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Physical activity in patients with hemophilia- advantages and prophylaxis. Current trends

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Abstract: Hemophilia is the most prevalent severe hereditary hemorrhagic disorder. Severe hemophilia symptoms encompass recurrent joint bleeding that can result in degenerative arthropathy. The manifestation of hemophilic arthropathy symptoms markedly diminishes the quality of life for affected patients and considerably restricts their social functioning. The approach to treating hemophilia has been transformed, focusing on preventing hemophilic arthropathy and helping patients lead normal lives alongside healthy individuals. Historically, involvement in sports was discouraged because to the elevated chance of injury and subsequent hemorrhaging; however, contemporary medical understanding advocates for sports engagement to enhance physical and social well-being. Prophylaxis effectively sustains a minimum level of clotting factor activity, enabling people with hemophilia to engage regularly in sports activities.

Aim of the study: The fundamental objective of this research is to clarify the latest management concepts related to hemophilia. Considerable emphasis is placed on the significance and safety of physical activity for persons affected by this disease.

Materials and methods: A review of the literature available in the PubMed and Google Scholar database was performed, using the key words: “hemophilia”, “prophylaxis”, “physical activity”, “gene therapy”, “hemophilic arthropathy”.

Conclusion: Advancements in treatment have increased the life expectancy of those with hemophilia, and the need to optimize health is underscored through preventing chronic conditions and promoting regular physical activity. Recent evidence indicates that physical activity is advantageous and safe in this condition. Additional study is required to formulate specific suggestions for patient education and enhance their long-term quality of life.

Keywords: hemophilia, prophylaxis, physical activity, gene therapy, hemophilic arthropathy.

1. Introduction

Hemophilia is the most prevalent severe hereditary hemorrhagic disorder. It is marked by a deficit or malfunction of blood coagulation factors, specifically factor VIII in hemophilia A and factor IX in hemophilia B [1]. The genes responsible for these vital blood clotting proteins are situated on the long arm of the X chromosome. This condition predominantly impacts males due to its sex-linked recessive inheritance pattern. Hemophilia A is expected to occur in 24.6 per 100,000 male births, while hemophilia B occurs in 5.0 per 100,000 male births [2]. Hemophilia A occurs 6-7 times more frequently than hemophilia B. Globally, there are 1,125,000 individuals diagnosed with hemophilia [3]. In roughly 30-50% of cases, the mutation arises spontaneously, and there is no familial history. Recent attention has been directed towards the subject of hemophilia in female carriers of the hemophilia gene, categorized as women with hemophilia [4].

Hemophilia A and hemophilia B exhibit analogous clinical manifestations. The condition is categorized according on the severity of factor VIII or IX deficiency: severe hemophilia is identified with factor activity below 1% of normal, moderate at 1-5% of normal, and mild at greater than 5% but less than 40% of normal. A recent proposal has introduced a more nuanced classification of illness severity based on bleeding tendency or phenotype, as these two criteria do not consistently align [5]. Severe hemophilia symptoms encompass recurrent joint bleeding and muscle hematomas, which can be either posttraumatic or

spontaneous. Moderate hemophilia is marked by infrequent spontaneous bleeding, with acute bleeding typically resulting from trauma or surgery. However, some patients with moderate hemophilia may experience multiple joint bleeds and substantial joint damage, similar to those with severe disease, suggesting that the correlation between the severity of the deficiency and the clinical manifestations is not consistently valid indicating the participation of multiple causes in the clinical phenotype [6] . Mild hemophilia may result in extended bleeding following dental, post-traumatic, or surgical interventions, spontaneous hemorrhaging into joints and muscles is exceedingly rare. A diagnosis of severe hemophilia phenotype is established when spontaneous bleeding manifests before the child reaches 6 months of age, spontaneous joint bleeding occurs within the first two years of life, there is at least one instance of spontaneous intracranial bleeding irrespective of age, or there are frequent or substantial spontaneous subcutaneous hematomas, or a minimum of 10 bleeding episodes annually [7].

Recurrent acute joint hemorrhages can result in degenerative arthropathy, the predominant consequence in individuals with severe and moderate hemophilia, and even a solitary instance of joint bleeding is adequate to trigger alterations in the joint tissues [8] . Arthropathy manifests as persistent synovial inflammation, accompanied by synovial enlargement, cartilage degradation, and atrophy of the periarticular muscles. This leads to joint instability and an increased vulnerability to additional injuries and chronic pain [9] . The manifestation of hemophilic arthropathy symptoms markedly diminishes the quality of life for affected patients and considerably restricts their social functioning.

Despite hemophilia being an uncommon condition, it is not classified as an orphan disease because to the availability of hemostatic agents and coagulation therapies [3].

In recent decades, the treatment approach for hemophilia has transformed; the objective has shifted from merely preserving life (e.g., preventing life-threatening intracranial hemorrhages) to preventing hemophilic arthropathy and facilitating patients' ability to lead normal lives alongside their healthy counterparts [10] . In mild cases, the primary approach to treatment is symptomatic management, with clotting factors supplied solely during hemorrhagic events or when there is a risk of bleeding, such as during major surgical procedures. Conversely, severe instances necessitate continuous preventative therapy, involving numerous injections of clotting factor concentrates, hospital visits, and regular social absences throughout the patient's lifetime. The illness and its management therefore

impact the daily existence, social engagement, and psychological well-being of sufferers [11]. The inadequacy of treatment adherence and, consequently, the efficacy of prophylaxis has resulted in the introduction of recombinant factor VIII and IX products with prolonged plasma half-life [12]. While undergoing treatment with coagulation factor concentrates, a significant problem may arise: the development of antibodies against certain components of factor VIII/IX, known as inhibitors, which leads to a reduction in its coagulative efficacy. Consequently, recent years have witnessed significant research resulting in the development of novel effective pharmaceuticals [2]. Emicizumab is the inaugural non-factor medication delivered subcutaneously to individuals with hemophilia A, regardless of the presence of an inhibitor. It is a monoclonal antibody that binds activated factor IX to factor X, hence restoring the activity of factor VIII [13]. The introduction of gene therapy represents significant advancement in treatment, addressing the unmet therapeutic demands of hemophilia patients. It encompasses a singular treatment intervention that offers the prospect of complete functional recovery. This is a novel method to hemophilia management; research has been undertaken for only a few years, necessitating patience for comprehensive results [14].

The undeniable advancements in treatment have markedly increased the life expectancy of those with hemophilia, now nearing the average life expectancy of the general population. The necessity to optimize health in patients afflicted by this disease is underscored, particularly through the prevention of various chronic conditions, which can be achieved by sustaining regular physical activity. Historically, involvement in sports was discouraged because to the elevated chance of injury and subsequent hemorrhaging; however, contemporary medical understanding advocates for sports engagement to enhance physical and social well-being. Prophylaxis effectively sustains a minimum level of clotting factor activity, enabling people with hemophilia to engage regularly in sports activities.

2. The advantages of physical exercise among patients with hemophilia

The elevated risk of hemorrhage associated with sports participation led to a prolonged prohibition of these activities for children with hemophilia. The primary reason for eschewing physical activity is the apprehension of hemorrhaging into a joint [15]. Repeated hemorrhage into a joint induces numerous pathological alterations, including hypertrophy of the synovial membrane, hemosiderin deposition, subchondral cyst formation, and cartilage degeneration, culminating in hemophilic arthropathy. This disorder may result in persistent pain and

impairment. Recently, due to substantial medical advancements and access to contemporary bleeding prevention, the perspective on physical activity and sports for persons with hemophilia has undergone considerable transformation. The advantages of frequent physical activity for these patients, tailored to age, overall fitness, the severity of hemophilia, and treatment approach, are now highlighted. The World Federation of Hemophilia states that physical activity may enhance the overall quality of life for persons with this condition.

The advantages of consistent physical exercise on the health of the general populace are widely recognized. The WHO underscores the necessity for children, adolescents, and adults to consistently participate in physical activity of at least moderate intensity, along with exercises that enhance the musculoskeletal system multiple times per week. Individuals with hemophilia are not excluded from these suggestions [16][17].

Appropriately chosen physical exercise diminishes the likelihood of overweight and obesity, hence preventing the onset of circulatory system diseases, metabolic disorders related to carbohydrates or lipids, and potentially lowering the risk of some cancers. Engaging in sports positively influences the psychological development and peer integration of children and adolescents. Supporting the development of coordination, strength, and endurance is also essential. The prevalence of overweight or obesity is reportedly greater among patients with hemophilia compared to earlier generations. Nearly one in three individuals with hemophilia residing in European and North American nations is afflicted by overweight or obesity [18]. This rate is comparable to that of the general population and, in certain subgroups of hemophilia patients, even elevated. In these individuals, sustaining a body mass index within a healthy range is crucial, as it prevents excessive strain on the joints, particularly the knees and ankles. Research indicates that these patients experience a reduction in intra-articular hemorrhage, even with mild weight loss [19].

Physical activity offers additional potential advantages for those with hemophilia. Motor coordination has improved, muscle mass and strength have grown, and the muscle-to-fat ratio has enhanced, contributing to long-term joint stability, a decrease in injuries, and a reduction in acute bleeding episodes. An appropriately chosen array of diverse activities can yield significant advantages for patients with hemophilia [17]. A notable benefit for hemophilia patients stemming from physical exercise is the enhancement of bone mineral density, which is typically diminished in this population relative to their healthy counterparts. Insufficient physical activity in childhood predisposes individuals to inadequate peak bone mass, hence increasing the risk of developing osteoporosis in later life [20]. Factor VIII activity has been observed to elevate during physical effort in both healthy individuals and

patients with coagulation problems, especially those with mild or moderate hemophilia [21]. Research indicates that elevated plasma lactate levels may influence the clearance of factor VIII, hence enhancing coagulation. Elevations in von Willebrand factor levels have been demonstrated to correlate with physical exercise. Regular exercise helps diminish pain perception in people with hemophilia [22].

Considering the substantial apprehensions of parents and the necessity to safeguard their chronically unwell children, they ought to be thoroughly informed, highlighting the numerous advantages, both physiological and psychological. The apprehension regarding bleeding risk can be mitigated through a personalized evaluation of the patient's risk factors, considering the severity of hemophilia, existing prophylactic treatment, current joint condition, and comorbidities, while also reassuring the parent about the professional tailoring of the most suitable exercise regimen. Proper training provided to childhood hemophilia patients can postpone the development of arthropathy by enhancing coordination, flexibility, and muscle strength, hence diminishing joint hemorrhage. The significance of an exercise program should be addressed promptly to foster enduring healthy habits and overall well-being. A customized, monitored fitness regimen has demonstrated a beneficial effect on mental health and social engagement, enhancing overall quality of life [23]. Consequently, it is prudent to encourage physical exercise among the younger patients.

Specialists managing hemophilia patients recognize the necessity for additional study about the advantages and safety of physical exercise for this population. A study is scheduled for early 2025 in Italy [24] to examine alterations in functional capacity following the completion of a personalized fitness program supervised by specialists. This study also will assess the effects of the exercise program on joint mobility and the intensity of kinesiophobia.

The evident advantages of physical activity for patients with hemophilia indicate that sustained participation can result in substantial health enhancements and enduring benefits for this population. Encouraging consistent and organized physical activity for individuals with hemophilia extends beyond only enhancing physical health.

3. Choice of sporting activities in patients with hemophilia

The type and severity of hemophilia play a crucial influence in selecting the appropriate sports activity. The patient's preferences, capabilities, physical state, and the existence of additional chronic conditions are also significant factors. To maximize benefits and mitigate risks, it is essential to evaluate the absence of contraindications, even those not

associated with hemophilia. Consequently, the most effective approach would be multidisciplinary care for a patient with hemophilia. A therapeutic team should comprise a hematologist, orthopedist, physiotherapist, and sports medicine specialist.

The National Hemophilia Foundation (NHF) has suggested a categorization of physical activities according to their associated risks [25]:

- designated as safe: archery, aquatic sports, utilization of cardiovascular apparatus (elliptical trainer, stationary bicycle), angling, frisbee, golf, hiking, tai chi, snorkeling, swimming, and strolling
- designated as dangerous: BMX racing, boxing, diving, soccer, hockey, lacrosse, motorbikes, motocross racing, weightlifting, outdoor rock climbing, rodeo, rugby, motor scooters, snowmobile, trampoline, and wrestling.

Following adequate training and preventive measures, sports activities deemed safe may be routinely advised for persons with hemophilia. The NHF does not endorse dangerous sports for individuals with hemophilia, even with effective preventive therapy. The NHF underscores the critical need of regular physical activity for children with hemophilia, asserting that those who maintain a sedentary lifestyle experience more spontaneous bleeding episodes than their active counterparts [25].

World Federation of Hemophilia (WFH) also compiled a list of safe sports for those with hemophilia, encompassing non-contact activities such as swimming, walking, jogging, golf, badminton, archery, cycling, rowing, sailing, and table tennis. Contact and collision sports, including football, hockey, rugby, boxing, and wrestling, along with high-velocity activities such as motocross and skiing, are discouraged due to the risk of life-threatening injuries, unless the individual is under suitable preventive care and possesses a comprehensive understanding of the associated risks post-participation [26].

The American Academy of Pediatrics (AAP) also recommends regular sports for children with bleeding disorders. Nonetheless, it highlights the significant risk of damage associated with trampoline sports and advises against engaging in boxing. The organization highlights the risk of concussion linked to team sports like American football and soccer, advising vigilant observation of children following their participation in these activities. The MEMO (Movement for individuals with haEMOphilia) has suggested various types and frequencies of physical activity tailored to distinct age demographics of patients [27].

In individuals with optimal joint health, physical activity programs should resemble those advised for their healthy counterparts. A 2020 study in the Netherlands [28] revealed

that hemophilia patients aged 6-18 exhibited high engagement in sports, including high-risk activities, which correlated with low injury rates.

In people with advanced hemophilic arthropathy and the elderly, there is an elevated risk of falls attributable to structural and/or functional joint instability, potentially leading to severe injuries, including head trauma and the danger of cerebral bleeding. Mitigating the risk of falls and associated injuries can be accomplished through consistent engagement in aerobic, strength, balance, and flexibility exercises [29]. Nonetheless, the issues related to hemophilia must always be considered in these instances, particularly in the elderly and individuals with arthropathy, necessitating consultation with suitably experienced physiotherapists.

The table below enumerates suitable sports activities, specifying frequency for both children and adolescents and adults without indications of hemophilic arthropathy.

Children and adolescents		
Every day	• walking to school, walking, riding a bike or non-electric scooter • using the stairs instead of elevator • getting off the bus a stop earlier	Prophylaxis
4-5 times a week	• outdoor and group games • running • helping out with home duties	
3-4 times a week	• high intensity activities, encompassing exercises to strenghten the musculoskeletal system • using the playground devices (slide, swings)	
1-2 times a week	• participating in structured and organized physical exercises	
Adults absent indications of arthropathy		
Every day	• at least 20-25 minutes of moderate aerobic physical activity • travelling by foot or by bicycle instead of by car or moped • getting off the bus a stop earlier or parking further • using the stairs instead of elevator • at least 10 000 steps a day	Prophylaxis
4-5 times a week	• at least 20 minutes of aerobic physical activity (swimming, jogging, brisk walking)	
3-4 times a week	• muscle-strenghtening exercises	
1-2 times a week	• participating in structured and organized physical exercises	

Tabela 1. Suitable sports activities for patients with hemophilia

Patients with hemophilia and inhibitors require particular attention, since their bleeding episodes are more challenging to manage and result in considerable decline in joint function, subsequently affecting their quality of life [30].

Consequently, physical activity in this patient cohort should be advocated, albeit with caution and consistent evaluation of the efficacy of prophylaxis in averting acute hemorrhage. The significant repercussions of poorly organized physical activity must not be overlooked. The suggested exercise regimens must be customized for each individual, progressively increased in duration and frequency, and conducted under the oversight of a multidisciplinary team. The introduction of novel prophylactic medications for bleeding presents an opportunity for individuals with hemophilia and inhibitors to enhance their physical activity and general quality of life. Reports indicate a satisfactory safety level of well structured training in this patient subgroup; nevertheless, randomized clinical research are necessary to validate these findings [31].

In recent years, a diverse array of electronic devices for monitoring physical activity has emerged in the market, assisting patients in performing everyday tasks, attaining objectives, and enhancing motivation. Utilizing them among young patients is advantageous, as they are drawn to technology developments. A compelling technique is integrating physical activity with virtual reality gaming. A study including people with hemophilia demonstrated an enhancement in physical activity through engagement in this sort of entertainment [32].

4. Preventing bleeding related to physical activity in patients with hemophilia

Preventing bleeding related to physical activity in all people with hemophilia, irrespective of illness severity, includes injury prevention. Prior to engaging in sports, the patient must have a comprehensive evaluation of joint and muscle functionality, balance and coordination, respiratory capacity, and overall physical fitness, with our findings considered in selecting the suitable form of physical activity. Appropriate protection measures should be implemented based on the specific sport profile to mitigate injury risk; the utilization of helmets, face masks, shin guards, knee pads, and wrist and forearm guards is advised. Warming up and strengthening prior to engaging in sports is essential [33]. Patients with factor levels of 5% or below exhibit an elevated risk of bleeding during sporting activities. Considering the hazards linked to an individual's athletic pursuits, the experts at the hemophilia treatment center are responsible for enhancing haemorrhagic prophylaxis. The hematologist, as a member of a multidisciplinary team, is responsible for developing individualized prophylaxis regimens (medication type, dosages, intervals) and meticulously

assessing their efficacy based on the physical activities undertaken by the individual with hemophilia.

Prophylaxis can significantly reduce the risk of severe hemorrhage and the frequency of bleeding incidents. An elevated factor level at the time of injury predicts bleeding occurrences [33] . While online resources, such as the National Bleeding Disorders Foundation [34] , provide information, target factor levels for different activities are based only on expert opinion, necessitating supporting data; recent papers suggest that research in this domain is ongoing [35] [36].

Long-term prophylaxis is recommended for all patients with severe hemophilia and for those with moderate hemophilia exhibiting a severe phenotype. Primary prophylaxis refers to injections administered prior to the second joint bleed and before the age of three, whereas secondary prophylaxis is initiated following the occurrence of at least two joint bleeds. This technique effectively safeguards the majority of children with severe hemophilia from developing arthropathy. The dosage of the formulations is individually determined based on the evaluation of their efficacy in a specific patient. The cornerstone of hemorrhage prevention is consistent intravenous administration of the deficient coagulation factor. Standard plasma-derived concentrates generally necessitate frequent infusions due to their comparatively brief half-life, typically ranging from 8 to 12 hours. This frequent dosage schedule frequently imposes a considerable burden on patients, impacting their quality of life and adherence. To address these problems, recombinant products with prolonged half-lives have been created to circulate longer, therefore extending the dose interval to every 3 to 7 days, contingent upon the specific product and the patient's pharmacokinetics. The introduction of these medications has significantly enhanced the management of hemophilia A, providing patients with increased flexibility, decreasing the frequency of infusions, and potentially augmenting adherence and overall quality of life [37]. The first of these drugs to be introduced in 2014 were efraloctocog alfa and eftrenonacog alfa. Pharmacokinetic studies have recently emerged as a crucial instrument in the customized therapy of hemophilia. Their objective is to tailor prophylaxis to the patient, considering age, body weight, and kind of factor concentrate. Utilizing patient data, algorithms forecast the duration a patient will sustain therapeutic levels of clotting factors, thereby enhancing treatment regimens and alleviating the total therapeutic burden.

In 2024, the findings of a notable study conducted in Thailand [38] involving individuals with moderate to severe hemophilia A were released. The study sought to evaluate the impact of moderate to vigorous intensity physical activity on patients undergoing

prophylaxis with extended half-life clotting factor concentrates, grounded in pharmacokinetics. Each patient was allocated a personalized moderate or vigorous intensity physical activity regimen designed by sports medicine experts. The combination of prophylaxis and exercise can decrease the frequency of bleeding episodes, which correlates with a reduction in annual factor concentrates intake. The incorporation of a personalized exercise regimen during suitable prophylaxis enhances the efficacy of hemophilia treatment.

Certain individuals undergoing replacement therapy may acquire antibodies that neutralize the clotting factors, referred to as inhibitors, thereby diminishing the therapy's efficacy. In such instances, bypassing drugs like activated prothrombin complex concentrate (APCC) and activated recombinant factor VIII may be utilized; nevertheless, their regular administration is necessary for efficacy, imposing a considerable strain on the patient [39]. Consequently, the subsequent objective was to develop contemporary pharmaceuticals that would remain efficacious in patients exhibiting an inhibitor. The inaugural medicine of this kind was emicizumab, a monoclonal antibody that binds to active factor IX and factor X, circumventing the necessity for factor VIIIa in thrombin production. This molecule possesses a half-life comparable to that of immunoglobulin G and can be administered subcutaneously on a weekly or monthly basis, ensuring hemostatic efficacy while alleviating the treatment burden for persons with hemophilia A [13]. Clinical trials of emicizumab prophylaxis have demonstrated efficient hemostatic control and favorable tolerability in individuals with hemophilia A, regardless of the presence of inhibitors [40]. The current TSUBASA study [41] is assessing the correlation between physical activity and bleeding, alongside safety and quality of life, in individuals with hemophilia. An initial preventative regimen utilizing emicizumab in a Japanese population. Preliminary findings from this investigation indicate that participants administered emicizumab exhibited no bleeding linked to physical exercise. Two novel monoclonal antibodies are presently undergoing clinical testing: NXT007 and denecimig (or Mim8) [42][43]. The aforementioned medications—clotting factor concentrates and emicizumab—diminish the danger of bleeding but do not eradicate it entirely; thus, hemophilic arthropathy and its related challenges persist as an issue. Reports indicate comparable rates of bleeding, particularly joint hemorrhage, in those with hemophilia who underwent emicizumab prophylaxis and those who got prophylaxis with clotting factor concentrates [44] [45].

Antibodies against tissue factor pathway inhibitor (TFPI) represent an additional preparation injected subcutaneously to avert hemorrhage. TFPI is a crucial modulator of the extrinsic thrombin production pathway and functions to diminish TF expression.

The inhibition of TFPI facilitates coagulation and enhances thrombin production. Two anti-TFPI molecules are undergoing clinical development: concizumab (authorized in Canada) and marstacimab (approved in the United States), however the development of a third molecule, befovacimab, has been discontinued due to the occurrence of thrombi observed in first clinical trials. These compounds are efficacious in individuals with hemophilia A and B, both with and without inhibitors [46]. Fitusiran is an antithrombin-antisense oligonucleotide that diminishes the expression of antithrombin [47].

Gene therapy provides promise for a viable solution. Three gene treatments have been granted FDA approval: one for hemophilia A (valoctocogene roxaparvovec/Roktavian) and two for hemophilia B (etranacogen dezaparvovec/Hemgenix and fidanacogene elaparvovec-dkzt/Beqvez) in the years 2022, 2023, and 2024, respectively [48]. This therapy will comprise a singular therapeutic intervention designed to provide a lifelong effect. A suitably altered gene (transgene) is to be introduced into the recipient's cells to facilitate the production of the absent clotting factors. Transgene carriers include of viral or non-viral vectors. Hemophilia serves as an exemplary model for gene therapy due to its classification as a monogenic disorder, characterized by a distinct phenotype and a broad treatment window. The endorsement of these gene therapies was predicated on efficacy studies demonstrating a decrease in bleeding relative to previous treatments involving clotting factor replacement products, and acceptable safety profiles [49]. The objective of gene therapy for hemophilia was to create a medication that would achieve enduring remission of illness symptoms with a single administration, so liberating the patient from recurrent healthcare interactions. This contemporary treatment presents several challenges, including liver dysfunction post-administration, the risk of carcinogenesis from genomic integration, a decline in factor expression levels approximately three years after treatment, and the inability to repeat gene therapy [50].

Despite significant advancements in hemophilia therapy, it is important to acknowledge that none of the presently licensed medications or those undergoing clinical trials can prevent the genetic transfer of the trait to offspring [10].

5. Fundamental management strategies for addressing hemorrhage in people with hemophilia

Notwithstanding adherence to instructions and consistent administration of bleeding prevention, bleeding related to sporting activities in individuals with hemophilia may nonetheless occur.

The fundamental principle in managing acute bleeding in hemophilia is to attain swift and vigorous hemostasis, preferably within two hours of symptom onset, with rectification of the coagulopathy [26] . The desired factor activity level is contingent upon the site and intensity of the hemorrhage, the anticipated half-life of the given product, and the existence of concomitant injuries.

The primary focus of management is the prompt commencement of treatment for severe or life-threatening hemorrhage in a patient with hemophilia, including instances arising from head trauma, which must be addressed in a hospital emergency room, even prior to the completion of diagnostic assessment [51] . Severe or life-threatening hemorrhaging encompasses any of the following: central nervous system, ocular, hip, muscular (e.g., iliopsoas), abdominal, gastrointestinal, and respiratory systems. This include bleeding severe enough to cause anemia and perhaps necessitate a blood transfusion, any extended bleeding that fails to respond enough to home treatment, and any significant damage, such as a fall from a height. In instances of significant hemorrhage, factor activity levels must be continually upheld above 50 percent. The cornerstone of treatment is the provision of the deficient clotting factors (factor VIII or IX). If the patient lacks personal preparation, recombinant concentrate is favored. Standard plasma concentrate may be utilized in the absence of recombinant concentrate. In the event of challenges in acquiring the selected agent, the readily available product should be utilized without unnecessary delay. The guideline is to avoid depleting the agent; administering an excess is permissible to prevent medication wastage. It is important to remember that in hemophilia A, emicizumab does not address severe bleeding once it has transpired; factor VIII concentrate should be administered instead [52] . Patients exhibiting high-titer inhibitors (>5 Bethesda units at any point in their history, irrespective of current titer) typically necessitate a bypassing agent (recombinant activated factor VII or activated prothrombin complex concentrate). In patients administered efanesoctacog alfa, which possesses a half-life of about 48 hours, supplementary factor should not be administered if the patient has undergone a preventive infusion during the preceding 2 days. Nonetheless, this does not supplant clinical judgment in exceptional situations, such as cerebral hemorrhage, where supplementary dosages may be administered as required according to factor VIII activity. Delayed hemorrhaging following a head injury may manifest within three to four weeks post-event. Individuals with head injuries or significant hemorrhaging should be informed about the indicators of delayed or recurrent bleeding, the dosage regimen for the factor if it arises, and the criteria for obtaining medical assistance to ensure that treatment commences at the initial signs of recurrent bleeding.

Patients with hemophilia frequently experience joint bleeding, leading to a restricted range of motion, edema, increased temperature, or atypical sensations such as tingling, which commonly precedes pain. In certain cases, a "target joint" may manifest, characterized by recurrent hemorrhagic episodes and persistent inflammatory alterations. The absent coagulation factor concentrate must be supplied promptly at the initial manifestation of joint bleeding symptoms (e.g., onset of tingling, discomfort, or characteristic signs of joint bleeding). The dosage is contingent upon the particular joint and its designation as a target joint, necessitating the administration of greater dosages of factor concentrate and an extension of therapy as appropriate. Arthrocentesis is unnecessary for diagnosing joint hemorrhage in individuals with hemophilia. Additional measures to mitigate bleeding, pain, and inflammation encompass refraining from weight-bearing activities or utilizing the affected limb, applying ice, and immobilizing and/or splinting (RICE protocol). Bleeding from both the hip and iliopsoas should be regarded as significant hemorrhagic events, as should bleeding in any region susceptible to compartment syndrome, including areas near the wrists, hands, and the anterior aspect of the lower leg. Most joint bleeds can be treated at home.

Medications that compromise platelet function, particularly most NSAIDs and aspirin, should be avoided. Paracetamol, selective COX-2 inhibitors, and opioids should be utilized for analgesia [53] . Following the cessation of joint hemorrhage, it is crucial to initiate a rehabilitation regimen that encompasses a progressive enhancement of range of motion, weight-bearing activities, and strength training. In instances of hemorrhage into peripheral joints (knees, elbows, or ankles), the factor activity level must be sustained at a minimum of 40 to 50 percent. Musculoskeletal ultrasonography (POC-MSKUS) is widely utilized in the diagnosis of acute joint hemorrhage [54] . This examination may also prove beneficial during arthrocentesis.

Muscle hemorrhages may manifest as pain, rigidity, discomfort, or edema. Soft tissue hemorrhages in muscle groups including the shoulder, forearm, wrist, palmar hand, and anterior or posterior tibial compartments may lead to compartment syndrome, resulting in compression of the neurovascular bundle. This may correlate with tingling, numbness, and, in severe instances, the absence of distal arterial pulses. Therapy should commence promptly, either at the initial manifestation of symptoms or immediately following the accident or trauma. For severe muscle hemorrhages, a minimum factor activity level of 50 percent is suitable; however, elevated peak values are typically employed for such conditions. Muscle

hemorrhages can lead to a substantial decrease in hemoglobin levels, necessitating ongoing monitoring of hemoglobin until it is evident that the bleeding has ceased.

Minor hemorrhaging, such as epistaxis or cutaneous bleeding, can be managed with localized interventions, such cryotherapy, compression, or elevation. Local treatments, such as antifibrinolytics or other supplementary local therapies, may prove beneficial. Occasionally, episodes of epistaxis may be prolonged or may lead to significant blood loss, necessitating replacement therapy.

6. Summary

Hemophilia is a severe hereditary hemorrhagic disorder characterized by a deficit or malfunction of blood coagulation factors, specifically factor VIII in hemophilia A and factor IX in hemophilia B. The condition predominantly affects males due to its sex-linked recessive inheritance pattern. The condition is classified according to the severity of factor VIII or IX deficiency, with severe hemophilia exhibiting symptoms such as recurrent joint bleeding and muscle hematomas. Moderate hemophilia is marked by infrequent spontaneous bleeding, while mild hemophilia may result in extended bleeding following dental, post-traumatic, or surgical interventions.

The approach to treating hemophilia has been transformed, focusing on preventing hemophilic arthropathy and helping patients lead normal lives alongside healthy individuals. Recent medical advancements have led to a shift in perspective on physical activity and sports for children with hemophilia. The World Federation of Hemophilia states that physical activity can enhance the overall quality of life for this population. Consistent physical exercise is essential for children, adolescents, and adults, as it reduces the likelihood of overweight and obesity, prevents circulatory system diseases, and potentially lowers the risk of some cancers. Engaging in sports positively influences the psychological development and peer integration of children and adolescents, supporting coordination, strength, and endurance. Physical activity also improves motor coordination, muscle mass and strength, and muscle-to-fat ratio, contributing to long-term joint stability, decreased injuries, and reduced acute bleeding episodes. Regular exercise helps diminish pain perception in people with hemophilia, enhancing their emotional and social well-being and self-esteem.

Specialists managing hemophilia patients recognize the need for further research on the advantages and safety of physical exercise for this population.

Hemophilia prevention involves injury prevention, including evaluating joint and muscle functionality, balance, coordination, respiratory capacity, and physical fitness before sports. Appropriate protection measures, individualized prophylaxis regimens, and pharmacokinetic studies are crucial for personalized therapy. Modern medications, such as emicizumab and antibodies against tissue factor pathway inhibitors, have been developed to reduce clotting factor replacement therapy effectiveness. Gene therapy offers potential solutions for hemophilia A and B, but faces challenges like liver dysfunction, factor expression decline, and the inability to repeat gene therapy. None of the licensed medications or those undergoing clinical trials can prevent genetic transfer of the trait to offspring.

The primary objective in managing bleeding in a patient with hemophilia is to attain prompt and effective haemostasis within two hours of symptom onset, while resolving coagulopathy. The management and requisite factor activity levels are contingent upon the location and severity of the hemorrhage, the anticipated half-life of the product, and the existence of concomitant injuries. It is crucial to evaluate if the hemorrhage poses a life-threatening risk (e.g., bleeding following a cranial injury), as medical intervention should occur in a hospital emergency room. Joint bleeding is common in individuals with hemophilia, leading to restricted range of motion, edema, increased temperature, or atypical sensations such as tingling. Additional measures to mitigate bleeding, pain, and inflammation include refraining from weight-bearing activities, applying ice, and immobilizing and/or splinting. Musculoskeletal ultrasonography (POC-MSKUS) is widely used in diagnosing acute joint hemorrhage.

Advancements in treatment have increased the life expectancy of those with hemophilia, and the need to optimize health is underscored through preventing chronic conditions and promoting regular physical activity. Additional study is required to formulate specific suggestions for patient education and enhance their long-term quality of life.

Disclosure

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