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Optimal treatment for children with haemophilia: a review

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Background. Haemophilia is a rare, sex-linked inherited disorder caused by deficiencies of coagulation factor VIII or IX. The hallmark of severe haemophilia is recurrent bleedings into joints, resulting in lasting and irreversible changes and leading to haemophilic arthropathy. Treatment of haemophiliacs has undergone a revolutionary development. Prevention of joint bleed and haemophiliac arthropathy is possible by early regular administration of the deficient clotting factor, defined as prophylactic treatment. The purpose of this paper is to review the current knowledge of prophylactic treatment in haemophilia and the related aspects, and to discuss haemophilia care development and capabilities in Lithuania.

Materials and methods. The literature data for the period 1992–2008 concerning prophylactic treatment from historical to current knowledge and haemophilia care development in Lithuania were analysed.

Results. Data from observational studies and a recent randomized trial have shown that early prophylaxis is superior to on-demand treatment to prevent joint bleeds and arthropathy development. Despite quite a long experience with prophylactic treatment in some countries and the fact that it is recommended by international authorities, opinions concerning the prophylaxis differ in the world, and there is no uniform clinical practice because of lots of barriers. On-demand treatment strategy with plasma-derived factor concentrates is the standard practice in most clinics of Lithuania.

Conclusions. The importance of prophylaxis is unquestioned today. Although definitive recommendations concerning one uniform prophylactic regimen cannot be made so far, primary prophylaxis nowadays is considered to be a standard care of children with severe haemophilia. In Lithuania, haemophilia still causes a significant morbidity because of its suboptimal treatment.

Key words: haemophilia, prophylaxis, bleeding, joints

INTRODUCTION

Haemophilia is a sex-linked inherited disorder caused by deficiencies of coagulation factor VIII (haemophilia A) or IX (haemophilia B). It is a rare disease with a comparable prevalence worldwide and an estimated frequency of 1 per 5–10000 live male births (1, 2). Haemophilia is classified as a severe, moderate or mild disease based on circulating coagulation factor levels of <1%, 1–5% and >5%, respectively. This classification serves as a guide to the expected frequency of bleeding. Patients with haemophilia experience a spectrum of bleeding manifestations that occur either spontaneously or after a minimal trauma. Examples of bleeding include intracranial haemorrhage, deep muscle and joint haemorrhage, haematomas, bleeding following teeth extraction, postsurgical bleeding, easy bruising and mucosal bleeding. The hallmark of severe haemophilia is recurrent bleedings into joints (haemarthroses) (3). These haemarthroses tend to occur from the early age in life, and almost 80% of them have been found to occur in the elbows, knee and ankles (4). Joint and other bleeds can be treated or prevented by replacement of the coagulation factor concentrate that haemophilia patients lack. If bleeds into joints are untreated or inadequately treated, lasting changes in the joint capsule, joint cartilage and bone occur and lead to haemophilic arthropathy. It brings increasing disability to haemophilia patients. Haemophilic arthropathy is possible to prevent by a regular replacement of the deficient clotting factor started before any significant joint changes have occurred.

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TREATMENT IN HAEMOPHILIA

Haemophilia is treated by replacing the missing clotting factor in blood. There are two models of delivering intravenous replacement therapy. Patients with severe haemophilia are treated either in case of the first evidence of bleeds to stop bleeding (on-demand), or with regular infusions of the clotting factor in order to prevent spontaneous bleeding episodes (prophylaxis). On-demand therapy, also known as episode-based therapy, is the administration of the deficient clotting factor in response to a bleeding episode at the level needed to stop bleeding. The goal of this therapy is to treat and stop bleeding as soon as possible with the aim of preventing a long-term damage of the musculoskeletal system. The effect of the treatment depends on how fast it is begun after the bleeding has started. Prophylaxis is a scheduled administration of clotting factors, usually 1–3 times a week. Prophylaxis is defined as "treatment by intravenous injection of factor concentrate in anticipation of and in order to prevent bleeding" (5). Consensus definitions for prophylaxis have been proposed by the European Paediatric Network for Haemophilia Management (PedNet) in 1998 and reviewed in 2002 (5–7) (Table). Primary prophylaxis defined by the PedNet in 1998 was "regular, continuous (long-term) treatment started before the age of 2 or after the first joint bleed". A later onset of prophylactic treatment was called secondary prophylaxis, if "regular continuous treatment is started at the age of >2 years or after more joint bleeds". Recently, the PedNet group has provided new definitions for different treatment schedules: "primary prophylaxis A is the regular continuous treatment started after the first joint bleed and before the age of 2 years", while primary prophylaxis B refers to "regular continuous treatment started before the age of 2 years without previous joint bleeds" (8).

EFFECTIVENESS OF PROPHYLAXIS

Prophylaxis offers the potential to avoid chronic haemophilic arhropathy in boys with severe haemophilia (9). Historically, it was based on the observation that the moderate form of haemophilia is associated with a considerably lower risk of spontaneous joint bleeds and arthropathy than severe haemophilia. Therefore, the concept behind the development of prophylaxis was to keep plasma levels of factor VIII or IX above 1%, thereby converting severe haemophilia to moderate. Introduction of primary prophylaxis was pioneered by Professor I. M. Nilsson and her colleagues in Malmö, Sweden, in the 1960s. The very first twenty-five year experience results, reported in 1992 and updated in 1997, clearly indicated that joint disease could be prevented if the factor level could be kept above 1% (10, 11). The later results of other long-term observational studies as well as data recently reported by Manco-Johnson et al. on a prospective randomized controlled clinical trial of primary prophylaxis versus on-demand therapy for young boys with severe haemophilia A also provided clear evidence in support of prophylaxis with the aim of preventing joint bleeds and arthropathy (3, 12–21). Ever since those observations have beeve reported, the effectiveness of prophylaxis to prevent bleeding in patients with severe haemophilia has been unquestioned. The excellent outcome measures, mainly musculoskeletal results, observed in patients on primary prophylaxis regimens, has led the World Haemophilia Organisation (WHO), the World Federation of Haemophilia (WFH) and a number of national haemophilia organizations to recommend primary prophylaxis as a standard care for young boys with severe haemophilia.

DEFINITIONS AND REGIMENS OF PROPHYLAXIS

Primary prophylaxis for haemophilia is defined as replacement of the missing clotting factor activity starting from 2 years of age or prior to the 2nd joint haemorrhage (5, 22). No optimal and universally adopted prophylactic regimen exists so far. The gold standard of primary prophylaxis regimen is considered to be the Malmö regimen. It involves the infusion of 25–40 units/kg of factor VIII on alternate days (minimum 3 times per week) for haemophilia A (HA) cases and 25–40 units/kg of factor IX twice weekly for haemophilia B (HB) cases (10, 11). There exist alternative or modified programs of primary prophylaxis, which include the Dutch intermediate dose and the Canadian dose-escalation protocols (3, 23). The Dutch regimen was presented as a strategy to give prophylaxis in intermediate dosages of 15–25 IU/kg 2–3 times a week for HA patients and 30–50 IU/kg 1–2 times a week for HB patients. Prophylaxis is started after the first

Table. **Revised definitions of primary and secondary prophylaxis**

Model	Revised definition
Primary prophylaxis determined by age	Long-term continuous* treatment started before the age of 2 years and prior to any clinically evident joint bleeding
Primary prophylaxis determined by first bleed	Long-term continuous* treatment started prior to the onset of joint damage (presumptively defined as having had no more than one joint bleed) irrespective of age
Secondary prophylaxis	Long-term continuous* treatment not fulfilling the criteria of primary prophylaxis
Short-term prophylaxis	Short-term treatment to prevent bleeding

* With the intent of treating 52 weeks / year until adulthood and receiving treatment at least 46 weeks / year.

one to two joint bleeds, and doses were increased depending on spontaneous bleeding frequency (16). An individualized approach to avoid the unnecessary administration of prophylaxis in patients with the mild clinical phenotype and to see whether a reduced clotting factor use could result in acceptable outcomes is currently used in an ongoing, prospective, dose-escalation primary prophylaxis study in Canada (3). In this study, started in 1997, tailored prophylaxis for boys aged 1–2.5 years with severe HA (defined as FVIII levels <2%) is started with once weekly factor infusions (dose 50 IU/kg) and is escalated according to defined criteria, if unacceptable bleeding occurs. All patients also receive episodic treatment for breakthrough bleeds. The long-term musculoskeletal outcomes with the so-called full-dose or high-dose Malmö regimen are excellent for compliant patients (11). Musculoskeletal outcomes with alternative prophylaxis regimens are also very good, with similar clinical and radiological scores and with significantly reduced costs (12, 13). It is possible that different prophylaxis regimens may achieve the common goal of preventing bleeds and the related joint damage (7). Analysis of the results of these three primary prophylactic strategies could lead to an optimal protocol for primary prophylaxis in young boys with severe haemophilia.

Secondary prophylaxis could be defined as a prophylaxis started after the onset of joint damage or any other significant joint bleeding (5, 22). Definitions may also be related to age (>2 years) or bleeding history (≥2 joint bleeds) (5). The chief goal in secondary prophylaxis is the same as in primary prophylaxis – to prevent recurrent bleedings and to stop the progression of joint destruction. Its benefits have also been proved. Studies show that older patients who had started prophylactic infusions later in life retained joint function and less pain and disability compared to historic controls (5, 24). It is assumed that the established joint disease will not regress after initiation of secondary prophylaxis, but the ongoing joint damage may be limited (7, 20).

OUTCOME MEASURES OF PROPHYLACTIC TREATMENT

According to the WFH, patients on prophylaxis should be evaluated once every 6–12 months for the musculoskeletal status (clinical and radiological scores), use of clotting factor concentrates, inhibitor development, transfusion-related infections and quality of life (QoL). Musculoskeletal outcome is the hallmark of the disease. Therefore, assessment of the musculoskeletal or orthopaedic status is crucial when assessing individuals with haemophilia. In the past, musculoskeletal assessment was hampered by the discrepant rating scales. A few measures existed as joint assessment instruments; however, they lacked sensitivity to small changes, did not accounted for normal development and were never formally validated (25–27). Progress has been recently achieved through the use of a defined set of international standards (28–31). Several International expert groups collaborated trying to construct the best methods to measure joint health in order to monitor the effectiveness of prophylaxis (26, 32). In 2002, the Physiotherapy Expert Working Group of the International Prophylaxis Study Group (IPSG) harmonized existing joint health scores (WFH, Colorado, and Stockholm) to develop a new, more sensitive tool. In 2003, a new consensus measure, the Haemophilia Joint Health Score (HJHS), based on the above-mentioned existing scoring systems was developed. The HJHS aims to provide one international scoring instrument for children with haemophilia. It is an 11-item scoring tool for assessing joint impairment in children aged 4 to 18 years, which is sensitive to normal growth and to early changes in joints (28). In September 2003, physiotherapists conducted a reliability study of the HJHS. Excellent results were obtained, with the inter-observer reliability coefficient of 0.83 and the test–retest coefficient of 0.89 (29). In 2006–2007, a two-year multi-centre validation study of the HJHS was completed (results have not yet been reported). Once the results are evaluated, this internationally developed scoring instrument will be available for the clinical use and allow for comparison of clinical studies worldwide (29).

Health-related quality of life (HRQoL) has emerged as an important measure of health outcomes as it allows observation of both clinical indicators of health benefit and data gathered from the patients' perspective. Only over the past few years haemophilia-specific questionnaires have been developed for children and adults (1, 32–37). One of the first self-report tools is the Haemo-QoL instrument, which is a set of disease-specific and age-related questionnaires to measure quality of life (QoL) in children with haemophilia (33). The questionnaire is validated in six European countries and comprises information on socio-demographic, psychosocial and health economic information (34). Prophylaxis seems to improve significantly HRQoL scores in various domains (38, 39).

ISSUES FOR DISCUSSION

Extensive data from observational studies and a recent randomized trial have established that early prophylactic treatment prevents bleeds and arthropathy in boys with severe haemophilia (40). However, opinions on how to perform prophylaxis differ in the world. Despite the controversies on the optimal dose and frequency issues of prophylactic regimens that are discussed above, the optimum time of starting, the time when to stop, if at all, are still under discussion. Therefore, at present, no definitive recommendation can be made regarding a single primary prophylaxis regimen. Further clinical studies are needed to define the optimal prophylaxis regimens that take into consideration the age and activities of an individual with haemophilia, the clinical severity of the disease and the available resources for implementing expensive prophylaxis programmes (3).

WHEN TO START AND WHEN TO STOP PROPHYLAXIS

Whether primary prophylaxis should be started before or shortly after the first joint bleed remains a matter of debate (15, 21, 41). The importance of starting prophylaxis before the onset of joint damage is well established, therefore some authors are of the opinion that the ideal time to start treatment is before the occurrence of the first joint bleed (9). In practice, it means the age of about one year, i. e. when a child starts to become more mobile and begins walking (11, 41). The rationale for this attitude is to avoid the risk of a target joint development that may result from recurrent bleeds into the joint (42). Observations have also shown that even a small number of clinically irrelevant or unrecognizable joint bleeds may cause irreversible joint alterations (41, 43, 44). This suggests that subclinical bleeds may trigger the development of arthropathy if the regular prophylaxis starts too late. In other centres, isolated joint bleeds before starting the prophylaxis are considered acceptable. The argument for accepting a few joint bleeds before starting the prophylaxis is that the bleeding phenotype may vary among children with severe haemophilia, and this allows to assess the child's individual proneness to bleeding episodes and to adjust the treatment accordingly (42). Earlier studies and clinical experience have shown that up to 10–15% of individuals with the laboratory phenotype of severe haemophilia may be free of spontaneous bleedings and behave clinically as those with a moderate or mild disease (3, 42). The first joint bleeds in these patients may occur slightly later than other haemorrhages – at 1.2–3 years and sometimes as late as at 7 years of age (45). Furthermore, according to some data, not all joints that undergo recurrent bleeding will develop into a target joint (13). Therefore, some authors assume that initiation at a uniform, predetermined age may lead to the over-treatment of patients and unnecessary costs (46). Another argument is that the later regular injections are started, the better the chance of avoiding the need for a central venous line (42). Astermark et al. in their study found that the age at the start of prophylaxis was an independent predictor for the development of arthropathy ($p = 0.0002$) (47). These results would justify an early start of the prophylaxis, i. e. at the age of one year. To establish the definitive optimal time of starting the primary prophylaxis, prospective studies with a minimum follow-up until adulthood should be performed. Until more data are available, an early start of prophylaxis following no more than two joint bleeds and continuation throughout childhood and youth are recommended today to allow undisturbed juvenile growth and maturation of the skeletal system (7, 47).

The time of prophylaxis discontinuation is also very important, but the related opinions still remain even more controversial. Although it is known that joints become less vulnerable during adolescence, i. e. with the cessation of linear growth and after joint maturation, the question whether and when the primary prophylaxis can be safely discontinued in adolescents and young adults remains unanswered (7). Relevant information on the long-term outcome of prophylaxis can be extrapolated from the experience of the haemophilia centres that have the longest experience in primary prophylaxis (Malmö, Sweden and the van Creveldkliniek in the Netherlands). Primary prophylaxis is recommended to be life-long. Dutch investigators have suggested that, in their experience, prophylaxis may be safely discontinued in subgroups of patients with severe haemophilia but with a milder bleeding phenotype (48). Additional information, provided by van Dijk et al., supports the data that the phenotype in patients with severe haemophilia varies, and some of them may require less therapy for the same outcome (49). More research with a long-term follow-up is needed to clarify the optimal policy regarding the discontinuation of prophylaxis and its role in QoL and orthopedic complications.

BARRIERS TO PROPHYLAXIS

Despite the undeniable advantages of prophylactic treatment, there are barriers such as absence of the perception of its need, difficulties of venous access, the costs and availability of the clotting factor concentrate that hamper the widespread use of primary prophylaxis.

Perception of need

Starting prophylaxis at the age of 1–2 years is certainly a physiological barrier for many families. At least 50% of the patients have no family history of haemophilia and no experience of the long-term effects of bleeding symptoms (50). Therefore, parental education and understanding of the development of haemophilic arthropathy as well as awareness that only early prophylaxis can prevent it are the key points.

Venous access and fear of complications

Prophylaxis with regular and frequent infusions requires the need for an adequate and stable venous access and represents the main barrier to treatment feasibility, especially in young kids. Two different approaches have been used to overcome such difficulties: an incremental schedule of prophylactic infusions and the use of alternative forms of venous access. In many haemophilia centres, peripheral veins are considered the first-choice access and preferred whenever possible; however, this requires a strong commitment by the healthcare personnel. Prophylactic treatment is usually started using a peripheral vein with 1–2 injections a week and slowly increases in the frequency (42, 51, 52). If peripheral vein access is not adequate, an implantable venous access device, such as a Port-a Cath, or creation of an arteriovenous fistula (AVF) are the alternatives (9, 53–58).

Costs and availability of factor concentrate

The greatest challenge regarding factor prophylaxis in the haemophilia population in many countries is the extremely high costs of clotting factor concentrates and their availability. It makes the prophylactic treatment a distant dream for the majority of patients with haemophilia worldwide.

HAEMOPHILIA CARE IN THE WORLD

Despite the clear evidence of prophylaxis effectiveness, it has not been uniformly adopted in clinical practice, even in developed countries. The fact is that long-term factor prophylaxis is very demanding on both patients and families and expensive for health resource providers. In 1998, the PedNet made a survey of the current status of treatment of haemophilic boys at 20 centres in 16 western European countries and showed significant disparities among the centres: 9 of 18 centres provided continuous prophylaxis to 80–100% of their patients, 5 centres provided it to 55–80% and the rest 4 centres to 15–40% of the boys (59). This survey was updated in 2003 and showed the changing pattern of haemophilia care in Western Europe. Regular, continuous long-term prophylaxis was provided in all PedNet centres, more than 50% and 80–100% of boys being treated this way in 20 / 22 and 15 / 22 centres, respectively (60). A survey conducted in 2002 confirmed that in the US only 33% of boys under 5 years of age with severe haemophilia A were on a full-dose prophylaxis (61).

HAEMOPHILIA CARE IN LITHUANIA: WHERE DO WE STAND?

Until 1990, diagnostics and treatment facilities for patients with coagulation disorders were scarce in Lithuania. When Lithuania restored its independence in 1990, all the facilities and care for patients with coagulation disorders started improving. In 1994, the Lithuanian Haemophilia Association (LHA) joined the World Federation of Haemophilia (WFH). Later, a haemophilia centre was established in Klaipėda, and further specialized units for haemophilia care became available in the haematological departments of Vilnius and Kaunas university clinics (62).

In 1994, the Malmö–Klaipėda (Sweden–Lithuania) twinning programme was approved by the WFH. One of the first steps in this collaboration was to set up a registry of the haemophilia patients in the Klaipėda area. In order to get an idea of the standard of haemophilia care in Lithuania, Lithuanian patients with haemophilia, treated on-demand, were compared with those in a matched cohort of prophylaxis patients from Malmö. The most objective parameter in this study was considered to be the orthopaedic joint score. Comparison between the groups showed that the joint score in the Klaipėda patients was by far worse that in the oldest patients (18–32 years) in the Malmö cohort, even though the Malmö patients were on a prophylactic regimen which would be inadequate by nowadays standards (63). Data from this study led to the conclusions that future steps should be made to implement a more intensive replacement therapy for Lithuanian haemophiliacs, started at a younger age, and to complete the registry.

In 1998, Ivaskevicius et al. conducted a stud, that assessed detailed phenotypic and genotypic data from 71 unrelated HA and HB families comprising about 80% of Lithuanian haemophilia patients (62). Causative mutations were identified in 96.8% of unrelated HA patients and in all HB patients. Based on the obtained data, the National Haemophilia Registry was supposed to be established in Lithuania. Despite the failure to establish the National Haemophilia Registry at that time, the major findings obtained over this period have dramatically improved the evolution of haemophilia care in Lithuania as regards treatment and genetic counselling. Such a registry is still of essential importance for Lithuania.

There is 144 haemophilia A and B patients in Lithuania (46 of them are children under 18 years of age). On-demand treatment strategy is the standard practice in most patients in Lithuania. Patients have access to an adequate on-demand therapy, but it is not unlimited. Most of the patients receive plasma-derived factor concentrates and only very few of them recombinant ones. Home treatment is practiced by the majority of patients with severe or moderate haemophilia, although difficulties with venous access exist in a number of families. They were overcome by the use of central venous access devices, Port-a Cath, in some children with severe haemophilia. As home treatment is essential and very important for early bleeding episodes, every haemophiliac should have an adequate amount of the factor concentrate at home to treat and stop bleeds. In Lithuania, an individual with haemophilia has to come to a health care provider for every three doses, because this is the amount of the factor concentrate that may be prescribed during one visit. This imposes special demands for the patient and family and sometimes hampers delivering an adequate and timely replacement therapy.

In 2007, guidelines for the care and treatment of haemophiliacs in the Baltic countries were published. They are based on the classical Swedish full-dose regimen and recommend using recombinant factor concentrates for haemophilia treatment. From 2007, primary prophylactic treatment is recommended in Lithuania as the treatment of choice for newly diagnosed severe haemophilia A or B in children. Introduction of prophylactic treatment is a big challenge for haemophiliac children as well as for their families. Factors limiting the acceptance of primary prophylaxis in Lithuania are similar to those in other countries. Despite occasional problems with factor availability, the lack of perceived need and the effort-demanding nature of prophylaxis are the most significant barriers to applying the prophylactic regimen in Lithuania.

CONCLUSIONS

Haemophilia care has improved dramatically. The prophylactic treatment of haemophilia was introduced some 40–45 years ago, and evidence clearly suggests that long-term prophylaxis is superior if compared with on-demand treatment and can prevent arthropahy in persons with severe haemophilia as well as enable them to live as normal life as possible. A consensus meeting concluded that "long-term prophylaxis should be the standard for treating children with severe haemophilia in developed countries with strong economies and health care resources" (5). Although the benefits of prophylaxis seem unquestionable, several issues remain to be more extensively investigated (64). The optimum prophylactic treatment for persons with haemophilia continues to be debated despite decades of experience (65). Other questions remaining to be answered include the reasons for inter-individual variability in bleeding phenotype, as well as predictors and reversibility of joint damage (64).

In Lithuania, where a shift from on-demand to prophylactic treatment is not possible, haemophilic arthropathy, due to repeated joint bleeds, remains the major cause of morbidity in haemophiliacs. The reasons include not only treatment on-demand, which is administered to most of Lithuanian haemophiliacs, but also difficulties with venous access, sometimes factor availability and the lack of perceived need to treat bleeds adequately. Despite the possibility to initiate primary prophylaxis in newly diagnosed haemophilia patients in Lthuania, the introduction of this model of treatment is a big challenge for children, their families and health care providers.

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OPTIMALUS HEMOFILIJA SERGANČIŲ VAIKŲ GYDYMAS (APŽVALGA)

Santrauka

Įvadas. Hemofilija yra reta paveldima liga, kai pažeidžiami X chromosomos genai ir tai nulemia VIII (hemofilija A) arba IX (hemofilija B) krešėjimo faktoriaus stoką. Pagrindinis sunkia hemofilijos forma sergančių ligonių klinikinis požymis yra pasikartojantys kraujavimai į sąnarių ertmę, sukeliantys ilgalaikius ir negrįžtamus sąnarių pokyčius bei nulemiantys hemofilinės artropatijos išsivystymą. Hemofilinės artropatijos galima išvengti tik taikant ankstyvą ir ilgalaikį pakaitinį profilaktinį gydymą trūkstamu krešėjimo faktoriumi. Šios apžvalgos tikslas – aptarti šiuolaikinius hemofilijos gydymo ypatumus ir jos priežiūros plėtrą bei galimybes Lietuvoje.

Metodai. Išanalizuota 1992–2008 m. literatūra, nagrinėjanti profilaktinį hemofilijos gydymą bei hemofilijos priežiūros plėtrą Lietuvoje.

Rezultatai. Stebimųjų tyrimų bei pastaruoju metu atlikto kontroliuojamo atsitiktinių imčių tyrimo rezultatai rodo, kad anksti pradėtas profilaktinis hemofilija sergančiųjų gydymas yra pranašesnis už gydymą pagal poreikį kraujavimų metu, kadangi užkerta kelią kraujavimams į sąnarius ir hemofilinės artropatijos išsivystymui. Nepaisant hemofilija sergančių ligonių profilaktinio gydymo patirties kai kuriose šalyse, požiūris į profilaktinį gydymą skiriasi, o jo įdiegimą į klinikinę praktiką apsunkina daugelis kliūčių. Didžiajai daliai hemofilija sergančių ligonių Lietuvoje kraujavimų metu yra skiriamas plazminės kilmės krešėjimo faktorius.

Išvados. Profilaktikos veiksmingumas šiandien nediskutuotinas. Nors bendro standartinio profilaktikos režimo iki šiol nėra, pirminės profilaktikos taikymas sunkia hemofilijos forma sergantiems vaikams laikomas standartiniu gydymo metodu. Neoptimalus hemofilija sergančių ligonių gydymas Lietuvoje yra pagrindinė negrįžtamų kaulų ir raumenų pokyčių, ilgainiui nulemiančių šių ligonių negalią, priežastis.

Raktažodžiai: hemofilija, profilaktika, kraujavimai, sąnariai