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Prophylaxis in hemophilia

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ABSTRACT

Hemophilia is an inherited X-linked coagulopathy defined by a deficiency or abnormality in the clotting function of factor VIII (Hemophilia A) or factor IX (Hemophilia B). Prophylaxis – the regular administration of therapeutic products to maintain hemostasis and prevent bleeding – is the mainstream of treatment. Addressing the development and scientific evidence for administrating prophylaxis is the goal of this review. Prophylaxis is the therapeutic modality of choice for people with severe hemophilia, being considered, in principle, a lifelong treatment. It should have an early onset, ideally as a primary, or at least secondary. Even lifelong tertiary prophylaxis seems to offer benefit, although further studies are still lacking. Individualized strategies should lead to an optimization of the dilemma between better joint outcomes versus involved costs.

Keywords: *Hemophilia A; Hemophilia B; Prophylaxis*

INTRODUCTION

Hemophilia is an inherited X-linked coagulopathy defined by a deficiency or abnormality in the clotting function of factor VIII (hemophilia A) or factor IX (hemophilia B)[1]. Data collected by the World Federation of Hemophilia (WFH), in 2020, identified 209,614 worldwide patients with hemophilia, of which 165,379 were diagnosed with hemophilia A (HA), and 33,076 with hemophilia B (HB). Brazil has, in absolute numbers, the fourth largest population of hemophilia patients in the world, with 13,149 reported[2,3]. The treatment of hemophilia in Brazil occurs through the Hereditary Coagulopathies Program[4,5]. Prophylaxis, through the administration of therapeutic products to maintain hemostasis, is the mainstream of treatment approaches, despite raising serious questions about cost effectiveness. The aim of this study was to review prophylaxis as a therapeutic strategy in patients with hemophilia.

PROPHYLAXIS IN HEMOPHILIA

Definitions

Prophylaxis in hemophilia is defined as the regular administration of therapeutic products to maintain hemostasis and prevent bleeding, especially hemarthrosis, that can lead to arthropathy and disability. Prophylaxis has the goal to keep people with hemophilia healthy and active, cultivating physical and social activities at a domestic, academic, labor and community domain[6].

In 2014, definitions for the replacement therapy of clotting factor concentrates were published[7]:

- Episodic treatment (on demand): treatment given at any time for clinically evident bleeding.
- Primary prophylaxis: continuous treatment, initiated in the absence of osteochondral joint disease, evaluated by clinical examination and/or

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imaging, before the second clinically documented hemarthrosis, and before three years of age.

- Secondary prophylaxis: continuous treatment, started after two or more hemarthroses, and before joint disease, detected by clinical and/or imaging examination.

- Tertiary prophylaxis: continuous treatment, initiated after the establishment of joint disease, detected by clinical and/or imaging examination.

- Intermittent (periodic) prophylaxis: performed to prevent bleeding, for periods not exceeding 45 weeks a year.

Evidences

The history of HA prophylaxis began in Malmö, Sweden, in 1958, when Professor Inga Marie Nilsson introduced prophylactic infusions of cryoprecipitate or intermediate-purity clotting factor concentrates at regular intervals, aiming to maintain plasma levels of factor VIII above 1% and prevent bleeding. Similar treatments for HB began in 1972[8].

Observational and retrospective studies regarding the long experience of Sweden and the Netherlands in the use of prophylaxis in people with hemophilia have demonstrated the benefits of this approach[9]. One of the first prospective observational studies described[10], in 1994, was a 6-year follow-up of 501 patients with severe HA under the age of 25 years, in 21 Treatment Centers in the United States, Europe and Japan. Orthopedic and radiological scores of ankles, knees and elbows were evaluated at study entry and after a 6-year follow-up. Approximately 10% of patients had all 6 normal joints at study enrollment, and, of these, 50% maintained them. The use of prophylaxis reduced the progression of arthropathy on clinical and radiological examination. Patients on prophylaxis had fewer days of absenteeism in school or work. The consumption of higher doses of clotting factors alone did not prevent joint worsening, but showed a reduction in joint bleeding. This observational study further demonstrated that secondary prophylaxis was beneficial for those who already had joint damage at baseline.

Another study[11], published in 1997, included 34 patients evaluated from 6 to 21 years, 29 with HA and 5 with HB, aged between 7 and 22 years at the time of inclusion, and age at the beginning of prophylaxis between 1 and 4.5 years. All patients had normal clinical and orthopedic scores at study entry. Two patients showed worsening of joint status, possibly related to poor adhesion, while the others maintained their scores identical to the initial ones. This small long-term cohort demonstrated the effectiveness of the prophylaxis regimen in maintaining joint health in patients with severe HA and HB. However, randomized clinical trials still remained necessary.

The catastrophic events of HIV and HCV infection related to blood products in the hemophilic population, in the 1980s, hampered the implementation of well-designed clinical studies for more than a decade. Improvements in pathogen reduction and inactivation techniques in plasma-derived concentrates[12] and the introduction of coagulation factors of recombinant origin have made the modern treatment practically free from contamination risks. Even so, the effectiveness of prophylaxis described in observational studies with a follow-up of more than 20 years, in some cases, overshadowed the search for randomized clinical trials in this scenario[10,11,13].

A systematic review, published in 2011 in the Cochrane Library, evaluated the available evidence for the effectiveness of prophylaxis[13]. For this review, 890 references were evaluated, of which 119 were considered for analysis, 29 subject to inclusion, but only 6 studies, with a total of 142 participants, were identified as relevant for systematic review. Of these, two studies were randomized, controlled, but open-label. The JOS study[14] included patients on primary prophylaxis, while the ESPRIT study enrolled patients on both primary and secondary[15]. The remaining studies described secondary prophylaxis data. They had a cross-over design, randomized intervention, and all patients received active and control treatments[16-19]. Different interventions were used in these cross-over studies, published in 1976[16,19], 1977[17] and 1997[18]. This systematic review highlighted that at least 30 observational studies described data that 1,960 patients were on prophylaxis, and 1,312 were treated on demand. Although lacking the methodological quality of randomized controlled trials, these observational studies indicate a clear benefit of prophylaxis on the outcomes of bleeding frequency and joint deformity[13]. Thereby, taken together, randomized and observational studies provided evidence that prophylactic administration of clotting factors was effective in preventing, or slowing, progression of hemophilic arthropathy[13].

In the first published randomized clinical trial[14], 65 boys with HA were randomly allocated to either the prophylaxis arm or the on-demand one. Children under 30 months of age, factor VIII activity below 2 IU/dL, history of 2 or fewer hemarthroses in the evaluated joints, and normal clinical and imaging examinations at admission were included. The primary endpoint was the incidence of bone or cartilage damage detected in the index joints by radiography or magnetic resonance imaging (MRI), assessed at 6 years of age. Children in the prophylaxis group (n = 32) received factor VIII infusions 25 IU/kg every other day. Boys allocated to the on-demand group were treated only for clinically recognized bleeding,

at a dose of 40 IU/kg on the day of the event and 20 IU/kg on the two subsequent days. At 6 years old, 93% of children in the prophylaxis group, and 55% of those treated on demand, had normal joint structure on MRI. Children on the prophylaxis regimen had a median of 1.2 bleeds/year, versus 17.1 bleeds/year in the on-demand group. Patients on prophylaxis had 0.6 hemarthroses/year, versus 4.9 in the on-demand group. Furthermore, 3/33 patients in the on-demand group had a life-threatening hemorrhage, compared to none in the prophylaxis group, a finding without statistical significance. The prophylaxis group had a consumption of clotting factors almost three times higher. In this study, at age 6 years, a child in the prophylaxis arm received 6,000 IU of factor VIII/kg/year, compared to about 2,500 IU/kg/year in the optimized on-demand modality. At approximately US$ 1 per IU of recombinant factor VIII, the cost of this prophylaxis regimen for a 50 kg individual reached US$ 300,000 per year. The episodic therapy used in this study was considered as experimental, as it used higher doses and a greater number of infusions than those provided in the usual management. This augmented modality was employed because the result of habitual on-demand management was considered insufficient[9]. Still, the outcome was clearly inferior compared to the alternate-day prophylaxis regimen[14].

Furthermore, about half of the joint abnormalities detected on MRI were not evident on traditional radiological studies, proving the lower sensitivity of this last method. Surprisingly, the number of clinically significant hemarthroses correlated poorly with outcomes determined by MRI. Joint abnormalities on MRI were not apparent on clinical examination of very young children. This absence of clinical examination findings may lead to the erroneous impression that episodic therapy is effective, particularly for young children. This work was remarkable because hypothesized that small chronic hemorrhages in the joints or subchondral bone of young boys with severe hemophilia caused joint deterioration in the absence of clinical evidence of hemarthrosis, and primary prophylaxis would prevent this process.

The second randomized trial[15] evaluated 55 boys with severe HA, aged between 1 and 7 years, with normal clinical-radiological joint evaluation at admission, and at least one bleeding episode in the previous 6 months. These were randomized to the recombinant factor VIII prophylaxis arm (25 IU/kg 3× week) or on-demand treatment (dose ≥ 25 IU/kg every 12 to 24 hours until clinical resolution of the bleeding episode). The follow-up period was 10 years. Children allocated to prophylaxis (n = 21) had fewer hemarthroses than those treated in the episodic modality (n = 19), with 0.2 versus 0.52 events per patient/month. Radiological evaluation displayed signs of arthropathy in 6 patients on prophylaxis (29%) versus 14 on the episodic regimen (74%). Prophylaxis was more effective when started early (before 36 months of age), since these patients had fewer hemarthroses and no radiological signs of joint damage.

On this study[15], the mean clotting factors consumption was 8,852 IU/patient/month in the prophylaxis group, versus 3,981 IU/patient/month in the episodic treatment. Half of the patients in the prophylaxis group required central venous access placement, and none in the episodic group. Of these 10, 6 patients experienced catheter infection within 1 to 60 months of placement (median 6 months). In two patients, the catheter was removed, and required hospitalization for 2 days.

On this investigation[15], prophylaxis at a dose of 30 IU/kg 3 times a week significantly reduced the frequency of bleeding, especially hemarthrosis. Even so, the incidence of joint bleeding was considered significant, for being four times higher than the previously described study[14]. This difference is possibly explained by patient`s different ages in the two studies. While the first included patients aged up to 2.5 years, the second included children aged between 1 and 7 years, with a median of 4. In the subgroup of children younger than 3 years, the incidence of bleeding was very similar among the other study group. Although the younger population had the best outcomes, prophylaxis was again able to reduce the risk of joint damage even in those patients who started it later. The high catheter infection rate was a matter for concern and may be associated with the development of inhibitors. As expected, the cost of prophylaxis was more than double compared to episodic treatment. In this prospective study, the cost per bleeding episode avoided was estimated at € 7,537. The cost of better preserving the joint health of a child with hemophilia, for a period of 7 years, has been estimated at about € 200,000 or € 2,500 per month. Still, the high cost of prophylaxis was considered valid, given the impact on orthopedic and quality-of-life outcomes[15].

Dosing

Prophylactic administration of clotting factor concentrates for people with hemophilia, usually 20 to 40 IU/kg 2 to 3 times a week, maintains their musculoskeletal function practically normal, but implies the consumption of about 2,500 to 6,000 IU/kg/year. In the absence of access to these quantities, the on demand treatment remains widely used to treat bleeding episodes. In the search for better care for people with hemophilia living in developing countries, major questions are raised: what would be the minimum amount of clotting factor concentrates required to improve long-term outcomes and what`s the best form of administration in terms of dosage

and interval[2,20,21]. In low income countries, would the increase in the availability of factor concentrates for episodic treatment impact the natural history of bleeding and musculoskeletal dysfunction?

The MUSFIH study, that included two Brazilian centers, evaluated the musculoskeletal outcome of children in episodic replacement therapy. This was a longitudinal study that included 255 children in 9 developing countries, with a 5-year follow-up[22]. Outcomes were documented by annual joint bleeding rate, clinical WFH scores, Pettersson radiology score, and FISH score for functional independence[22,23]. 86% were diagnosed with HA. Of the 203 patients for whom data was available, 164 remained on the episodic treatment modality only and were enrolled in the study, and 39 received continuous prophylaxis. The median age at study entry was 10 years (5 to 12). During follow-up, three patients (1.4%) had intracranial bleeding, of which one was fatal. The median use of clotting factor concentrates was 662 IU/kg. The median annual dose in the different centers ranged from 72 to 2,124 IU/kg. For the purpose of comparing outcomes, participants were divided by ranges of annual use of concentrates. The annual joint bleeding rate was 10, and the median change in clinical WFH and radiological Pettersson scores was 0.4 per year for both, while the FISH score deteriorated by 0.2 per year, without correlation between the consumption of concentrates and the cited scores. In line with the episodic nature of the proposed therapy, patients with higher annual joint bleeding rates consumed the highest doses of factor concentrates, creating the paradoxical impression that higher products consumption is associated with worse bleeding outcomes. The correlation of joint scores with the consumption of concentrates went in the same direction.

At the beginning of the study, all participating centers used episodic therapy in the management of people with hemophilia, but with wide variation in the availability of factor concentrates (100 to 2,000 IU/kg/year). It was clearly shown that patients with the highest rates of bleeding consumed the highest amounts of factors, and yet had worse outcomes. This was an evidence that episodic therapy, even at higher levels of consumption, is not able to change the bleeding profile of patients and the musculoskeletal health. Therefore, the episodic treatment modality is not recommended for the long-term management of people with hemophilia[24].

This research, in addition, led to a comment in the same issue of the journal[25], in which it was mentioned that, even in Western Europe, primary prophylaxis was effectively implemented in only 80% of children with severe hemophilia[26]. In the United States, differences in joint outcomes between patients with severe and moderate hemophilia still persisted, with at least one-third of people with severe hemophilia born after 1992 reporting more than five bleeds in a 6-month period[27]. This commentary further proposed that, especially in young children, low-dose prophylaxis of 1,000 to 2,000 IU/kg/year could make a dramatic difference, and dosages as low as 10 to 15 IU/kg 2 to 3 times per week were able to prevent 80% of bleeding episodes[27].

Age at onset of prophylaxis is a powerful predictor of long-term musculoskeletal outcomes, besides reducing the risk of intracranial bleeding, which is more frequent in very young children[6,28]. Long-follow-up cohort studies have shown that even a small number of joint bleeds, occurring before prophylaxis is initiated, can result in definitive hemophilic arthropathy in some patients[8].

Although there is a consensus that regular prophylaxis, started early and with adequate doses, is the standard of care in the treatment of hemophilia, the best approach to this therapy is still open to debate. The main models of primary prophylaxis based on factor concentrates initially employ escalated high or low doses. The main difference between these two approaches concerns especially about the frequency of application of factor concentrates. The suggested prophylaxis regimens by the WFH with conventional half-life clotting factor concentrates can be seen in Table 1[6].

Table 1: Prophylaxis regimens according to the World Federation of Hemophilia (60).

	Dosing (UI/kg)	Frequency	Annual consumption (UI/kg)
High	25–40 40–60	Every 2 days 2 times a week	> 4,000
Intermediate	15–25 20–40	3 times a week 2 times a week	1,500–4,000
Low	10–15	2–3 days a week 2 times a week	1,000–1,500

The escalated dose prophylaxis regimen has a less intensive onset, usually with weekly infusions. This model allows children and their families to greater accept the initiation of prophylaxis and better

adapt to venous punctures, possibly increasing adherence. This approach also results in less need for implantation of central venous devices. Besides, since early exposure to frequent and high doses of clotting factors seems to be associated with a higher risk of inhibitor development, another hypothetical benefit, not yet demonstrated, would be related to the lower development of neutralizing antibodies. However, young children starting the low-dose prophylaxis protocol need close supervision, and rapid dose escalation should be considered in order to prevent bleeding and avoid morbidity[6].

Brazilian reality

In 2009, a publication[29] involving the coordination of the National Policy on Blood and Blood Products of the Brazilian Ministry of Health described the first compilation of data of the Brazilian registry of hereditary coagulopathies. In this study, it was emphasized that these patients were mostly treated with concentrates of plasma-derived coagulation factors, imported in their entirety. Although the treatment had made significant progress in the previous decade, it was still as an episodic modality. It was also described that patients had low socioeconomic status and were mainly affected by chronic musculoskeletal complications[29]. This study was the basis for the discussion about prophylaxis in Brazil.

Therefore, the Brazilian protocol for the use of primary prophylaxis for severe hemophilia was implemented in 2011, although it was only published on 2014. The goal was the treatment of children with severe HA and HB, with escalated doses of the deficient clotting factor, aiming to prevent the development of hemophilic arthropathy, reduce bleedings and improve quality of life. Patients should be included by the responsible physician at the Hemophilia Treatment Centers (HTC). The inclusion criteria to the Brazilian protocol can be seen in Table 2, and the exclusion in Table 3. Dosing recommendation can be seen in Table 4. Situations that require stage modification are listed on Table 5.

Table 2: Inclusion criteria for the Brazilian protocol of prophylaxis in hemophilic patients.

Have a confirmed diagnosis of severe hemophilia A or B, defined by factor VIII or IX dosage activity of less than 2%.
Being aged up to 36 months incomplete or having presented hemarthrosis in any joint or any severe bleeding.
Have a negative inhibitor test or inhibitor quantification lower than 0.6 UB/mL in a test performed immediately before inclusion. Patients with a maximum historical titer of less than 5 UB/mL may be included as long as the inhibitor test is negative (or the inhibitor quantification is less than 0.6 UB/mL) immediately prior to inclusion and there is no anamnestic response to factor VIII.
Be registered and regularly monitored in a HTC.
Sign a consent and responsibility term.
Obtain approval of the medical, nursing, psychosocial and musculoskeletal assessments carried out by the multidisciplinary team of the HTC. The multidisciplinary team must be minimally composed of medical and nursing professionals.
Commit to recording all infusions in a proper spreadsheet, for traceability of information about infusion and intercurrences.

Table 3: Exclusion criteria for the Brazilian protocol of prophylaxis in hemophilic patients.

Historical inhibitor peak greater than 5 UB/mL, confirmed on at least two occasions with an interval of 2–4 weeks between dosage.
Age equal to or greater than 36 months.

Table 4: Stages of dose-escalation.

Stage A: initial dose of 25 IU/kg of the deficient factor twice a week.
Stage B: when using the deficient factor concentrate at a dose of 25 IU/kg twice a week, and if one or more of the three types of bleeding described below, the dose should be increased to 30 IU/kg twice a week, with a minimum interval of 2 days between doses.
Stage C: when using the deficient factor concentrate at a dose of 30 IU/kg twice a week, and with one or more of the three bleeding modes described below, the dose should be increased to 25 IU/kg three times a week in alternating days. If bleeding persists, it is recommended to increase 5 IU per kg, without changing the frequency.

Table 5: Situations that demand stage escalation.

2 clinically detected hemarthroses in the same joint, in a period of up to 3 consecutive months.
3 clinically detected bleedings, whether from soft tissues or joints – even if in different joints – in a period of 3 consecutive months.
3 or more clinically detected hemarthroses, while receiving the same dose of factor deficient concentrate, in any period of time.

Regarding the duration of treatment, the patient should be encouraged to maintain prophylaxis until reaching physical maturity, which occurs, in most patients, at 18 years of age. Upon reaching 18 years of age, the continuity of primary prophylaxis should be defined between the multidisciplinary team and the patient[30].

The Brazilian protocol for primary prophylaxis with escalation has similarities with the Canadian protocol, whose initial results were published in 2006[31]. The initial hypothesis of the Canadian prospective study was that a customized primary prophylaxis regimen would allow a lower consumption of clotting factor concentrates, while maintaining acceptable joint outcomes. In this study, 25 boys diagnosed with severe HA, followed at 10 Canadian centers, were initially treated with a weekly application of 50 IU/kg of recombinant factor VIII. Assessments took place every three months, and the frequency of infusions was escalated in the presence of bleeding. The outcomes of bleeding frequency, target joint development, physical therapy and radiological findings, as well as resource utilization, were prospectively determined. Patients were followed between 1.3 and 5 years, with a median follow-up time of 4.1 years. Thirteen children met the criteria for escalation, and the median time to increase the application to twice a week was 3.42 years. At age 5, 40% of children still required only weekly applications. Thirteen of the allocated patients had not any joint bleeding at the time of inclusion, and they had a lower tendency to escalate, but this finding was not statistically significant. Four children in this cohort required escalation to the third level of prophylaxis.

Nine patients developed a target joint, the youngest at 23 months of age and the oldest at 69 months, at a rate of 0.09 per person/year. Two children remained with target joint even after escalation to level 2. By age 3.5 years, about 40% of children had a target joint. An average of 1.2 joint bleeding per person/year was found. This cohort consumed an average of 3,656 IU/kg/year of factor VIII concentrates. Ten patients had central venous access, seven prior to the study, and three implanted during the study, with no associated complications. Two patients developed transient inhibitors.

Adherence was excellent. In the first step, 96% of the expected infusions were effectively applied, and a similar level of adherence in steps 2 (twice a week) and 3 (alternate days) was achieved. Level of parental satisfaction was very high. At the end of the study, the clinical and radiological joint assessment was normal or close to normal for all patients.

The discussion from this study, which uses a model of primary prophylaxis similar to the Brazilian one, mentions favorable joint outcomes with considerably lower expenditure of factor concentrates. It also addresses that no prophylaxis regimen is capable of curbing all joint bleeding, even the most intensive. In addition, the obtained results remain intermediate between those obtained with high-dose protocols, emphasizing the need for a longer follow-up to better define the joint outcomes of these children[31].

Cost-effectiveness analysis

Using a theoretical decision-analytic model, a cost-utility analysis was performed comparing the increment in terms of cost for each joint hemorrhage avoided, and the gain in terms of quality-adjusted-life years (QALY). This research was conducted with boys with severe HA, at age 6, according to treatment modalities with standard prophylaxis, Canadian-style prophylaxis, and on-demand therapy[32].

This analysis focused on the costs and outcomes of different treatment strategies using factor VIII concentrates. Using the Markov decision tree, children started with the six normal joints (ankles, knees, and elbows), and the natural history of joint bleeding and target joints was modeled for each group. Data for episodic treatment were obtained from the chart review of 24 children treated at the Hospital for Sick Children in Toronto. The reduction in bleeding with prophylaxis was determined by evaluating three non-randomized comparative studies. Direct costs included those related to factor VIII concentrates, laboratory tests, medical, physiotherapy and nursing visits, education for home care, central venous catheter insertion and possible associated complications, emergency room visits and hospitalization days for bleeding events. Indirect costs were related to lost workdays for guardians.

The expected 5-year costs, total number of joint bleeds and other bleeds, and QALY were calculated with decision models using TreeAge Data Prosuite (TreeAge, Boston, MA, USA). Based on this model, 89% of children treated on demand would have a

target joint by age 6 years, compared to 47% for escalating prophylaxis, and 12% for those treated with a standard prophylaxis regimen. Furthermore, this model estimated that, in the escalating prophylaxis modality, at age 6 years, 19% would remain in the low-dose arm, 64% in the intermediate level, and 19% would progress to level 3.

The cost-utility ratio obtained was, in Canadian dollars, $ 542,939 per QALY acquired with standard prophylaxis, $ 443,185 for dose-escalation prophylaxis, and $ 277,209 for on-demand therapy. The spent costs on factor concentrates corresponded to 82% of the escalating prophylaxis, and 86% of the standard. Compared with episodic treatment, dose-escalation prophylaxis decreased 52 joint bleeding events, at a total cost of $ 165,976, or $ 33,195 per year. Comparison with standard prophylaxis, it reduced 65 joint bleeds at an additional cost of $ 292,626. These data demonstrate a substantial cost for a relatively small increase in quality of life, measured by the HRQoL (health-related-quality-of-life). The increase in cost per QALY acquired in the comparison between standard and escalating prophylaxis strategies was greater than $ 1,000,000, demonstrating that escalating prophylaxis appears to be a cost-effective strategy, with little repercussion in terms of QALY loss. A review prior to this study demonstrated a lower incremental cost-effectiveness of $ 112,560 per QALY acquired with the episodic prophylaxis modality, however using different criteria for case definitions[33].

Considering the proposed therapeutic modalities, the two prophylaxis regimens were more expensive than the episodic strategy, but with considerable reduction in joint bleeding and morbidity. Still, the projections made for a period of five years may be unable to capture the totality of associated benefits with the reduction of bleeding episodes.

The Canadian group published clinical follow-up data from this cohort in 2013[34]. At that time, 56 patients with a median age at study entry of 19 months (12–30), and a median follow-up of 92 months (2–156), had their joint scores assessed by The Colorado Haemophilia Pediatric Joint Physical Examination (Child PE scale). This scale assesses eight items: joint swelling, muscle atrophy, axial deformity, crepitus, range of motion, flexion contracture, gait and strength performance, in addition to subjective measures of pain and use of orthoses. The Chidhood Health Assessment Questionnaire (CHAQ) was also used to assess physical activity. Children were assessed by study physical therapists at 3, 6, and 10 years of age.

Eleven Canadian centers included the 56 children with a median pre-study joint bleeds of 0 (0 to 4 for all joints combined), and non-joint 4 (0 to 28 for all non-joint bleeds). In general, joint scores remained very low throughout the study, increasing slightly with age. Adherence to the protocol was very good, with a median of 96% in the weekly application, 94% in the second escalation and 97% in the third. Over the course of the study, 47 of 54 patients received more than 80% of the planned infusions. Two patients, both from the same center, underwent radiosynovectomy due to the development of a target joint.

Some patients were apparently undertreated due to undiagnosed bleeding, with consequent joint and functional damage. This fact, added to the poor adherence to treatment, led to a greater number of bleeding in a few patients, which resulted in worse joint scores. The escalating of prophylactic infusions is foreseen in the protocol, however, if bleeding is not detected, this increase is postponed, with consequent permanent damage. This is a shortcoming of these protocols, which can be circumvented by earlier detection of joint events[34].

The last update of the Canadian primary prophylaxis protocol, with a dose escalation similar to that adopted in Brazil, occurred in a publication in 2018[35]. Fifty-six boys were followed up for a median of 10.2 years (maximum 16.1), with the primary outcome being the joint score assessment using the modified Colorado Child Physical Examination Scores (CCPES). With a median consumption of recombinant factor VIII concentrate of 3,600 IU/kg/year, at the end of follow-up, joint scores had a median of 1 for ankles (interquartile range 1–3; range from 0 to 12) and 0 for the other joints. There were no treatment-related adverse events, not even catheter infections. The annual rate of joint bleeds was 0.95 (interquartile range 0.44 to 1.35, range 0 to 13.4). Breakthrough bleeding occurred in 17 (30%) of the patients at some point in the follow-up. However, some patients had permanent joint damage, which led this group, with longer follow-up, to consider more intensive escalation protocols[35].

Prophylaxis in adults with hemophilia

Although prophylaxis is the standard of care for children, many adults remain on an episodic treatment modality, either because they were never exposed to prophylaxis, or because they choose to discontinue this therapy in adulthood. In contrast to the unanimity of the indication of prophylaxis in childhood, there was a scarcity of studies and a consequent lack of consensus regarding the maintenance of prophylaxis in adulthood[36]. Animal models suggest that, once joint growth ceases, the risk of hemarthrosis is lower[37]. This may be especially the case for patients who received primary prophylaxis during childhood and adolescence, and who maintain joint health. While for some individuals reaching adulthood can increase adherence to infusions, others autonomously choose to reduce intravenous applications. Furthermore, the pattern of physical activity may transition to a more consciously active, or more sedentary, lifestyle.

An European study, published in 2007, evaluated the position of 21 physicians working in centers involved in the care of almost 5,000 people with hereditary coagulopathies, in relation to their practices regarding prophylaxis in patients with severe hemophilia aged between 16 and 24, and over 50 years old. Initially, professionals from fifteen centers stated that the use of prophylaxis reached about 70% of their patients under the age of 5 years[36].

Eighteen out of nineteen respondents considered the possibility of modifying the prophylaxis regimen adopted in childhood once adolescence was reached. The reasons listed for this possible change in the protocol included: risks associated with exposure to high doses of concentrates; costs; expectation of lower adherence; lower physiological need. No one considered reducing the prophylaxis regimen before age 16 years. In addition to the age criteria, the following were considered relevant for the decision to change the regimen: patient`s bleeding phenotype; patient's desire; joint status and maturity. All considered appropriate the future reintroduction of the prophylaxis regimen, if necessary.

Nineteen respondents provided data for 218 people with hemophilia between the ages of 16 and 22 years. Of these, 92 patients completely discontinued the prophylaxis regimen, 59 reduced it, and 67 remained on the regular prophylaxis initiated before 5 years of age. The duration of follow-up varied between centers, with the shortest being 3 months and the longest, 72 months. Of the 92 patients who completely discontinued prophylaxis, 48% returned to a regular regimen due to recurrence of bleeding.

The physicians reported a total of 251 follow-up patients over the age of 50 years. Of these, 58 (23%) were under some regular therapeutic modality. The main reasons for indicating prophylaxis in this age group were the occurrence of more than two episodes of hemarthrosis per year, and the presence of chronic arthropathy[36].

Right after this publication, one study more consistently assessed outcomes related to secondary prophylaxis in adolescent and adults[38]. A retrospective observational cohort evaluated 84 patients from 10 Italian centers who had a high frequency of bleeding, and who were switched from an episodic to a prophylactic therapeutic modality during adolescence (30 patients) or adulthood (54 patients). In 50 (59.5%), the reason for changing the regimen was the development of a target joint with worsening of the orthopedic score; in 21 (25%), a significant worsening in the frequency of bleeding.

The migration to a prophylaxis regimen, in this group of patients, significantly reduced the mean annual joint and any nature bleeding, as well as the absenteeism in work or school. Secondary prophylaxis also reduced the mean orthopedic score, but this finding was statistically significant only in the adolescents group. Protocol adherence was excellent, with only 4 adults (4.8%) reporting brief interruptions in treatment. This finding differs from previous studies, in which the transition to adolescence was accompanied by poorer adherence or even discontinuation of regular therapy[36,39]. The discussion mentions that, similarly to the Brazilian population with severe hemophilia, Italian patients started the prophylaxis program later and experienced frequent hemarthrosis in the episodic modality. Therefore, they may have appreciated the clinical and quality-of-life benefits associated with prophylaxis, and remained motivated to continue this regimen[38].

In another study, the evaluation of 124 people with severe hemophilia aged 18 to 35 years (median 26.9 years), whose data were obtained from a questionnaire-type instrument, showed that long-term prophylaxis, when compared to episodic treatment or intermittent prophylaxis, resulted in a lower frequency of target joints, severe bleeding, recurrent bleeding episodes and the need for surgical interventions[40].

The Malmö Center, which is a pioneer institution in prophylactic therapy, described outcomes related to primary prophylaxis in a retrospective cohort of adults who used prophylaxis for most of their lives[41]. All patients with severe hemophilia born between 1932 and 1992 were evaluated. The 81 patients were divided into two groups: the first started prophylaxis before the age of three (n = 30), and the second, after it (n = 51). Outcomes were assessed using the Hemophilia Joint Health Score (HJHS). The annual rate of joint bleeding at the end of the three years of observation was lower in the early-onset prophylaxis group. In the early prophylaxis group, 25/30 patients (83%) had no joint bleeding, against 27/51 (53%) in the later-onset prophylaxis group, with the first group also having better joint scores on the HJHS scale. Bleeding frequency had a statistically significant correlation with the HJHS score in patients with later onset of prophylaxis. The median joint score in the group of adults with early initiation of prophylaxis was only 3 out of 148 possible points. Treatment interruption was a rare phenomenon[41].

Similar to what was seen in primary prophylaxis in childhood, the benefit of this modality in adulthood was supported only by observational studies, being corroborated by the first randomized clinical trial in 2013, called SPINART[42]. This study evaluated 84 adult patients diagnosed with severe hemophilia A and a median age of 30.6 years (15-50 years), with at least 150 days of prior exposure to factor VIII and 6 to 24 bleeding episodes in the 6 months prior to enrollment. These were randomized between primary prophylaxis with 25 IU/kg of factor VIII concentrate 3 times a week (n = 42), or on-demand therapy (n = 42). The median of total bleeding episodes over the

course of the study, and total bleeding over the one year period, was significantly lower in the prophylaxis group. Data analysis indicated a 14.7 increased risk of bleeding episodes for the on-demand group when compared to the prophylaxis regimen, corresponding to a 93% reduction in bleeding frequency. The annual bleeding rate was 30.5 in the on-demand group and 2 in the prophylaxis group. Most bleeding were hemarthrosis, and, of these, the highest frequency occurred in the target joints. Although the benefits of primary prophylaxis are most evident when started early in childhood, data from this study demonstrate an improvement in outcomes when compared to episodic treatment, even in the adult group[42].

The reversal, interruption or reduction in the progression of an already installed joint damage, through the institution of regular prophylaxis strategies, is still considered controversial. While there are observational reports showing that improvement would be a possibility[10], this randomized trial was unable to demonstrate a lesser progression of arthropathy, even with a very significant reduction in bleeding rates. Prophylaxis is likely to be effective in preventing chronic arthropathy, but less or not effective in changing the natural history of progression of an established joint damage[43].

The largest prospective study in prophylaxis is an American population-based study that evaluated 6,196 people with severe hemophilia A, older than 2 years of age, followed in 134 treatment centers between 1999 and 2010[44]. The mean age at study entry was 17.1 years. Over time, the adoption of prophylaxis increased from 31 to 59%; in 2010, 75% of those under 20 years of age were under prophylaxis regimen. Lower rates of joint bleeding were demonstrated among people on prophylaxis of all ages and during the 12 years of follow-up, corresponding to about half of those observed in the episodic treatment group.

The employment of prophylaxis in adults encompasses two distinct patient populations. In the first group are those who were exposed to primary or secondary prophylaxis at an early age and have good joint health in adulthood. There is some evidence from observational studies with a follow-up of up to 30 years that maintenance the prophylaxis regimen initiated in childhood preserves joint health, with detection of very mild arthropathy at 30 to 40 years of age[41]. In this regard, a more intensive regimen has been shown to be more effective than intermediate doses, but at a much higher financial cost[45]. There are also reports of young patients who discontinued prophylaxis early and yet experienced little bleeding and mild arthropathy[39,45]. However, no follow-up studies are available for patients over 40 or 50 years of age[46].

The second group of adults under prophylaxis refers to patients who have advanced chronic arthropathy, and who are under an episodic or tertiary prophylactic therapeutic modality, which is the case of the Brazilian population of adults with severe hemophilia. Few studies describe this patient population, with SPINART finding a median of 54.5 annual bleeding episodes in the on-demand group, compared to a median of 0 in the prophylaxis group[42]. Still, the three-year follow-up of these patients showed that prophylaxis was not able to improve the joint scores assessed by MRI compared to the group on episodic therapy, with both groups showing progressive deterioration in their joints[43].

CONCLUSIONS

Individualizing prophylactic regimen is the best strategy for its optimization, taking into account factors such as risk and bleeding rates, pharmacokinetic profile, joint status, physical activity and lifestyle. Understanding the variability of these conditions, and adjusting the prophylaxis regimen to them, would allow an optimization of resources and the preservation of patients' health and quality of life. In developed countries, zero tolerance to bleeding episodes may prove to be a reality to be achieved. In less affluent countries, prophylaxis must be a balance between the availability of factor concentrates and the optimization of these quantities, since even lower-dose prophylaxis has already been shown to be more effective than on-demand therapy[47].

Effective prophylaxis is essential for a favorable long-term outcome for adults and children with severe hemophilia. This effectiveness must take into account the available resources (mainly clotting factor concentrates), the triggers of bleeding episodes (presence of chronic synovitis or arthropathy, level of physical activity) and, mainly, the number of bleedings considered acceptable, in a personal context. In an ideal scenario, the number of bleeds should be kept to a minimum in order to prevent the development of permanent joint damage. The severity of chronic arthropathy cumulatively reflects the quality of care provided to a given patient[46]. Once joint damage has occurred, its progression will occur even if further bleeding in this topography is avoided[10].

Prophylaxis is the therapeutic modality of choice for people with severe hemophilia, being considered, in principle, a lifelong treatment. It should have an early onset, ideally as a primary, or at least secondary. Even lifelong tertiary prophylaxis seems to offer benefit, although further studies are still lacking. Individualized strategies should lead to an optimization of the dilemma between better joint outcomes versus involved costs.

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