

Hyaluronic Acid and Chondroitin Sulfate Viscosupplementation in Severe Arthropathy of Hemophilic Patients

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Type A hemophilia is a hereditary coagulopathy caused by coagulation factor VIII deficiency, clinically characterized by hemorrhagic phenomena of different intensity, depending on disease severity or on the intensity of the injury suffered by the patient. The severe forms of the condition may become complicated by spontaneous sometimes even life-threatening bleeding, in the absence of factor VIII substitution treatment. Considerable bleeding may occur at the intraarticular, intramuscular or mucosa level, whereas life-threatening bleeding may occur anywhere in severe injuries. Two types of hemorrhagic are specific to the disease and are also the most common: hemarthroses and hematomas. As far as hemarthroses are concerned, each joint hemorrhage episode causes a topical disorder, which predisposes to recurrence, with the onset over time of the main chronic complication of this condition, hemophilic arthropathy, which progresses slowly throughout the patient's life and generates severe sequelae (ankylosis). This paper aims at emphasizing the importance of viscosupplementation by the injection of hyaluronic acid and chondroitin sulfate in the joints of hemophilic patients with severe arthropathy, with a view to improving the locomotor function, to reducing the number of bleeding episodes and joint pain.

Key words: hemophilia, hemophilic arthropathy, hyaluronic acid, chondroitin sulfate.

Hemophilias are constitutional hemorrhagic diseases, which have a plasma coagulation deficiency in common (lack of a particular antihemophilic globulin), and they are characterized by similar physical symptoms and identical genetic transmission (recessive and gender-related) [1].

Their classification in A and B can only be done further to laboratory tests; type A hemophilia is due to coagulation factor VIII deficiency (A antihemophilic factor), whereas type B hemophilia is due to coagulation factor IX deficiency (B antihemophilic factor). The disease sets in at the end of the first year of life, i.e. when the baby starts walking, and it is caused by injuries inherent to locomotion attempts. The hemorrhagic tendency is maintained throughout the patient's life. Disease progress materializes in alternating hemorrhagic bursts and periods of normal life [1,2].

The hemorrhagic bursts may be triggered by minor injuries, by small surgical procedures, by an i.m. or s.c. injection or even spontaneously. They may be classified in two major groups: external bleedings and internal bleedings. External bleedings, with varied localization and reduced incidence, are not very serious: gingivorragia, epistaxis, hematuria, digestive bleeding, tongue bleeding due to tongue bites, skin bleeding. Internal bleedings are much more frequent and much more severe. They may be: subcutaneous (superficial bruises and hematomas); intramuscular (deep hematomas); intra- and inter-visceral (pharynx, mediastinum, intestinal wall, periosteum, mesentery and CNS); intra-cavitary (abdomen, pleura, pericardium, joints and subarachnoid space). Two of them, which are specific to the disease, are also the most common: hemarthroses and hematomas [2-4].

Hemarthroses are the most common and the most dangerous physical manifestation of hemorrhage in a hemophilia patient (75 %). It sets in between the age of 1

and 5; when it occurs after the age of 10, it is a sign of a mild form of the disease. The other occurrences are relapses. The triggering factor is always an injury, which often goes unnoticed. The topography of the impaired joints is the following, in a decreasing order of occurrence: knees (36 %), ankle (30 %), elbow (23 %), hand (6 %), shoulder (3 %) and hip (2 %). Most of the times, hemarthroses impair only one joint; sometimes they may impair two joints, not necessarily symmetrically. Recurrences are usually in the same place. Each joint bleeding episode causes a local disorder, which predisposes to relapses: the anatomic structures are weakened, the muscles are affected by atrophy and fibrosis (joint mechanics becomes deficient), the synovial joint becomes hypertrophied and hypervascularized and bleeds easier. It marks the beginning of a chronic condition, hemophilic arthropathy, which progresses slowly throughout the patient's life and has a disabling potential [2-5].

The therapeutic goals in chronic painful hemophilic arthropathy are the locomotor function improvement, joint pain reduction and implicitly patient's life quality improvement. One of the minimally invasive procedures conducted in case of severe hemophilic arthropathy is viscosupplementation by the injection of hyaluronic acid and chondroitin sulfate.

Hyaluronic acid

Hyaluronic acid, discovered about 60 years ago, is a natural mucopolysaccharide, which is present in the entire human body and is extracted from rooster comb or manufactured in laboratory conditions, by bacteria fermentation. It is a white odorless powder (sodium salt, zinc salt), which is also known as sodium hyaluronate. Large concentrations of it exist in fluids, in the joints (in the synovial fluid and cartilages), in the eyes and tendons, in the umbilical cord or in the aortic walls [2,4,6].

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In the joints, in addition to its plastic role of collagen formation, to which it confers resistance and flexibility, hyaluronic acid contributes to synovial fluid secretion, which ensures joint component lubrication. In the absence of an adequate quantity of hyaluronic acid, the joint becomes fragile and deteriorates. This accounts for the use of hyaluronic acid in joint pathology, including in chronic arthropathy of hemophilia patients. In addition to maintaining the joints lubricated, the hyaluronic acid supports water retention in other bodily tissues as well [2,4,6].

From the chemical point of view, it is a big molecule glycosaminoglycan (its molecular mass ranges from 1 to 5 million daltons). The molecule is made up of a repetitive sequence of two simple modified sugars, one called glucuronic acid and the other N-acetyl glucosamine. Hyaluronic acid molecules are long, big and have high viscosity, which resist compression and allow the joints and the skin to carry the body weight (fig. 1) [6].

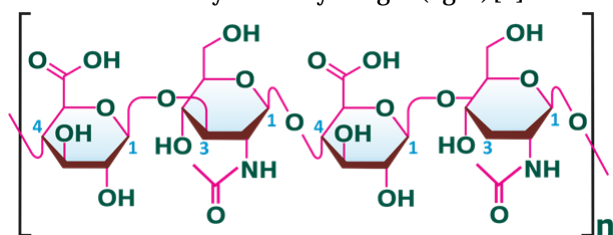


Fig. 1. Chemical structure of the hyaluronic acid

Chondroitin sulfate

Chondroitin is one of the most abundant substances in the glycosaminoglycan class found in joint cartilages. When these molecules are intact, they provide protection to the tissues, by preventing the action of enzymes responsible for joint wear and inflammation. It has been proven that the intake of dietary supplement containing chondroitin improves the inflammatory symptoms of the bone and joint systems. In association with glucosamine, it may contribute to damaged cartilage regeneration. If we were to synthesize the advantages of chondroitin in osteoarticular disorder therapies, we may say that: it supports pain alleviation, it helps the lubrication of the impaired tissues, it contributes to cell regeneration, it stimulates collagen synthesis, it participates in cartilage production and it prevents old cartilage damage [2,4,7,8].

From the chemical point of view, chondroitin occurring as chondroitin sulfate belongs to the class of substances known as glycosaminoglycans (fig.2). It comprises an alternant sugar chain, which may sometimes be associated to proteins. The chondroitin chain may include up to 100 sugars, and each of these molecules may be bound to other sulfate ions.

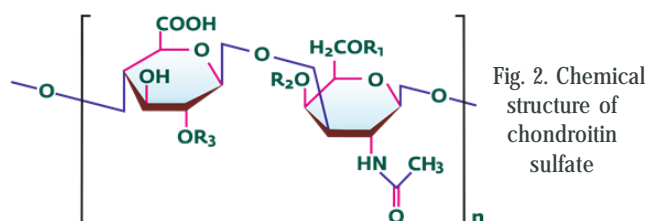


Fig. 2. Chemical structure of chondroitin sulfate

Case report

We report the case of a 45-year-old male living in the countryside, with a history of type A hemophilia - severe form (FVIIIc<1%), on record with the Vaslui County Hospital, for which he received on demand therapy in the territory for several hemorrhagic phenomena. His first hospitalization in the Hematology Department of Sf. Spiridon Hospital took place in December 2015, for

hematological and orthopedic assessment. As concerns his anamnesis, the patient was diagnosed with type A hemophilia - severe form (FVIIIc<1%) at the age of 7, and has had a history of multiple hemophilic arthropathies and chronic hepatitis (HCV positive) as a result of his multiple plasma transfusions. His physical examination revealed intense left knee pain, with multiple bleedings in this knee joint and in the left hip joint, and severe motor deficiency in his lower limbs. His paraclinical examination revealed: the hematological tests: ApTT=67.5s, anti FVIII antibodies=9.3 Bethesda/ml units; biochemical tests: hepatic cytolysis syndrome and cholestasis; immunological tests: AgHbS=negative, anti HCV antibodies =present. His orthopedic examination and imagery scan set the diagnosis: 1.severe left knee osteoarthritis (fig. 3) 2. Right knee joint fusion, 3. severe bilateral hip osteoarthritis, 4. equinus right foot with ankle osteoarthritis, 5. Bilateral elbow and shoulder arthropathy, 6.systemic osteoporosis. Considering his advanced osteoarthritis lesions and synovitis in his left knee joint, the limited movements of this joint and intense pain, the viscosupplementation of this joint was decided using a combination of hyaluronic acid and chondroitin sulfate.

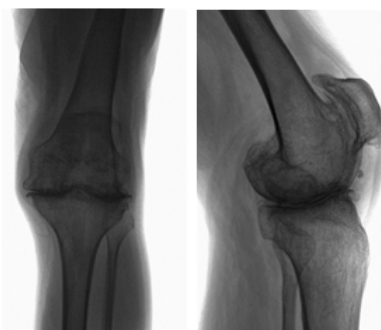


Fig.3. Severe osteoarthritis of the left knee in a patient with type A Hemophilia with inhibitors (requiring viscosupplementation with hyaluronic acid)

Since the patient's basic condition consisted of coagulopathy with major bleeding risk in any type of surgical procedure, hemostasis was a key element in this procedure. The surgical procedure was done with eptacog alpha recombinant support, which was administered in the bolus before performing the surgery.

A vial of 3 mL Hialurom Hondro, a viscoelastic supplement containing 60 milligrams of sodium hyaluronate and 90 milligrams of chondroitin sulfate was injected in the left knee joint, after the synovial fluid aspiration.

No hemorrhagic phenomena were reported during the surgical procedure or after it.

The patient's evolution after the procedure was positive, with significant pain reduction in his left knee joint, improved joint functionality and reduction of the number of hemorrhagic episodes.

The pathogenesis of the progression from recurrent hemarthrosis to disabling arthropathy has not been fully elucidated yet, but it is characterized by inflammatory synovitis and joint cartilage damage [4,9]. The hemosiderin deposits in the synovial tissues cause proliferative phenomena here and sub-synovial tissue neo-vascularization, thus leading to its turning into an inflamed and villous synovial tissue [4,9]. This brittle and extremely well vascularized synovial is more susceptible to hemorrhagic phenomena due to minor stresses, thus creating a vicious circle difficult to break [4,9]. Iron seems to play an important role in arthropathy development in hemophilia patients by inducing genes involved in cell proliferation and inflammatory cytokine stimulation. In vitro studies assessing the effect of iron on human synovial tissue have shown that c-myc proto-oncogene expression

increase and synovial proliferation are dose dependent [10]. Synovial proliferation may be stopped by means of apoptosis-inducing ceramides [10]. Iron also induces mdm2 expression, a p53 tumor suppressor binding protein (11). In addition to their proliferative effect in the synovial, iron deposits contribute to joint cartilage damage by stimulating the inflammatory cytokines interleukin-6, interleukin-1 and tumor necrosis factor, although the pathogenic mechanisms involved here are still unclear [4,12]. In vivo and in vitro studies suggest that blood may have a direct toxic effect on joint cartilage. In vitro studies reveal marked proteoglycan synthesis inhibition by total blood [9]. Experiments conducted on dogs have shown that cartilage exposure to blood for four days triggers biochemical and histochemical alterations both in the cartilage matrix and in the metabolic chondrocyte activity [13]. As chronic hypertrophic synovitis progresses, the synovial becomes palpable and the joint may always be swollen. Synovial hypertrophy and cartilage degeneration lead to bone erosion, which finally leads to advanced arthropathy, joint stiffness, chronic pain and severe joint movement limitations with the onset of secondary disabilities [4,14]. Bone condensation occurs in the most severe cases of joint impairment, the result being a non-functional deformed joint [4,14]. Many hemophilia patients have several joints impaired and may develop severe atrophies in one or both lower or upper limbs, which lead to physical disabilities and implicitly to the decrease of their quality of life. The number of bleeding episodes required for the production of irreversible lesions of the joint cartilage is not known and it probably varies from one patient to another. This progress is also influenced by the manner in which hemarthrosis was treated. Prompt coagulation factor substitution has had much better results than the delays in or absence altogether of this treatment [4,15].

Hyaluronic acid has become one of the most well-known agents for intraarticular injections in osteoarthritis patients. Hyaluronic acid is a natural viscous substance and the main component of the cartilage matrix and synovial fluid. Intraarticular injections with this substance may reduce pain in arthritis patients, although its action mechanism is not fully known [4,16]. Pain reduction and motor function improvement after 3-5 injections in patients with hemophilic arthropathy have been reported in about 75% of the hemophilia patients receiving this treatment [4,16,17].

Conclusions

The major chronic complication of hemophilia patients is currently represented by joint pathology, following repetitive bleedings in the joint area. Although the correct administration of coagulation factor with a view to bleeding prophylaxis has shown that this prevents joint pathology, repeated intraarticular bleeding episodes trigger synovitis onset, which is irreversible and may progress despite the prophylactic treatment.

Orthopedic surgical procedures are able to reduce both hemophilic arthropathy pain and future bleeding episodes.

Hemophilia patients in whom inhibitors are present run the highest risk of developing different joint pathologies and also represent the biggest therapeutic challenges when a surgical procedure is necessary.

The viscosupplementation with hyaluronic acid and chondroitin sulfate injection, reduce the number of hemorrhagic episodes, reduce pain and improve joint functionality in patients with severe hemophilic arthropathy.

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