orthopedic surgical intervention Brain damage, STROKE, other paralysis Other diseases such as cardiovascular, hepatitis B and C Age >70 Serious psychological problems

### Survey Instrument

HJHS questioner

FISH questioner

VAS scale

## Results

**A. Eid et al. (2013)** [44] in his study demonstrate that resistance training and aerobic exercises are effective in increasing bone mineral density and improve muscle strength and functional ability. In the study were taken 30 hemophilic boys selected in two groups. Control group I did physical therapy program with stretching exercises 115 min and aerobic exercises in form of a routine 30 min 1

hour 3 times a week for 3 months. Group II did the same program but additional treatment program with resistance in form of ergo metric bicycle 20 min and resistance with weight 20 min lasted 1 hour 40 min 3 times a week for 3 months. Changes were seen in the study group before and after treatment ( $p < 0.05$ ) while the control group had no significant changes before and after treatment ( $p > 0.05$ )

**Rubén Cuesta-Barriuso PhD et al. (2016)** [45] in his study saw the effectiveness of combining a physiotherapeutic education with an exercise program at home. 20 hemophilic patients were randomly selected. The experimental treatment group received education 60 min every 2 weeks and in parallel received a 15 week exercise program. Control group didn't take education or an exercise program. Educational intervention based on physiotherapeutic exercises improves quality of life and disease behavior and this improvement comes after 6 months of follow up with Gilbert scale examination.

**Necati Muhammed TAT (2019)** [46] investigates the effects of Kaltborn method manual therapy on a simple home exercise program at the level of functional hemophilia independence, kinesio phobia functional level, ROM pain of hemophilic patients with arthropathy.

*According to the results supported by the above studies we see that exercises therapy combined another manual method like Kaltborn or ergo metric bicycle are positive in the effects they bring to hemophilic patients.*

**Alaa R Morgan (2018)** [47] makes a comparison in the effects that pulsed ultrasound brings against low level laser in hemophilic patients with knee swelling. According to the study the author concludes that US is more effective than LLT in reducing swelling and increasing ROM in patients with hem arthritis of the knee. ( $p < 0.005$ )

**Manuel Gomis et al. (2009)** [48] study determines the changes that occur from electrically stimulated treatment. The electrical stimulation in muscle in hemophilic patients was effective in increasing muscle strength combined with exercises. 30 subject, group A with severe hemophilia, group B without hemophilia. Group A performed an electrical stimulation program  $f = 45\text{Hz}$  10 sec for 8 weeks. Group A had significant changes in diameter increase. ( $p < 0.01$ ), strength ( $p < 0.05$ ), EMG activities ( $p < 0.05$ )

**Behrouz Parhampour et al. (2013)** [49] study estimates that treatment with short term resistance and electromagnetic impulse is effective in improving bone formation and joint activity in severe hemophilia A with osteoporosis. 48 randomly selected patients where training resistance  $n = 13$ , training resistance combined with electromagnetic pulse  $n = 12$ , electromagnetic pulse  $n = 11$ , control group  $n = 12$ . Through the Colorado Questionnaire there was significant improvement in RT group and RTPMF compared to PEFM and control gr.

**Mohamed Khawaji et al. (2010)** [50] describes the intensity and duration of physical activity with early long term prophylaxis concluding from the information

gathered from the assessment with HJHS that hemophilia treatment strategies including treatment early general, primary prophylaxis was successful in reducing the frequency of bleeding and preventing chronic diseases of the joint.

**Mazloun V et al. (2014)** [51] study compares the impact of conventional exercise therapy with hydrotherapy concluding that the use of hydrotherapy in addition to routine rehabilitation may be beneficial in joint pain and ROM. And that hydrotherapy is quite effective in reducing pain.

**L. VALLEJO et al. (2010)** [52] study concludes that after the proposed training program significant changes were seen in the increase of aerobic and mechanical capacity and that aquatic therapy had positive effects on motor performance and improved aerobic and mechanical capacity without causing further complications.

**Mehdi Kargarfard et al. (2013)** [53] in his study showed the importance of water therapy in hemophilic patients improvements that brought in muscle strength and articular ROM compared to gr who did not attend any physical therapy. 20 men were selected 10 of them in experimental gr and 10 in control gr. The changes were made with Biodex test. ( $p < 0,01$ )

**De la Corte-Rodriguez H et al. (2013)** [54] in his study show the role that both physical and drug therapies have in hemophilic patients and concludes that both therapies are quite effective in reducing the impact of injury and bleeding and increase the quality of life in these patients. Performing physical examination and performing measurements according to HJHS and Gilbert scale. Drug therapy reduces pain, bleeding in the joints and muscles while physical therapy brings better physical abilities and increase strength in ROM.

**Chan Yuan-Chi et al. (2015)** [55] in his study were seen the effects that kinesio taping has on hemophilic patients in functional activities and balance skills compared to the group who didn't receive kinesio taping treatment. 30 participants were selected randomly and in the group who did physical therapy including kinesio taping were seen significant changes that in the other group with physical therapy only.

**LAMBING et al., (2012)** [56] included 9 subjects in his study. Some of them received treatment with 15% coagulation factor replacement and some others who did not receive this treatment but perform about 14 acupuncture treatments. 6 of 9 subjects reported improvement in pain by 50 % points. 7 of 9 had an improvement in quality of life. Assessment were made with QOL SF-36 and VAS scale. As a result none of the patients treated with acupuncture had any episodes of bleeding, bruising or tanning of the skin, and studies suggested acupuncture as an effective and safe therapy for hemophilic patients.

**Patricia Ribeiro Pinto et al. (2017)** [57] in his study appreciates the effect that two psychological therapies like cognition therapy and hypnosis bring on the management of pain and emotions by increasing well being and quality of life and

enabling these patients to learn to live with this disease. Functional assessment was measured with Peterson Scale and Gilbert Score while psychological assessment was measured with A36Hemophilia-Qol.

**Noushin Beheshtipoor et al. (2015)** [58] in his study about Yoga we look at the effects that brings on the quality of life in children and adolescents with hemophilia which are very positive and Yoga is a therapy that not only brings improvement in the quality of life but also reduces bleeding episodes. According to Friedman test results there was a significant change in QOL before and after treatment ( $p < 0.001$ ). A significant reduction in bleeding was seen ( $p < 0.001$ )

**Bak, Won-Sook et al. (2012)** [59] in his study shows that having Tai Chi in a program of its own in hemophilic patients improves joint movement, strength and psychological condition.

**Matthew Slattery et al. (2001)** [60] in his study shows the effects that functional orthosis of the foot brings as a great help in reducing pain and increasing the ability of movements performed by the sole of the foot. But the authors said that we have to make others studies in the future for the real effects of the orthosis.

**Reza Mahdavinejad et al. (2012)** [61] in his study showed that correctly physical activities and psychological activity can improve physical and psychological activities in hemophilic patients. 20 male with hemophilia A were chosen and after completing the formulary the therapy began and were seen significant changes in the group that the therapy were combined. ( $p < 0.05$ ).

**S. HARRIS et al. (2006)** [62] according to his study it was included that the group that performed an exercise program had further reduction of joint destruction compared to the group that did not perform exercises and the exercises performed regularly are the best solution in hemophilic patients.

**L M González et al. (2011)** [63] in his study compared physical activity versus sedentary behaviors between hemophilic and healthy patients and concluded that physical activity has positive effects not only on hemophiliacs but also on healthy individuals and should be encouraged as healthy children spend more time making sedentary rather than active in a sport. A total of 41 patients with hemophilia A and 25 healthy patients included the study. Differences were found between the total amount of physical activity ( $p < 0.001$ ) and energy expenditure between the two group ( $p < 0.001$ ) for the group of hemophilic patients performing exercise therapy such as walking, climbing, cycling etc.

## Discussion

In this review study we will focus mostly on the various combined physiotherapeutic methods where the main basis are exercises where physical therapy is an important component in the management of hemophilia symptoms. About 50 years of drug treatment of hemophilia has evolved giving physiotherapeutic treatment safety and



importance resulting in effective prevention of bleeding episodes. To support these various studies have been found which have combined methods based on exercises that share the same thoughts as the authors above as there may be contradictions.

**T. HILBERG et al., (2003)** [64] in his study evaluated the safety of two physiotherapeutic programs that combine manual therapy with exercises at home with educational session in hemophilic patients concluding that treatment with manual therapy improved articular ROM and movements and reduced pain.

**D. CZEPA et al. (2012)** [65] evaluates the effects of surface electrical stimulation on the quadriceps muscle concluded that the group doing electrical stimulation and exercise had an increase in strength in the stimulated leg and results showed that the surface electrical stimulation poses no risk to the patients health and is used for therapeutic purposes.

**Ruth Mulvan et al. (2010)** [66] examine the feasibility and safety of a 6 week individualized exercise program in hemophilic patients concluding that an exercise program according to the requirements of each hemophilic individual had positive effects on improving symptoms by being safe and professionally supervised.

**Ruben Cuesta-Barriuso et al. (2018)** [67] evaluated the safety of two physiotherapeutic programs that combine manual therapy with exercise at home with educational sessions in hemophilic patients with elbow arthropathy concluding that treatment with manual therapy improved joint ROM and reduced pain.

in his study showed the effects brought by the combination of modalities with exercises and only one exercise treatment where the treatment of manual therapy with traction, passive stretching, proprioception, isometric exercises, thermotherapy and local krio therapy improved muscle perimeters and pain impact.

These 4 studies confirm even more and support the studies mentioned above the effectiveness and importance of exercises in hemophilic patients versus a physical sampling.

**F. QUEROL et al. (2006)** [68] evaluated the effects of superficial electrical stimulation on the quadriceps muscle concluded that the group performing electrical stimulation and exercise had an increase in strength in the stimulated leg and the result showed that the superficial electrical stimulation poses no risk to the patients health and is used for therapeutic purposes.

**A. CEPONIS et al. (2013)** [69] in his study evaluated painful episodes in hemophilic patients by rapid skeletal muscle US where it demonstrated that the fast high resolution MSKUS is a valuable point of care image tool to distinguish whether episodes of articular pain is related to bleeding or not.

**R. CUESTA-BARRIUSO et al. (2013)** [70] in his study showed the effects brought by the combination of modalities with exercises and only one exercise treatment where the treatment of manual therapy with traction, passive stretching, proprioception, isometric exercises, thermotherapy and local cryotherapy improved muscle perimeters and pain impact

Looking at these studies and based on the above studies we understand that modalities are an important therapy in the treatment of hemophilia combined with an exercise program to give more compromising effects and that US is one of the modalities that has more effective result in the treatment of hemophilic patients.

**Matthew Alexander et al. (2012)** [71] conclude that although the use of a prophylactic treatment will still have bleeding episodes in hemophilic patients but prophylactic treatment plus modern treatment will significantly reduce the rate of bleeding episodes compared only to prophylactic treatment.

**Rasha A. Mohamed et al. (2014)** [72] concluded that the combination of a routine aerobic exercise treatment with routine apparatus EN Tred is more effective than treatment with ergo metric bicycle alone. Aerobic exercise in a form of a routine treatment in children with hemophiliacs an excellent supplement to the regularly planned physiotherapeutic intervention.

Even this is a study that supports combined physiotherapeutic methods like the above authors who argue that exercises combined with ergo metric bicycle or other apparatus are more effective than just ergo metric bicycle.

**M. K. GARCIA et al. (2009)** [73] demonstrated the overall articular improvement of movement in hemophilic patients when subjected to an active movement in warm water and investigate how it happens looking the physiology of immersion, hydrostatic pressure to compare the results came to the conclusion that active free movement exercises in a hot water pool represent an approach of great importance in order to gain the amplitude of movement in the leg and knee joint preventing dysfunctions arising from hemorrhage predisposing the joint for the functional activities and facilitating muscle strengthens.

## Conclusion

Combining the exercise program with different physiotherapeutic methods is more effective in the treatment of hemophilia A.

Hydrotherapy has a positive effect combined with the ground exercise program.

Sports therapy and continuous activity of patients with hemophilia brings many benefits increase muscle strength and quality of life.

## Recommendations

Medical treatment is only part of good health. From this review literature study we can give some recommendations for improving life and developing activities in daily life in hemophilic patients:

Exercise and stay in shape

Wear protective suitable sport for activity

Perform regular medical checkups including examination of muscle and joints.

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