

Event Report: EHC Round Table of Stakeholders on 'Orthopaedic Aspects in Haemophilia'

About the event

On Tuesday 27 July 2017, the European Haemophilia Consortium (EHC) held its second Round Table of Stakeholders of the year at the Warwick Brussels Hotel in Brussels, Belgium. The event brought together over 50 participants representing patients, healthcare professionals and the pharmaceutical industry to discuss orthopaedic aspects in haemophilia.

The event's agenda, list of speakers and presentations can be consulted online on the [EHC website](#). Pictures from the event can be viewed on the [EHC Facebook page](#).

During the event, Dr Miroslav Mikolášik (Slovakia/EPP) gave a speech to the audience to highlight the importance of a multidisciplinary approach in the treatment of haemophilia, as well as the importance of access to treatment to maintain musculoskeletal health.

On Orthopaedic Aspects in Haemophilia

Haemophilia is a rare and congenital bleeding disorder caused by a genetic defect, resulting in a lack of or insufficient coagulation factors VIII or IX in the body. In affected individuals, this causes an inability to clot blood, leading to bleeds in the joints, muscles and soft tissues. Although haemophilia is traditionally viewed as a bleeding disorder, it can also be seen as a disorder affecting the musculoskeletal system. In fact, joint bleeds, or hemarthrosis, will over time damage the joints, sometimes severely, which can lead to disability. Therefore, increasing the patients' clotting ability and maintaining the health of his/her musculoskeletal system are closely interlinked objectives that should be sought when treating people with haemophilia. This is why it is important to have a multidisciplinary approach to the treatment of haemophilia and include all the necessary healthcare professionals, such as orthopaedic surgeons and physiotherapists. In particular, patients with haemophilia and inhibitors are at increased risk of disability. This is because of the development of antibodies (inhibitors) to the regular treatment and therefore, replacement therapy cannot be used. These patients rely on bypassing agents, which have a shorter half-life and, as a result, offer less protection against bleeds compared to traditional replacement factor concentrates. Inhibitors lead to increased and accelerated joint damage and therefore, these patients will require more surgical procedures to replace affected joints. However, performing surgeries on these patients is particularly difficult and requires much preparation from the patient and expertise from the medical team in charge of the surgery.

Findings and discussions

On bleeds prevention and treatment

As noted above, bleeds in the joints are the main cause of hemarthrosis in haemophilia. Therefore, it is essential to prevent bleeds and, if they occur, to treat them quickly. Currently, the best method to prevent bleeds is the administration of prophylactic replacement treatment to patients from an early age, combined with regular physiotherapy and exercise. In fact, the benefits of prophylactic as opposed to only on-demand¹ treatment are well established and are even observed when prophylaxis is started in adult or

1 A. Coppola et al. *Blood transfus.* 2008 Sep; 6(Suppl 2): s4-s11; Liesner et al. *Br J Haematol.* 1996;92(4):973-978; Szucs et al. *Haemophilia.* 1998;4(4):498-501; Yee et al. *Haemophilia.* 2002;8(2):76-82; Panicker et al. *Haemophilia.* 2003;9(3):272-278; Feldman et al. *J Thromb Haemost.* 2006;4(6):1228-1236 ; Manco-Johnson M. et al, *NEJM*, 2007; 357:535-44.



elderly patients². This is also why it is important to not stop prophylaxis once patients reach adulthood, as all the investment made during childhood will be lost if prophylactic treatment is discontinued.

To ensure that prophylaxis is most beneficial, patients need to be adherent and comply with a specific treatment regimen, which can be burdensome and lead to non-adherence. This is why patients should be encouraged to have a basic understanding of pharmacokinetics and how the factor concentrate works (i.e. concepts of peaks and troughs) so that it is clear to them that lower factor levels will increase the risk of bleeds. To this end, it was noted that the management of haemophilia is becoming increasingly challenging as it needs to be increasingly tailored to each patient. This means that personalised treatment approaches are developed for each patient based on several parameters, such as joint health, lifestyle, pharmacokinetics and genetics. Such an approach aims to ensure that patients have the highest possible level of protection at all times and a minimised risk of bleeds. However, it was stressed that determining patients' treatment goals should be agreed by both the patient and clinicians. A joint approach to establishing treatment goals will promote adherence and minimise the risk of bleeds.

The role of the physiotherapist in preventing and treating joint bleeds is also very important. Specialised physiotherapists are involved in a number of activities within the haemophilia treatment centre, including carrying out research, treating patients both in acute and chronic phases, performing joint assessments and ultrasounds. They also work alongside haematologists and orthopaedic surgeons to identify and recommend conservative treatments to improve the patient's health, such as providing advice on the safe practice of sport activities and weight management, as well as prescribing rehabilitation exercises and orthosis. Additionally, they provide support in identifying good candidates for orthopaedic surgery. Physiotherapists are also an important player in linking the haemophilia treatment centres to the local non-specialist physiotherapists who will work on a weekly basis with patients. By informing the non-specialist physiotherapists on the specifics that need to be considered when working with haemophilia patients, it is ensured that the patients still receive the maximum benefit of physiotherapy without having to visit the treatment centre.

Practicing safe sports and weight management are both key to maintaining joint health. In fact, patients with a body mass index (BMI) of over 30 are five times more at risk of developing osteoarthritis and increasing risks of joint bleeds. Finally, it was reminded that physiotherapy is very inexpensive compared to replacement factor treatment and that unlike replacement factor, physiotherapy has practically no side-effects.

Once a bleed occurs, treatment should be administered as fast as possible and therefore availability of home treatment, the patient's ability of recognising a bleed and good venous access are all required to correctly treat the bleed. However, even in individuals that have been on prophylactic treatment since birth, bleeds, and even subclinical bleeds, can still occur and can damage the joints over time³. This is why early detection of joint damage is an important part of treating joint diseases.

Currently, there are several methods available to diagnose joint damage: magnetic resonance imaging (MRI), X-ray and ultrasonography. MRI is the gold standard for identifying joint damage because it allows to thoroughly examine soft tissue. However, this technique has several downsides, including its high cost and long waiting lists to use the machine. Furthermore, it is time consuming and it is very unpractical in young children, who often require sedation during the examination. X-rays only show advanced stages of joint damage and therefore, do not help in preventing joint diseases. Ultrasonography is widely available in all hospitals, inexpensive, sensitive to soft tissues and allows to detect biomarkers of joint disease activity and degenerative damages. However, it also has downsides, as examination methods and results are not standardised and findings are very operative-dependent, which leads to variable findings for a

² Kempton C, et al. Presented at: XXXth International Congress of the World Federation of Hemophilia; July 8-12, 2012; Paris, Franco; Manco-Johnson MJ. et al. Randomized, controlled, parallel-group trial of routine prophylaxis versus on-demand treatment with rFVIII-FS in adults with severe hemophilia A (SPINART) [published correction appears in *J Thromb Haemost.* 2014;12:119–122.] *J Thromb Haemost.* 2013;11:1119-1127.

³ J. Oldenburg *Blood.* 2015 Mar 26;125(13):2038-44.

single patient. It is for these reasons that a few years ago a protocol, HEAD-US, was proposed to diagnose joint damage of the ankles, knees and elbows- the most affected joints in haemophilia patients - using ultrasonography. The training for this protocol can be easily taught and allows practitioners to grade the changes within cartilage and synovium up to a maximum score of eight. This protocol has proven both very practical, as it allows to carry out an evaluation in 15 minutes, and sensitive, as it can detect minor changes in joints and subclinical bleeds. This has shown to promote adherence amongst patients with minimally damaged joints. However, it should be noted that this technique is not useful for patients with severely damaged joints. A number of studies⁴ were performed to ensure that the findings of the protocol are relevant, meaningful, reliant and reproducible and it was shown that the protocol is more sensitive compared to other techniques. Studies were carried out both in adults and children and they show that HEAD-US brings additional information to joints health scores. A downside of this system is that maintaining skills is difficult unless the ultrasound technique is used in daily medical practice.

Whenever individuals with haemophilia (with or without inhibitors) are exposed to repeated bleeds in a single joint (i.e. target joints), radioactive synovectomy should be considered as an option to stop bleeds, alleviate pain, improve range of movement and allow sport practice to strengthen joints, which in return will reduce the risks of bleeds and halt cartilage and joint destruction. However, this procedure will not reverse a joint's health.

Radioactive synovectomy consists of the removal of the synovial membrane by intra-articular application of radioisotopes. Although it uses radiopharmaceuticals, the penetration of these products is very limited and therefore the risk of radiation is minimal and mostly theoretical. Additionally, this procedure will be performed together with a nuclear therapist and in accordance to guidelines from the European Association Nuclear for Medicines, as well as European and/or national guidelines on safe chemical elements that can be used in radiotherapy. Currently, in Europe, the chemical elements rhenium and yttrium are approved for this procedure.

This procedure is effective in 60 to 80 per cent of patients, while for some 20 to 25 per cent of patients it is ineffective and will have to be repeated after six months. The procedure can be done in two joints at once, as long as it is not in the same joints. Clinicians need to be careful in considering candidate joints to ensure that, for instance, patients can comfortably use crutches after the procedure.

Side effects to this procedure are mainly at the site of injection, such as bruises, infections at local site, extravasation, allergies, fever and the theoretical risk of exposures to radiations. To reduce the transport of radioactive material into the lymphatic system, the patient's joint should be immobilised after the procedure. In some cases, steroids can be locally administered to minimise allergic reactions from the radioactive material.

Radioactive synovectomy services should be set up jointly with the nuclear medicine department of the hospital where the haemophilia centre is located. The procedure should be done by a qualified healthcare professional, such as an orthopaedic surgeon, with guidance from a radiologist and the support of the staff from the haemophilia centre.

Finally, radioactive synovectomy is very cost-effective compared to surgery, as it can be done on outpatients, several patients can be treated in one day and the use of coagulation factor is limited. In particular, this procedure can be very beneficial in countries with limited resources.

On orthopaedic aspects in people with haemophilia and inhibitors

As noted above, inhibitor development is a serious complication in haemophilia care that arises when an individual affected by haemophilia develops an immune response to the replacement coagulation factor concentrate used in his/her treatment. This leads to difficulties in preventing and managing bleeds because the individual does not respond to replacement prophylactic treatment and bleeds cannot be easily controlled. This quickly leads to decreased quality of life through increased and more severe joint

4 Fischer K, et al. *Thromb Haemost* 2015; 13 (Suppl. 2):1-997. Poster presented at ISTH 2015 Toronto, Canada. PO256-TUE.

arthropathy. Although orthopaedic surgery in people with haemophilia has become very common, there are still concerns in performing orthopaedic replacement surgery in people with inhibitors. This is due to the difficulty of managing bleeds, potential side effects, which include uncontrollable bleeds and death, poor wound healing, risk of infection, anamnestic response (i.e. an increase in inhibitor levels), thromboembolism as well as associated costs with these types of surgery and fear from treaters to carry out surgeries on these patients. For all of these reasons, this type of procedure should be carefully considered, discussed and prepared in close consultation with the patient.

Bleeds in people with haemophilia and inhibitors can be managed with bypassing agents, but as it is still unclear exactly how this treatment works, it is difficult to measure factor levels in the patient, giving an unclear picture of the factor level activity of the patient during surgery. Therefore, in addition to bypassing agents, thrombin generation products are used during surgery in people with inhibitors. Other limitations for people with inhibitors are the fact that not all bypassing agents work in the same way and that some of these agents can sometimes be prothrombotic, requiring close monitoring of patients, especially following surgery. This can be straining on the human resources of the haemophilia treatment centre and therefore, one should consider the use of an infusion pump. Another product that should be used in addition to bypassing agents is tranexamic acid, which prevents clots from breaking down. Porcine factor VIII can also be used as it shares a lot of the features of human factor VIII. This product is no longer made from animal product but from recombinant technology. Finally, novel non-replacement therapies could also be useful in surgery in patients with inhibitors. In terms of after-surgery care, a blood transfusion is often required.

In order to carry out surgery on people with inhibitors, the haemophilia treatment centre needs to have both funds and medical expertise to manage potential surgery side-effects (as noted above). The clinicians that will carry out the surgery need to take into consideration many variables, including the type of surgery, the levels of inhibitors, the patient anamnestic response and the patient response to bypassing agents and comorbidities, in particular liver damage. The recommendation from speakers was that whenever a joint is getting swelled and damaged, action needs to be taken either in terms of treatment upgrade, arthrocentesis, synovectomy, arthroscopic treatment or angiographic embolization.

Finally, it was mentioned that, despite the potential complications, surgery outcomes have considerably improved in the last 15 years, which has allowed patients with inhibitors to undergo them and to improve their quality of life.

From a patient perspective, preparation is of high significance, in particular attending meetings with the whole multidisciplinary team to increase patient confidence. The choice of treatment used during surgery is also very important and to support this decision patients should undergo thrombin generation tests as well as ROTEM tests. Another key aspect is to be in good physical health so to strengthen muscles and to minimise risks of infections. Patients are advised to ensure that their dental care is optimal and to start physiotherapy and exercise, if possible, at least one year before surgery. They also need to prepare mentally and engage with their family and social circles to seek emotional support in preparation for the surgery and during the recovery process. Patients need to understand that recovery will be slow and should, together with the healthcare professionals, develop a post-surgery treatment plan and set shared objectives. This will reduce stress.

It is recommended that patients with port-a-cath should not undergo surgery, as the risks of infection are too high.

Conclusions

All speakers stressed the importance of multidisciplinary collaboration amongst different healthcare professionals and healthcare services to ensure comprehensive care for people with haemophilia. To this end, it was noted that the European Association for Haemophilia and Allied Disorders (EAHAD) had set up two working groups to establish best practices and promote European collaboration for nurses and physiotherapists specialised in haemophilia. Additionally, all speakers emphasized the importance of

consulting with specialised healthcare professionals when wishing to address orthopaedic issues in people with haemophilia.

There were some discussions on novel replacement and non-replacement haemophilia therapies and their potential to turn severe haemophilia patients into moderate or even mild haemophilia patients. Additionally, with the advent of early prophylaxis and novel therapies, it is likely that clinicians will see less and less acute major hemarthrosis and therefore, it is important to develop sensitive tools to monitor the progress of joint damage, even if this will occur over many years. On this point, participants remarked that new treatments are developed and evaluated based on very subjective measures, such as pain, annual bleeding rates and joint mobility. It was suggested that more standardised tools, such as HEAD-US and ultrasound technology, are more precise⁵ than the perception of doctors and patients. For instance, studies⁶ showed that ultrasound imaging helped to change 70 per cent of patients' treatment protocols. In fact, hemarthrosis leads to increased inflammation, which also causes pain. Ultrasound technology can help discern whether pain is caused by a bleed or by inflammation, such as arthritis. In the case of arthritis-mediated pain, this cannot be treated with factor replacement therapy and therefore, it should be considered to couple replacement therapy with other treatment methods. For these reasons, it is expected that ultrasound technology will be increasingly used to complement other measures used in joint health assessment scores. As the medical technology progresses, it may even be possible for individual patients to monitor their joint health on their own, thanks to portable ultrasound devices.

Considering all the new treatment and technology advances, it is of utmost importance to continue educating patients so that they can make an informed decision about the overall management of their condition.

5 Timmer et al. *Haemophilia* (2017), 23, e133-e69.

6 Aznar J et al. *Haemophilia* (2015), 21, e122-e50.