Nonacog Alpha - an Efficient Therapeutic Option in Hemostase Management for Hemophilia Type B in Patients with Elective Arthropalsties

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Hemophilia is a hereditary coagulopathy that is largely in the attention of developing countries, not because of its low incidence, but because of the high costs involved in the treatment of the disease and its disabling consequences of the disease, if treated inappropriately. The concentrates of coagulation factors currently available for the substitution treatment of hemophilic patients have undergone additional viral purification and inactivation techniques, in order to achieve a higher infectious safety, an aspect that also implies an increase in treatment costs for these patients. Currently, the major morbidity of patients with hemophilia is represented by the disabling articular pathology, secondary to repetitive bleeding episodes developed in the articular space. Although it has been proved that the prophylactic administration of coagulation factors helps to prevent joint disease in the case of patients that were not subject to prophylaxis, the repeated bleeding in the joints induces synovitis, which is irreversible and may progress despite subsequent prophylaxis. Under these conditions, total joint arthroplasty remains the only solution to reduce both, pain and subsequent bleeding episodes of hemophilic arthropathy. Effective hemostasis is a basic condition for successful interventions in hemophilic patients. In this regard, this paper aims to highlight the effectiveness of Nonacog Alpha, a product that contains recombinant factor IX, in the management of hemostasis, in the case of a patient with type B hemophilia, with indication of total endoprosthesis of the left hip.

Keywords: hemophilia, Nonacog Alpha, hemarthrosis, total arthroplasty.

Hemophilia B is an X-linked coagulopathy caused by a series of mutations in the gene of coagulation factor IX (FIX), leading to a deficiency thereof. Coagulation factor IX is a protein, component of the prothrombin complex, which is vitamin K-dependent and intervenes in the coagulation cascade. The active form of factor IX, known as factor IXa, leads to the activation of coagulation factor VIII, which in turn activates coagulation factor X, which plays an essential role in the activation of the intrinsic mechanism. Historically speaking, factor IX substitution therapy in hemophilia type B was performed by intravenous plasma, initially in the form of fresh frozen plasma, then in the form of a *prothrombin complex* and most recently by means of plasma concentrates of FIX coagulation with increased purity. Plasma concentrate administration, however, has two main types of complications: volume overload and the transmission of viral diseases. Following the drama of 1980-90, when a large number of hemophilic patients were infected with human immunodeficiency virus (HIV), coagulation factor concentrates have been subject toadditional viral purification and inactivation techniques, in order to achieve major infectious safety. However, prices have also increased proportionally, especially because raw material resources (plasma) have decreased. Moreover, numerous viral securing procedures make it possible to recover only 10-15% of factor VIII or IX for the finished medicinal product, while the remaining 85-90% is lost in the manufacturing process. It can be said that the wish to ensure safety for factor VIII or factor IX plasma concentrates has been achieved. Seroconversions have been annihilated for hepatitis (A, B, C) and HIV and minimized for Parvovirus B19. Only the fear of infection with new prions or germs (flaviviruses, coronaroviruses) remained. Therefore, in order to increase safety and as an expression of the technological process, the production at industrial scale was initiated and then extended by means of the genetic engineering of recombinant factors, aiming to avoid contamination with blood plasma components. Thus, the price of these new recombinant products exceeds by far the price of products derived from blood.

However, after the experience with HIV and hepatitis, it is never possible to assert the existence of absolute security. It is not possible even in the case of recombinant products, if we consider that many of them come into contact with proteins of hamster cell cultures or mouse monoclonal immunoglobulin. Only virucidal methods guarantee the safety of these products. The lack of evidence of new infections over the last decade suggests that and gives the necessary peace and confidence to hemophilic patients and the physicians that treat them.

It was predicted that recombinant human factor IX (rIX) is a therapeutic agent in hemophilia B, immediately after FIX DNAc was cloned in 1982.[1,2]The expression of rFIX protein in various cell types in 1985 led to the development of many expression systems [3-7]and became the basis for the production technology of therapeutic rFIX in the ovary cell line of a Chinese hamster[8-10]. The presence of vitamin K in the medium is required for y-carboxylation and for the production of a functional FIX molecule[11-

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14]. The originally obtained product had a specific activity of 35 up to 75 IU/mg, compared to the FIX protein [18]. rFIX was produced by means of a serum-free process [23] and purified by a biochemical process, which did not require the use of animal proteins [24]. These processes have produced proteins with a high purity level and a specific activity slightly higher than the one of plasma factor IX [15].

The commercially available rFIX (BeneFIX®) is not exposed to human or animal protein derivatives and therefore it has an improved viral safety profile compared to plasma-derived factor IX (pdFIX) [16-18].

Hemophilic arthropathy is the main chronic complication of this pathology and it can affect one or more joints, mainly the knees, hips, ankles and elbows, in approximately 90% of hemophilic patients.Indications for arthroplasty are: pain and joint disability, which do not respond to conservative treatment, as well as advanced radiological changes [19]. The objectives of such intervention are to reduce pain, improve joint amplitude and correct deformations. Postoperative bleeding is the major complication that may occur in the case of hemophilic patients submitted to total arthroplasty, regardless of its type.

Total hip arthroplasty (THA), which we refer to in this paper, is one of the most successful procedures in the orthopedic elective surgery used for the final stage of hip joint pathologies [20]. It is estimated that the demand for THA will increase by 174% until 2030[21]. However, THA is associated with substantial blood loss, ranging from 1188 to 1651 mL,[22] and the transfusion rate is between 16 and 37%, which often results in postoperative transfusion therapy [23,24]

In this regard, this paper aims to highlight the effectiveness of Nonacog Alpha, a product that contains recombinant factor IX, in the management of hemostasis, in the case of a patient with type B hemophilia, with indication of total endoprosthesis of the hip.

Nonacocog Alpha

BeneFIX® contains the recombinant coagulation factor IX (Nonacog Alpha). Nonacog Alpha is a purified protein consisting of a single chain of 415 amino acids with a molecular weight of approximately 55,000 daltons and belongs to the family of vitamin K-dependent serine proteases. It presents a primary amino acid sequence comparable to the Ala148 allelic form of the plasma-derived factor IX. Some post-translational modifications of the recombinant molecule are different from those of the plasma-derived molecule. The recombinant coagulation factor IX is a glycoprotein secreted by genetically modified mammalian cells derived from the ovary cell line of a Chinese hamster.

Experimental part

Material and method

There was carried out the orthopedic evaluation of a patient with moderate B-type Hemophilia (factor IX = 5%), aged 57, with chronic hip arthropathy, secondary to frequent intra-articular bleeding, with algic and functional decompensation, seropositive for chronic hepatitis C virus (HCV). Chronic hemophilic arthropathy, stage V, with refractory pain in conservative treatment, with severe motor deficit, is a clear indication of total arthroplasty. The primary objectives of total arthroplasty were relieving pain and ensuring a satisfactory joint function, which is an aspect that depends on the stability and proper movement of the joint. Postoperatively, the degree of motion depends on several factors, including surgical technique, preoperative initial movement, and adequate articular recovery.

By presenting all the criteria of total endoprosthesis, total left hip arthroplasty was performed by a complex multidisciplinary team (hematology - orthopedics - ATI). Orthopedic surgery has benefited from well-established hematological support through the national specialty protocol, which provides the necessary amount of coagulation factor IX for substitution treatment. During both, the orthopedic intervention and the postoperative period, there were monitored the blood count, the parameters of the coagulation profile, the transfusion requirements and the eventual orthopedic complications that could have appeared. The duration of hospitalization was 18 days (average duration = 14-21 days), and the average consumption of coagulation factor IX was around 120,000 units. The postoperative bleeding of the patient was around 550 mL, andthe variations in hemoglobin concentration during the preoperative period vs. the postoperative period were 14g/dL vs. 9.1 g/dL, so no transfusion treatment was required.Also, given that the patient associated a diabetes type 2, which is a pathology with infectious risk, the glycemic profile and inflammatory markers were monitored daily, in order to exclude the development of an infection. The prophylactic therapy with antibiotics was prolonged.

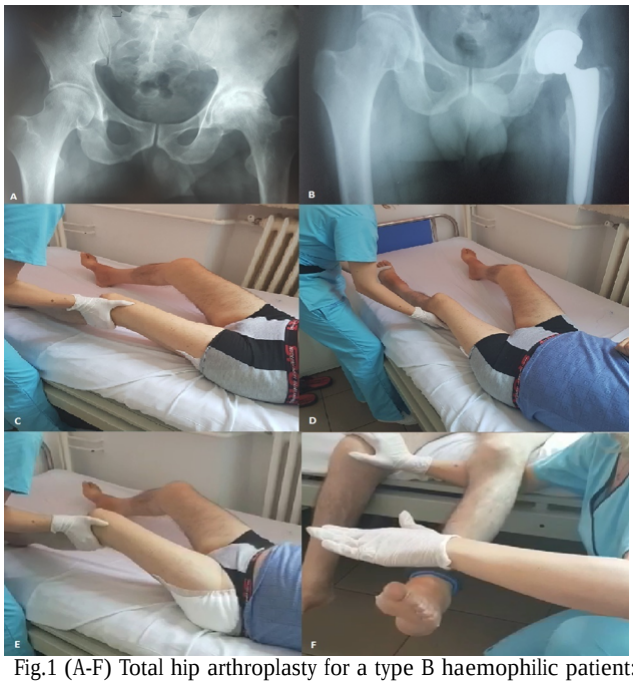

Fig.1 (A-F) Total hip arthroplasty for a type B haemophilic patient: (A) Ostheoarthritis of the left hip; (B) Uncemented total hip arthroplasty; (C-F) Postoperative rehabilitation

Taking into consideration the normalization of the coagulation profile after the Nonacog Alpha substitution treatment, as well as the presence of co-morbidities associated with thrombotic potential, there was carried out a postoperative thromboembolic prophylaxis with low molecular weight heparin (Enoxaparin, sc, 0.4 mL/day). The results after an average follow-up period of 12 months did not reveal perioperative and postoperative thromboembolic or hemorrhagic complications or any infection. In spite of the fact that the patient was 57 years old, his postoperative progression was as good as in the case of young hemophilic patients with A-type hemophilia subject to total endoprosthesis, achieving significant pain reduction in the prosthetic joint, improved joint functionality and, implicitly, an increase in the quality of

life, i.e. the advanced age was not an impediment for the performance of these complex surgical interventions.

Results and discussions

A series of studies have evaluated the efficacy of hemostasis with Nonacog Alpha in hemophiliac patients who have undergone surgery. Twelve patients were submitted to 13 minor surgical interventions, including dental procedures, tegument biopsies, cystectomies and nerve ablations. Nineteen patients were submitted to 23 major surgical interventions, including a liver transplant, a splenectomy, 3 inguinal hernia interventions, 11 orthopedic procedures and 7 complicated dental extractions.The hemostasis performed with Nonacog Alpha proved to be effective during the surgical interventions. A patient required the evacuation of a hematoma at the surgical intervention site, while another patient that underwent a dental extraction required a subsequent surgical reintervention due to complications at the site of extraction. There was no clinical evidence of thrombotic complications in any of the patients that received Nonacog Alpha replacement therapy [25-27].

In 2005, Andrea Gerhardt et al [28] reported their experience related to the total knee arthroplasty of 7 patients with severe hemophilia, 4 patients with hemophilia type A and 3 patients with hemophilia type B. The surgical interventions were performed with hematological replacement factor IX in the case of patients with hemophilia type B. The average consumption of coagulation factor was 113,742 units, the postoperative loss of blood was 831 mL and the postoperative hemoglobin level was over 9 g/dL without transfusion treatment. The hemostatic outcome was assessed as very good without the occurrence of hemorrhagic or thromboembolic complications. Six of the seven patients presented a significant improvement of the locomotor activity, while just one low-compliance patient suffered from post-operative joint fibrosis, which required open arthrolysis.

Subsequently, in 2007, [29] the same authors reported in *Blood* their experience related to the total knee arthroplasty of 2 patients with severe hemophilia type B. The surgical interventions were performed with recombinant factor IX replacement therapy. The average length of hospitalization was 15.5 days. The postoperative loss of blood was 950 mL in the first patient and 750 mL in the second patient. The postoperative level of hemoglobin was 12.6 g/dL in the first patient and 11.5 g/dL in the second patient respectively. No transfusion therapy was necessary. The hemostatic outcome was assessed as very good without the occurrence of hemorrhagic or thromboembolic complications.

Regarding the safety profile, the administration of recombinant factor IX concentrates to hemophilic patients has rarely been associated with thrombotic complications. Thrombotic risk is considered to be related to the dosages of administered factor agents, the duration of treatment, other associated comorbidities (hepatic, cardiovascular and metabolic infections as well as active infections), prolonged bed rest and surgical interventions, which increase the likelihood of developing thrombotic events. Concomitant thromboprophylaxis with low molecular weight heparins avoids the occurrence of thrombotic events. In addition to that, recombinant factor IX is not exposed to human or animal derived proteins and therefore it has a higher viral safety profile compared to current plasma derivatives (pdFIX).

The case of the patient endoprosthesized in the Orthopedic Clinic of Saint Spiridon Hospital confirmed the results of previous studies and namely that Nonacog Alpha, administered according to the National Hemophilia Protocol, demonstrated its effectiveness in the management of hemostasis in the case of patients with hemophilia type B and indication of total arthroplasty.

Conclusions

In comparison to the general population, the total endoprosthesis of hemophilic patients is more difficult from the point of view of surgical techniques, while an effective hemostasis represents a basic condition for successful interventions in this patient population.

Our treatment protocol, applied to orthopedic surgery, demonstrates that total arthroplasty can be performed in hemophilic patients, a category of patients that have vital operator risk, a low rate of complications and improved quality of life due to pain relief and the improvement of joint functionality. A replacement therapy with high doses of coagulation factor is justified by clinical results and is beneficial to patients.

In the orthopedic surgery of the hemophilic patients, recombinant FIX seems to be an effective and safe therapeutic option for the prophylaxis of bleeding episodes in patients with hemophilia type B and total endoprosthesis, as confirmed by the case in the Orthopedic Clinic of our hospital.

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