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Research Article

Optimal Management of Haemarthrosis in Patients with Haemophilia in Emergency Room

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Abstract

The hallmark of haemophilia is the musculoskeletal bleeding. Acute haemarthrosis is the most common bleeding event in Patients with Haemophilia (PwH). Most of PwH have knowledge of initial measures that needs to be taken ina bleeding, such as immobilization, place local ice, rest, etc., although these measures, some patients have to go to the Emergency Room (ER) to continue treatment. With this rises the concern about the lack of acknowledge about haemarthrosis in PwH and its treatment by medical staff in the ER, since the initial management is pivotal to relief pain, restore motility and prevent chronic synovitis. This paper reviews the management of haemarthrosis in the ER and propose an algorithms tool to evaluate and treat an acute haemarthrosis in PwH in the ER.

Keywords: Haemarthrosis management; Articular bleeding; Joint bleeding management; Haemophilia; Emergency room

Abbreviations

PwH: Patients with Haemophilia; ER: Emergency Room; HA: Haemophilia A; HB: Haemophilia B; CFC: Coagulation Factor Concentrate; BU: Bethesda Unit; WFH: World Federation of Hemophilia; FEIBA: FVIII Inhibitor Bypassing Activity; HTC: Haemophilia Treatment Center

Introduction

Haemophilia is an inherited bleeding disorder characterized by deficiency of clotting factor VIII: Haemophilia (HA) or Factor IX: Haemophilia B (HB). Haemophilia severity is classified based on plasma levels of factor (VIII or IX). Is severe if the level of factor is less than 1% in untreated state, moderate between 1% to 5% and mild if >5% to 40%, and is related with bleeding phenotype [1,2]. The main bleeding manifestations are in musculoskeletal system (80%).

Treatment in PwH severe or moderate can be on-demand or prophylactic (with two or three administrations per week), in order to prevent spontaneous bleeding episodes. Based on age of the first haemarthrosis and joint disease have been proposed three categories of prophylaxis (primary, secondary and tertiary). Despite effective prophylactic regimen, acute haemarthrosis remains as the main bleeding manifestation in PwH that will require appropriate management on the first hours after bleeding onset [3]. Management of PwH with bleeding is a challenge to emergency medical staff because they have had little, if any, experience with such patients; any delays in diagnosis and treatment with Coagulation Factor Concentrate (CFC) replacement implies a risk of permanent damage and chronic arthropathy. Evidence suggests suboptimal management of bleeding disorders in ER and literature in this setting is limited. As the majority of visits of PwH to ER are for acute bleeding, mainly haemarthrosis, an appropriate management by medical staff in ER is critical to limited morbidity [4].

This paper reviews the optimal management by non-hematologists medical staffs who face PwH and acute haemarthrosis in the emergency room through an algorithm tool that is easy to check up and apply. This work describe the basic definition in haemophilia background, initial approach and main resources to the optimal management of haemarthrosis, which included CFC infusion in PwH (with or without inhibitor), pain treatment, radiologist assessment and when to request the hematologist evaluation or hospitalization. The algorithm suggested not including other topics as fractures or physiotherapy.

Materials and Methods

Using the electronic database PubMed from 2010 to 2021 a research was made reviewing the guidelines and reviews of hemophilia that includes management of acute haemarthrosis including paper writing in English or Spanish using the keywords haemophilia, haemarthrosis, joint bleeding, management or treatment and emergency room or department.

Definitions and background

The hallmark of bleeding in severe haemophilia is recurrent joint bleed (haemarthrosis), mainly affecting large synovial joints, which involves two connected bones into a capsule with synovial tissue on the inside and surrounded by ligaments, such as knee, ankles and elbows in over 80% of cases [5]. Clinical manifestations of an acute haemarthrosis includes an unusual sensation in the joint that involves any of the following symptoms: increasing swelling or warmth of the skin over the joint, increasing pain, or progressive loss of range on motion or difficulty in using the limb, that may be preceded by a prodrome "aura" of tingling sensation and tightness within the joint [1,2,6]. Unwillingness to use the limb alone in children may be indicative of an acute haemarthrosis.

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The milestone of treatment in haemophilia is intravenous clotting factor replacement infusion [7]. They are two types of CFC: plasma derived and recombinant factors; selection between these factors is according to local criteria and availability. The most serious complication related to CFC infusion is development of IgG alloantibodies (inhibitors) that neutralized the exogenous FVIII or FIX infused. The cumulative incidence is approximately 30% and up to 5% of patients with severe haemophilia A or B respectively.

Inhibitors are measuring using the Bethesda or Bethesda-Nijmegen modified assay and quantified in Bethesda Units (BU) per ml., and classified into low-responding titers (≤ 5 BU/ml), or high-responding titers with levels >5 BU/ml. Bleeding manifestations in PwH with inhibitor are not well controlled with routine CFC replacement therapy. The World Federation of Hemophilia (WFH) recommends that PwH with inhibitors and acute haemarthrosis receive treatment based on actual inhibitor level, low or high responding [1,2,6-8]. The two available bypassing agents include recombinant activated factor VII (rFVIIa), Novo Seven (Novo Nordisk) or the Activated Prothrombin Complex Concentrate (aPCC) FVIII Inhibitor Bypassing Activity (FEIBA) by Baxter. rFVIIa is produces by recombinant techniques in baby hamster kidney. Promotes coagulation through tissue factor-dependent by activating FX over platelet surface, bypassing the tenasa complex, increasing thrombin generation, enhancing platelet aggregation and fibrin plug formation with half-life of 2.3 hours. FEIBA is plasma-derived concentrate, vitamin K- dependent active and no active clotting factors (FII, FVII, FIX, and FX). It has a multifactorial mechanism of action with FII and FX most important components [6,9].

Emicizumab (Hemlibra®) is a chimeric bispecific antibody that activates FX to FXa in the absence of FVIII that promotes thrombin generation. Is effective to prevent bleeds in PwH A with or without inhibitor, but is ineffective in treating acute bleeding [6,9,10]. The most important issues in PwH treated with emicizumab are the recommendations and warning with concomitant use of bypass agents in acute haemarthrosis.

General approach

Patients with bleeding disorders such as haemophilia need urgent action in order to prevent further morbidity. PwH can presents to the hospital ER requiring treatment for bleeding in some circumstances: a) significant pain bleeding or poor responding to home treatment, b) inability to vein access, particularly in small children, or c) run out of CFC at home [11]. Assessment and treatment of PwH should be within 15 or 30 minutes of arrival at ER. Initial clinical evaluation focus on vital signs, presenting symptoms, and physical findings.

The elemental information for emergency clinicians are type and severity of haemophilia, product that they use and inhibitor status. Baseline factor levels (FVIII or FIX) generally are not available in the ER and if severity of haemophilia is unknown, emergency clinical must assume that patient has severe haemophilia and treated as well [12]. Patient with mild haemophilia presenting to ER with acute haemarthrosis that do not response to home management, such as local ice, immobilization and/or desmopressin should be treated with CFC. Patient or families advice may help to guideline ongoing therapy, because they are well informed and prepared to attend bleeding complications [11].

The initial recommendation on the algorithm (Figure 1) advice what to do, and not to do in PwH in emergency room reported by Lobet et al. [13]. Additional advice to the algorithm include not to change semi-flexion joint position because exacerbates pain. External compression reduce joint swelling and minimize the risk of rebleeding throughout increasing external pressure and limiting joint capsule distension; this should configure as best possible to the joint/limb shape and be comfortable [14]; it is not recommended in young children due their inability to warning adverse symptoms such as paresthesia. The WFH guideline recommends unload the affected joint with immobilization until pain resolves, and no to use circular plaster for immobilization. Elevation of the limbs above heart level reduce capillary hydrostatic pressure, and may help to reduce joint pain and swelling, however, is not a practical option for young children [15]. Therapies that avoid the normal hemostatic and could aggravate bleeding are contraindicated in acute phase, such as heat sources and massages [9], as well as the use of aspirin-containing drugs or other non-steroidal anti-inflammatory [16].

PwH with acute haemarthrosis who comes to the ER should be treated immediately with factor replacement [6] and not be delayed waiting for a hematologist or Haemophilia Treatment Center (HTC) consultation [12]. Therefore, the implementation of a diagnosis and management tool to improve the treatment in PwH is highly needed in ER. Some of the advantages of an early and optimal treatment is the restriction of the extent of the bleeding, optimizes a single treatment setting, minimizing incapacity and factor consumption.

Management in ER

Pain control: Pain relief should be prescribed by a stepwise process of progression: initial treatment with paracetamol/acetaminophen for mild or moderate pain, followed by COX-2 inhibitor (celecoxib, meloxicam, nimesulide), and opioid analgesia if pain persist, such as paracetamol/acetaminophen plus codeine or paracetamol/acetaminophen plus tramadol; or morphine for limited duration, and adjunctive measure such as compression, immobilization and splinting [3,6,14].

CFC: PwH with acute haemarthrosis who comes to the ER should be treated as soon as possible (≤30 minutes) with CFC replacement. The goal of initial replacement is to raise level of deficiency factor to a desired hemostatic level in order to stop intra-articular bleeding, prevent recurrence and permanent damage. In emergency bleeding, any available factor (derived-plasma or recombinant) are highly effective, safe and can be used. Switching from one type of factor to another or among different factors brands does not increased the risk of inhibitor development, however, must be avoided, if it is possible [6,8,11,16,17].

In the absence of an inhibitor, each unit of FVIII/Kg infused rise 2% plasmatic level of FVIII, with a half-life of 8 h to 12 h. To calculate dosage multiply the ideal patient´s weight in Kg by the FVIII level desired in percentage × 0.5:An example of initial doses in acute haemarthrosis in PwH A is 70 Kg × 40% × 0.5=1400 IU of FVIII.

In the absence of an inhibitor, each unit of FIX/Kg infused intravenously increase the factor IX level 1%, with a half-life of 18 h to 24 h [18]. Dose calculation is performed according to the ideal weight of PwH and multiply the FIX level desired: An example of initial doses in acute haemarthrosis in PwH B is 70 Kg × 40%=2800 IU of FIX.

WFH recommend desired peak plasma level of clotting factor for joint bleeding in 40% to 60% [6]. Several reviews recommended initial doses of FVIII in PwH A without inhibitor of 25 IU/Kg to 40 IU/Kg;

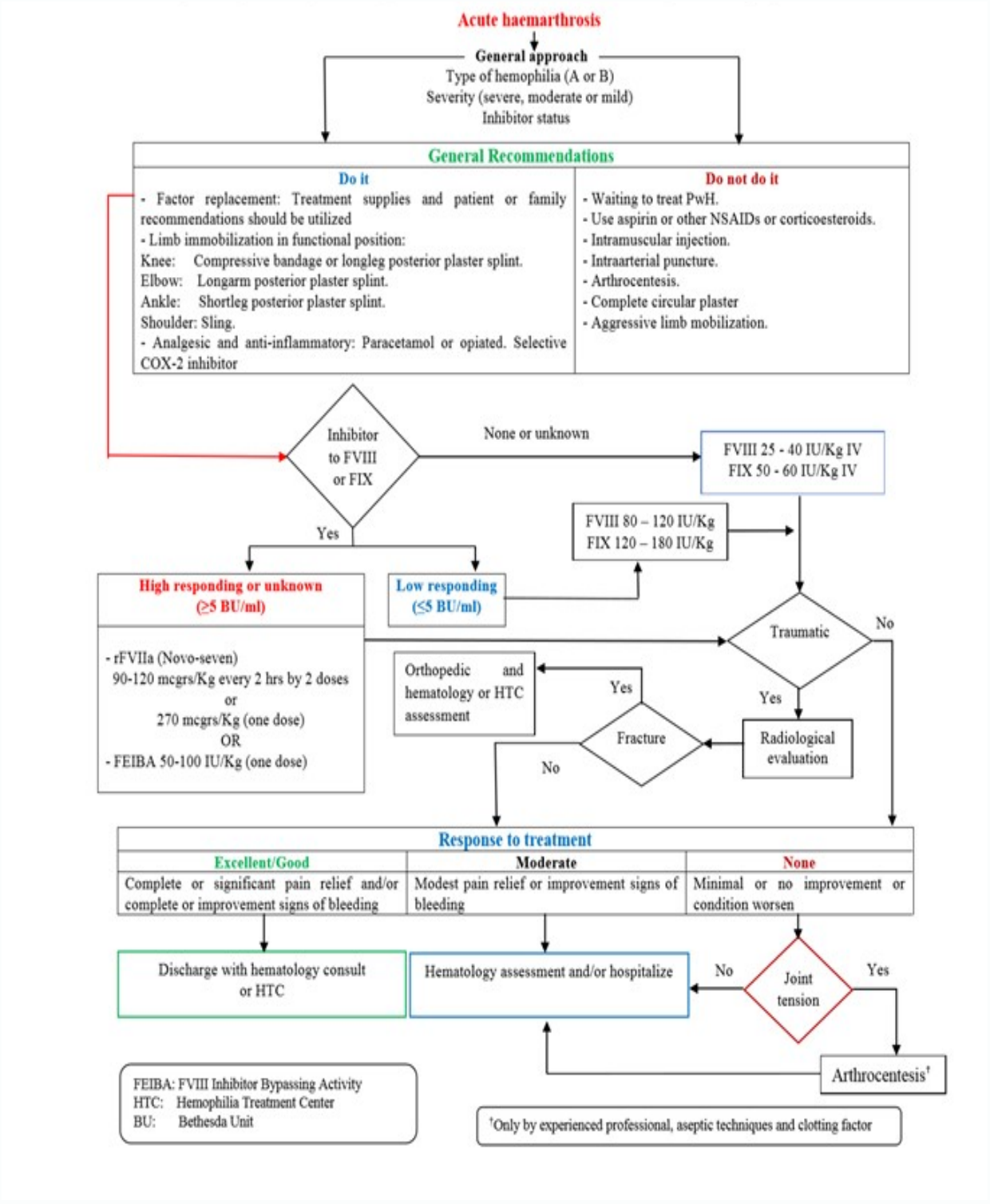

Figure 1: Algorithm to optional management of haemarthrosis in patients with haemophilia in emergency room.

higher doses (50 IU/Kg) are suggested for severe bleeds, such as post-traumatic. In PwH B recommended doses is 40 IU/Kg to 60 IU/Kg for IX [11,13-15]. CFC replacement must be administered intravenously slowly over 1 minute to 2 minutes or per label instructions and cannot be administered with other fluids. Full content of each vial should be infused, since rounding up the dose to the nearest numbers of vials are safe when is necessary [8].

The management of PwH with known inhibitors who presents to the ER is more complex than in patients without inhibitors, because bleeding manifestations will not be controlled with the standard factor replacement therapy. The optimal treatment of bleeding will depend on the inhibitors titer. PwH with lower-responding inhibitor should receive very high doses of CFC to saturate the existing antibody, allowing the excess factor to circulate and provide hemostasis. The

WFH suggests the following formula to estimate the amount of FVIII needed to neutralize the inhibitor:

Body weight (Kg) × 80 × [(1-hematocrit) × antibody titer (BU/ml)]+50 IU/Kg.

The recommendation for management of PwH and low-responding inhibitors is the use of two or three times the standard factor dose for a non-inhibitor patient [11]; in the algorithm the pragmatic suggested doses is two to three times the upper conventional doses. In PwH B with low-responding inhibitor and no previous allergic reaction to FIX the WFH recommends FIX concentrate; patients with previous anaphylaxis reaction to FIX should be treated with rFVIIa against FEIBA, as it contains trace of FIX and may trigger an allergic reaction [6]. To facilitate the management of PwH B in the ER, the difference in factor IX recovery between plasma-derived and unmodified recombinant products was not considered. If patient and families do not have details of inhibitor, they should receive management as a high-responding inhibitor with one of the bypassing therapies available. PwH A with inhibitor not on emicizumab prophylaxis can be treated with any bypass agent. According to the Cochrane review, both bypass agents have a similar haemostatic effect controlling bleeding symptoms in PwH with inhibitors [11,18].

PwH A with haemarthrosis and low responding inhibitor the WFH recommends FVIII replacement, if the hemostatic response is poor then switch to bypass agent and hematology evaluation. Early and uncomplicated (non-tense) haemarthrosis in PwH A with high response inhibitor could be treated either rFVIIa 90 μg/Kg 2 to 3 hourly rounded up the doses to the nearest vial size, with assessment clinical response after each dose; or FEIBA 50 IU/Kg to 100 IU/Kg and assessment 8 hours later. Single dose of rFVIIa 270 μ/Kg is more convenient in the ER than conventional doses of 90 μ/Kg [14] and may be more effective than a single dose of FEIBA at 9 hours post-treatment and is preferred in PwH with poor venous access. PwH B with high-responding inhibitors should receive rFVIIa at convectional doses over FEIBA [6,19].

PwH A who receives prophylaxis with Emicizumab and acute haemarthrosis with or without inhibitor should receive bypass agent or FVIII respectively, according to the algorithm approach. No adjustment in FVIII or bypass agent dosing is recommended, however first line treatment of bleeds in PwH treated with Emicizumab should be rFVIIa. The initial doses should not exceed 90 μg/Kg; based on pragmatic approach lower doses of 45 μg/Kg every 4 hours may be efficient for some bleeds and could be increase to 90 μg/Kg 2 hourly in case of inadequate haemostasis control. Alternative factor therapy such as, human or recombinant porcine FVIII, or switch to FEIBA should be indicated by hematologist and patient should be admitted to hospital. Bleeds should not be treated with FEIBA®, unless no other alternative is available, as FEIBA may develop venous thrombosis, skin necrosis or thrombotic microangiopathy [12]. Lower doses can be used, not exceeding 50 IU/Kg, with close monitoring in patient with risk factors to thrombosis [10].

Assessment response: Assessment of PwH in ER with haemarthrosis depends on severity of haemophilia, knowledge of inhibitor titer and previous response to replacement therapy. Clinical evaluation to treatment is essential in ER, that include patient reported outcome and subjective feedback [6] Response to treatment of acute haemarthrosis is evaluating within 8 hours after initial CFC replacement. For purposes of easy-making decisions in the emergency department, the response definitions published by Blanchette et al. [1] were grouped into thealgorithm in three options: excellent/good, moderate or none. Excellent/moderate response is a complete or significant pain relief and/or complete or improvement of signs of bleeding; moderate is a modest pain relief and/or improvement signs of bleeding; and none with negative or minimal improvement in pain relief or signs of bleed. If symptoms and signs of bleeding continues over the 6 hours to 8 hours in the ER, treatment must include intensification of CFC replacement therapy and a hematologist consultation, considering the presence of inhibitor, septic arthritis or fracture [6,11]. In PwH with inhibitor and minimal response after an adequate bypass doses, the hematologist or the HTC evaluate the option to switch to another bypass agent, or sequential therapy in the hope of synergistic effect between both bypass agents. Pharmacological alternative therapies, such as antifibrinolitic agents (tranexamic or epsilon aminocaproic acid) should be indicated by hematologist or HTC.

Haemarthrosis is clinically apparent, therefore, no diagnosis imaging is necessary. Radiologist evaluation as simple imaging have poor sensitivity in demonstrating early soft-tissue and may be indicated in traumatic mechanism and concern for fracture [8,13,16]. Ultrasound and MRI are not recommended unless suspected fractures, infection or bleeding of the hip [3]. PwH who needs any diagnosis studies, such as x-rays, CT scans, etc., factor replacement should be given before studies. Coagulation test assessment is not indicated in PwH and acute haemarthrosis unless requested by hematologist and treatment should not be delayed waiting for laboratory results; also, if a PwH with haemarthrosis requires transport to another hospital, he must receive CFC and adequate immobilization before transport [12]. Majority of PwH will respond with one dose of CFC [18] that allows the emergency physician to assess response and decide the need to required hematologist evaluation, admitted to hospital, or discharged patientto home and follow medical attention in his HTC or hematology office. PwH with knee or ankle acute haemarthrosis resolved in ER should be leaving the hospital using walking aids (crutches, walker), to avoid weight-bearing; for an elbow, shoulder or wrist haemarthrosis is advisable to immobilize with a sling or splinting [6].

Discussion

The algorithm to optimal management of haemarthrosis in PwH comes out as an answer to Miguel Izquierdo´s concern about multiple complaints from patients about care received in hospital emergency departments: "there should be an optimal management chart in emergency room to haemarthrosis in PwH…" Miguel was president of Haemophilia Federation of Mexican Republic from July 2015 to May 2017. In 2018, this algorithm was presented as a cartel at the WFH World Congress and received some feedbacks: a: Early joint aspiration in ER: authors like Rodriguez-Merchán as in favor of early joint aspiration and intra-articular blood evacuation in order to prevent synovitis and articular damage, relieve pain and muscular spam; and faster return to work or school. This option is reserved for selected cases, such as hip haemarthrosis where there is a risk of avascular necrosis [16], painful and tense haemarthrosis, often post-traumatic, where pain and swelling outweigh bleeding and/or evidence of neurovascular compromise [20], infection suspicion, and in those patients who do not respond to CFC replacement within 24 hours to 72 hours.

In this setting joint aspiration should be performed after

hematologist evaluation [11], in aseptic conditions by qualified personnel, CFC must be administered to raise the factor level to 100% or bypass agent prior the puncture and using a large-bore needle at least 16 G. After puncture, the joint should be immobilized with mild compression for at least 1 hour [6,16]. Therefore, arthroscopy and systematic joint aspiration is not recommended in guidelines [5,9,20]; should be avoided because potential risk of septic arthritis, and is not indicated for mild haemarthrosis [13,14]. Intra-articular steroid is not recommended for acute haemarthrosis [14], as well as neither oral dose because its side effects [3]. B: Ice useful in the ER: The regimen PRICE (protection, rest, ice, compression and elevation) was described as standard treatment in PwH as an adjunctive management for pain relief and could be useful in the way to the ER. Use of local ice on haemarthrosis without direct skin contact is useful after haemarthrosis setting, for shorts periods of 15 minutes to 20 minutes at two-hour intervals, into 6 hours after bleeding. A systematic review by Bleakley in Hanley et al. [14] suggested there is not clinical evidence in the management of haemarthrosis, but subjectively PwH have reported pain decrease [14], reducing nerve conduction velocity, edema and inducing vasoconstriction; however could interference the coagulation intraarticular system slowing blood flow, coagulation system and platelet function [6,8,13,15]. Review by Forsyth et al. [21] reported in animal and human models that cooling intraarticular space are within the temperature range where interfering with the hemostasis, can interference platelet adhesion and aggregation, affected activity of clotting factors, prolonged bleeding and clotting time. These impairments can leadto increased bleeding during acute haemarthrosis in PwH.

Ice application can be effective, as a temporary pain reliever, however, the anesthetics effect is a temporary measure, and does not reduce swelling from haemarthrosis [21]. Last edition of WFH guideline replace the acronym PRICE with POLICE (protection, optimal loading, ice, compression, elevation), in order to encourage establish a balance between rest, early mobilization, and weight bearing to prevent muscle atrophy and minimizing rebleeding. These adjunctive measures help manage and reduce pain and inflammation [6].

Conclusion

A rational and pragmatic therapeutic approach to haemarthrosis in PwH who show up to ER should follow an algorithm that attends clinical features, patients and families advices, accurate medical assessment and supporting decision on medical evidence to get an optimal management. Considering the complementary treatment in ER, the transient benefits of ice application in the management of acute haemarthrosis in PwH could be limited to temporary pain relief on the way to the hospital, instead the external compression limited joint capsule distensibility, halt bleeding and consequence limit joint swelling [21]. Physiotherapy is not a therapeutic option in ER, because is recommended after the acute haemarthrosis resolves in median of 7 days. This paper addresses one of the four key themes of the SHIELD group (Supporting Hemophilia through International Education, Learning and Development): Guidelines and algorithms for hemophilia care [22], and focuses on the most frequent bleeding manifestation inPwH.

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