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Physical Activity Guidelines in Patients with Hemophilia: Benefits, Barriers, and Recommendations

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Introduction

Hemophilia describes a group of genetic disorders that lead to the dysfunction of proteins involved in the clotting cascade.[1] These proteins, also known as coagulation factors, are required to form clots and ultimately cessate bleeding. Although there are three distinct forms of congenital hemophilia (hemophilia A, hemophilia B, and hemophilia C), the affected proteins (factor VIII, factor IX, and factor XI, respectively), are within the same pathway leading to the formation of a clot. In condensed terms, each of these factors play a role in the ultimate activation of thrombin, which activates fibrinogen to form a fibrin clot and solidify the platelet plug. In patients with hemophilia, the affected protein is absent or deficient, leading to prolonged bleeding times.

Hemophilia A and B are the most common forms of hemophilia with an incidence of 1 in 5,000 and 1 in 25,000, respectively.[1] Because the genes for both factors VIII and IX are present on the long-arm of the X chromosome, hemophilia A and B follow an x-linked inheritance pattern and are much more common in males, though some female carriers may show manifestations of the disorder. Additionally, hemophilia may be secondary to spontaneous mutations, but this is relatively uncommon.

The manifestations of hemophilia A and B are essentially identical, however, each disorder can be categorized into mild, moderate, or severe based on the patient's baseline level of factor.[1] Mild hemophilia is defined as having greater than 5%, but less than 40%, of normal levels of factor VIII or IX. These patients do not typically develop spontaneous bleeds, but will bleed due to significant trauma. Moderate forms of hemophilia, those with factor levels between 1 to 5% of normal, also do not typically bleed spontaneously, but may with trauma, surgery, or

dental procedures. Finally, the most severe manifestations of hemophilia, those with factor levels less than 1% of normal, will develop spontaneous and recurrent bleeds without obvious trauma.

Unlike disorders of primary hemostasis, such as von Willebrand disease, which presents with mucosal bleeding or easy bruising, patients with hemophilia present with patterns of delayed bleeding. Serious sites of bleeding in patients with hemophilia include joints (hemarthrosis), deep compartment muscles such as iliopsoas, calf, and forearm, and within mucous membranes in the mouth, gums, nose, and genitourinary tract.[2] Life-threatening sites of joint bleeding including intracranial hemorrhage, neck/throat, and gastrointestinal. After initial presentation, screening tests may be done to identify potential sources of bleeding. Diagnosis of hemophilia is suspected in patients with a prolonged activated partial thromboplastin time (aPTT) that corrects upon 1:1 normal plasma mixing.[1] The confirmation of a definitive diagnosis can be made through factor assay analysis.

Proper management requires comprehensive care with prevention of bleeding as well as prompt management of acute bleeding.[2] Prophylaxis with factor concentrate is the current gold standard of care and, though expensive, gives patients the best outcomes for joint function and reduction of spontaneous joint bleeding. Recommended dosing of infusions range from 15-40 IU/kg per dose, two to three times per week, though should be individualized based on the patient. When possible, this is managed through a home therapy setting using self-infusions. Additionally, patients should seek prompt treatment in cases of severe to life-threatening bleeding. Modalities may include “on demand” factor replacement (at home in mild to moderate cases), joint splinting, ice, compression, and elevation. In more serious bleeds, patients may need to present to an emergency setting for more invasive modalities.

Though current prophylactic treatments are quite effective, this has not always been the case. Prior to the 1970s, when factor concentrations were made available, it was recommended that patients with hemophilia utilize a different strategy to prevent bleeds: the avoidance of physical activity.[3] This strategy was meant to minimize the impact on patient's joints, decreasing their episodes of hemarthrosis. By limiting these episodes, providers hoped to prolong the time to inevitable joint damage and disability.[4] However, the quality of life in these patients, as well as their overall health, suffered.[3] Fortunately, with the advancement of treatment options, the World Federation of Haemophilia now recommends physical activity with some stipulations.[2] Specifically, they recommend that the focus should be on physical activities that promote "muscle strengthening, coordination, general fitness, physical functioning, healthy body weight, and self-esteem" with a focus on non-contact sports and avoidance of high contact and collision sports. The benefits of physical activity in patients with hemophilia, who are on proper prophylaxis and performing under the above guidelines, are discussed below. Additionally, several barriers to compliance to these recommendations are identified.

Background

Benefits of physical activity

As mentioned above, prior to the introduction of factor concentrates, prophylaxis for bleeding in patients with hemophilia was strict avoidance of activities that may lead to joint trauma. Unfortunately, avoidance of physical activity in patients with hemophilia come the same increased morbidity and mortality associated with inactivity in the general population. Further, it is now known that physical activity will not only benefit the overall health and well-being of the patient, including improved cardiovascular and muscular fitness, bone health, cognitive function,

sleep and decreased risk of heart disease, stroke, high blood pressure, diabetes mellitus type 2, and certain cancers, but may also improve outcomes specific to a hemophilia diagnosis.[5]

Decreased joint destruction

Perhaps the most important benefit of physical activity in patients with hemophilia who utilize proper prophylaxis is the improvement of joint outcomes. Infrequent exercise, especially in patients prone to trauma, such as in patients with hemophilia, leads to weakness and instability, causing increased risk for stress on the joint and further muscular atrophy.[6] This process, without proper intervention, causes further instability, risk of lesions, and ultimate pain and immobility. Fortunately, in a review article by Gomis et al., it was shown that physical activity can help prevent this destructive process in patients with hemophilia by improving strength, proprioception, and range of motion.[7] Several types of exercise, including, but not limited to "strength exercises for 1 year," "strength with low resistance for 6 months," "general exercises for postural training, coordination and proprioception and kinetics therapy for two sessions a week for 1 hour and 3 months," and "weights, swimming, cycling, martial arts, golf, walks, basketball, yoga thrice per week for 30 minutes minimum" showed positive improvement in each of these areas, suggesting a decrease in future injury risk and subsequently, decreased joint destruction.

Not only does physical activity improve muscle and joint activity in order to slow the vicious cycle of joint destruction, but exercise also has an association with decreased acute bleeding episodes overall, again, preventing further joint damage and hemophilic arthropathy.[7] The same review by Gomis et al. reviewed several observational studies, and though most had small sample sizes and lacked a control group, the results suggested that physical activity reduced overall bleeding risk.[7] Similar results have been seen in post-operative patients and

strengthen the argument that physical activity is beneficial in the prevention of acute bleeding episodes. For example, Franco et al. (2006) found that there was a 68% decrease in knee hemarthrosis in patients who participated in strength exercises, ROM, and proprioception of the lower extremity following arthroscopic knee surgery.[8] Physical activity in patients with hemophilia prevents joint damage by both improving long-term joint functioning as well as by reducing acute bleeding episodes.

Reduction of BMI

The prevalence of overweight and obese patients with hemophilia are comparable to rates in the general population and are reported as high as 43.3% in adults and 26.9% in children and adolescents.[9] Though all patients can benefit from weight maintenance through physical activity, being at ideal body weight is especially important for patients with hemophilia.

The benefits of physical activity in terms of joint outcomes are two-fold. Not only does exercise lead to improved strength and decreased acute bleeds, which both result in less joint destruction, but it also improves weight management. With obesity being the greatest modifiable risk factor for osteoarthritis, it is essential that patients with hemophilia use this to their advantage to further improve their joint health.[10] In a review specifically discussing the effects of BMI on joint destruction in patients with hemophilia, it was noted that increased weight is related to hemophilic joint disease and causes decreased active range of motion in the lower extremities.[11] Additionally, the authors found and that obese patients tend to have more joints with arthropathy than non-obese patients. Though these results reflect what was already known in the general population, it is important that they could be replicated in a population of patients with hemophilia.

Weight loss due to physical activity is also beneficial from a management perspective. Because factor dosing is typically based on weight, overweight and obese patients are often "over-treated" because blood volume is overestimated when using this dosing calculation method.[11] Not only can this cause adverse health outcomes, but may also have a negative economic impact. One center in the United States estimated a loss of nearly $1.5 million per year due to overtreatment with factor prophylaxis. Finally, it has been observed that overweight patients may have issues with home infusion due to difficulties with venous access.[9]

Improved quality of life outcomes

Another important aspect of physical activity in patients with hemophilia is the potential for improved health-related quality of life (HRQoL), a measurement based on health diagnoses, treatments, and personal characteristics.[3] Unfortunately, because patients with hemophilia cannot change their diagnosis, it is important that patients optimize HRQoL factors that they *can* control. The "personal characteristic" determinant can be increased through improved social support, self-esteem, anxiety, and depression, all of which can be achieved with the recommended amount of physical activity. First, participation in sports activities gives patients with hemophilia the feeling of being part of a larger group through strengthened group cohesion and increased number of friends.[3,12]

Additionally, improvements in self-esteem have been reported. In one study, it was found that prior to starting a swimming routine, 60% of participants had low self-esteem.[12] However, at the end of the ten month period, no participants had low self-esteem, and 88% had a high level of self-esteem. This same study showed that participants had decreased stress and were able to better control their anxiety after consistent physical activity. As in patients without chronic

medical diagnosis,[13] physical activity has been shown to improve quality of life through improved mental health in patients with hemophilia.

Barriers to adherence to physical activity regimens

Although the benefits of physical activity in patients with hemophilia are expansive, there are many barriers to adhering to these recommendations. Unfortunately, misunderstanding of the disease process and preventative nature of this management options is a large factor in the avoidance of physical activity.[14] This may be due to previous recommendations that patients attempt to avoid physical activity, causing confusion on whether physical activity is detrimental or beneficial.[14]

The lack of knowledge was shown in a national survey done by the National Hemophilia Foundation and the Centers for Disease Control and Prevention.[16] In this survey, patients with hemophilia were asked about their knowledge, attitudes, and behaviors towards various prevention strategies, including physical activity. Performed in 2000, it was found that 36% of youth patients with hemophilia believed that joint disease cannot be prevented. Additionally, 60% responded that they avoid physical activity. This suggests that patients have a lack of knowledge regarding the protective measures that physical activity has on joint maintenance, and are possibly avoiding it due to these false beliefes.

Though this survey was able to suggest that knowledge is a large contributor to non-adherence, Bérubé et al. discussed the possible psychosocial factors to explain these adherence issues.[16] The authors found that although the "intention" was high, the patients' attitudes were neutral: patients often reported that they did not see the "usefulness" of performing regular physical activity. This finding is consistent with that of the 2000 survey: though patients may have the intent to follow the recommendations made by their healthcare providers, they lack the

knowledge to understand the importance of this preventative management option. The authors note that a large reason for this may be caused by parents over-stressing the risks of avoiding non-recommended exercise activities.[16] Of course, it is warranted that parents worry about dangerous physical activity, as this could lead to life-threatening injuries, however, this may be contributing to decreased communication to patients regarding the benefits of physical activity in the management of their disease.

Unfortunately, this is one of the few studies specifically discussing reasons for non-adherence to physical activity recommendations. However, there are several publications that discuss non-adherence to management for hemophilia overall, which includes treatment with prophylaxis as well as preventative measures. These papers report qualitative measures from self-reports of healthcare providers and patients and include barriers such as being "forgetful", not having enough time, and the disappearance of symptoms.[15] Additionally, the barriers to being active for the general population can also be applied to patients with hemophilia, and include reasons such as lack of time, social influences, lack of influence, lack of willpower, fear of injury, lack of skill, and lack of resources.[5]

Overall, the misunderstanding on the benefits of exercise, which may be influenced by fear of injury while practicing non-recommended physical activity, is a large barrier. This is likely exacerbated by the previous recommendations against physical activity in patients with hemophilia. Additionally, self-reported reasons, similar to what would be found in the general public regarding a lack of physical activity, are contributing factors.

Methods

The methods for this paper were two-part. First, a review of the literature was performed by searching the electronic databases PubMed, EBSCOhost, Academic OneFile, BioMed

Central, MEDLINE, ScienceDirect, World Federation of Hemophilia, and the National Hemophilia Foundation. The following search terms were used: hemophilia physical activity guidelines, physical activity and hemophilia, quality of life and hemophilia, risks of physical activity hemophilia, obesity and hemophilia, mental health and hemophilia, and joint outcomes hemophilia. Search criteria included peer-reviewed articles and anything within the past 10 years. This search was done between May 6, 2019 to July 26, 2019. Additionally, the discussion section was written by integrating the literature searches above with my experience while attending bleeding disorders camp at Camp Courage from July 7, 2019 to July 12, 2019.

Discussion

Through a literature review of peer-reviewed articles, the benefits of physical activity in patients with hemophilia, as well as potential barriers to adherence to the recommendations, were discussed above. To add to these results, I will integrate the experiences that I had during my participation in a 5-day experience alongside pediatric patients with hemophilia at summer camp. Though camp was only a small window into the everyday lives of these children, I feel fortunate that I am able to utilize these interactions to analyze the objective data with an understanding of the patient experience. For the most part, my time at camp mirrored the literature and strengthened the argument towards increasing awareness of physical activity benefits for patients and families of patients with hemophilia.

Because the time I spent at camp cannot take the place of a long-term observational study, it is hard to say, based solely on my experience, whether the campers had improved joint outcomes if they met the physical activity recommendations. However, I can attest to the fact that the children were very astute to their disorders and were able to, for the most part, judge when they had pushed their boundaries. When injuries did come to light, they communicated

their concerns to a health center volunteer so that proper treatment could be initiated. Though some activities would likely be considered in the "not highly recommended" physical activity category, such as capture the flag, I think that the benefits of allowing the kids to be active in a safe place with others with similar disorders, as well as their amazing awareness towards potential symptoms, far outweigh the risks. Certainly, when they do not have as easy of access to healthcare providers when they are at home or school, recommendations for activity levels may need to be looked into a little more closely, depending on the patient. Though patients should try to become interested in activities that are recommended, I think any activity is better than none, and the benefits of decreased future joint damage and reduced BMI will likely overcome the long-term risks of inadequate exercise.

The biggest benefit that I can speak towards for the kids at camp was my observation of improved quality of life that they achieved while playing in a group setting. Of course, the benefits of camp do not only relate to physical activity, but this was a huge motivator for the children to make friends in a group setting and to feel a more cohesive bond towards their peers. For those who is was their first year attending camp, there were no worries about making friends after the first night of capture the flag. The team aspect of these games allowed everyone to be included, and showed me the social benefits of physical activity. This is especially important for those with a chronic disease, as many already feel that they are not part of a "normal" group. These positive feelings bring the kids back year after year, and some campers even return to become counselors. The social benefits of being part of a larger group were undeniable, and should certainly be considered when discussing the advantages of physical activity in patients with hemophilia.

Conclusion

With the advancement of prophylactic treatment and management options for patients with hemophilia comes the ability for healthcare providers to recommend higher levels of physical activity. Fortunately, there has been increasing research regarding what these recommendations should be, and how providers should educate their patients. Though these recommendations are not requirements for patients, they are often used for guidance towards safe participation.

In 2017, the National Hemophilia Foundation updated their recommendations for physical activity in patients with hemophilia.[5] This publications notes that patients with mild to moderate bleeding disorders, who are not receiving prophylaxis, are typically able to participate in more vigorous activity than those with severe bleeding disorders who are not on prophylaxis. However, bleeds are typically not as obvious in patients with milder forms of hemophilia, so they should be very observant when watching for symptoms. Additionally, the history of bleeding frequency during exercise can be used as a tool to determine prophylaxis need. In patients with mild to moderate hemophilia who are on prophylaxis due to a long bleeding history, as well as in patients with severe hemophilia on prophylaxis, physical activity can be continued per the recommendations as long as the patient is not recovering from an acute bleed, and is utilizing their prophylaxis correctly.

The National Hemophilia Foundation also recommends that patients meet with their healthcare provider for a musculoskeletal evaluation before starting a new activity.[5] During that visit, providers and patients should determine how to identify and manage bleeding episodes. Additionally, they recommend that conditioning should be performed prior to higher level activity in order to help prevent injury. This should be taken slowly and increased over a time period as agreed upon with the healthcare provider.

Further, the foundation gives guidelines for considering what type of physical activity should be chosen. Patients should take into account their interests, goals, personal bleeding history, risks and benefits of the potential activities, current activity level, and team versus individual activities.[5] Once the patient has an idea of what type of activity they may want to start, they can use the "Playing It Safe Physical Activity Ratings" to determine which option may be safest for their situation. This document rates various activities on a scale from 1 to 3 in 0.5 increments. The scale has values of low risk, low to moderate risk, moderate risk, moderate to high risk, and high risk. Ratings from 1 to 2 indicate that the benefits of the exercises likely outweigh the risks, whereas sports with ratings of 2.5 to 3 should be discussed in great detail with healthcare providers prior to initiation. Additionally, the patients age, position they may be interested in playing, and competitiveness of the league they intend to join should be considered as this scale is an overview of the sport or activity in general and may differ based on the participation of the patient.

Finally, the Playing It Safe publication includes a quiz that can be used by patients to determine their barriers against being active.[5] This quiz can be used by those who are having a hard time getting started on being physically active, and the results can aid patients in motivation. They also give a link to the "Steps for Living" hemophilia website which gives tips for increasing activity in patients with bleeding disorders at every stage of life.

With benefits in general health, joint maintenance, BMI reduction, improved management outcomes, and increased quality of life, physical activity should be recommended for all patients with hemophilia. As part of the healthcare team, patients, families, and providers should utilize the accepted recommendations to identify activities that are best for their situation. Although getting started is often one of the hardest parts to becoming physically active, there are

many resources that can aid in overcoming barriers, with educating patients on the benefits of exercise being one of the best tools for providers.

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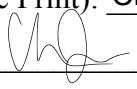
Author's Signature:  Date: 08-15-2019

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