Efficiency of Tranexamic Acid in Management of Surgical Orthopedic Bleeding in Patients with Haemophilia

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Haemophilia is an inherited bleeding disorder (gonosomala recessive, related to chromosome X, with transmission from carrying women to male descendents) characterised from the clinic point of view by important bleeding, secondary to some minimum and biologic traumas by deficiency of trombo-plastino-formation, consecutive to either a deficit of factor VIII (haemophilia A), or the factor IX (haemophilia B). The most characteristic manifestation of hemophilia is intra-articular – hemarthrosis. Its repetitive character leads to irreversible lesions of the articular structures, inducing lesions of the synovium with degenerative effects over the articular cartilage and destructive effects for the subchondral bone tissue. In time, these lesions require orthopaedic surgery to improve the locomotor activity. Managing an efficient hemostasis is vital during surgery, due to high risk of bleeding triggered by coagulopathy and surgery. Numerous studies carried out underlined the efficiency of the tranexamic acid (TXA) in reducing bleeding, in different surgery branches, by inhibiting the enzymatic degradation of fibrin. In orthopaedic surgery, the tranexamic acid is frequently used in case of hip and knee arthroplasties, reducing the bleeding and blood transfusion necessary to the treatment of posthaemorrhagic anemia. This paper wants to assess the efficiency of the tranexamic acid in realization of hemostasis to another category of patients, haemophiliac patients with indication of total hip and knee endoprosthesis.

Keywords: haemophilia, total hip replacement, total knee replacement, tranexamic acid

Haemophilia is a mostly inherited coagulopathy due to the factor VIII coagulation deficiency (haemophilia A) or factor IX coagulation deficiency (haemophilia B). Haemophilia affects about 600,000 people worldwide, 20% of which develop antibodies for factor coagulation deficiency. From the clinic point of view, it is characterised by bleeding events of different intensity, depending on how severe the disease is or the intensity of the trauma the patient is exposed to. The patients with severe form of disease (VIII factor coagulation is under 1%) can present spontaneous bleeding, in most cases in joins (hemarthrosis) or muscles (hematomas), some even with vital risk in the absence of treatment of substitution with antihemofilic factor. The severity of bleeding in haemophilia is commonly related to the level of coagulation factor, as it is mentioned in table 1 [1-4].

The recurrent intraarticular bleeding leads to irreversible lesions of the articular structures. Thus, the repeated haemarthroses produce synovial hypertrophy, synovitis, initially acute, then chronic with degenerative effects on the articular cartilage by chondrocyte apoptosis, and with destructive effects on the subchondral bone tissue, in time occurring the main chronic complication: haemophilia arthropathy [3-5].

Table 1
RELATIONSHIP OF BLEEDING SEVERITY WITH CLOTTING FACTOR LEVEL –ADAPTED FROM [1,3]

Severity	Clotting factor level
Severe	<1% of normal
Moderate	1 to 5% of normal
Mild	5 to <40% of normal

The hemophilia arthropathy can affect one or more joints, mainly in the knee, hip, ankle and elbow, in 90% of haemophilic patients [5]. At the same time, it generates increased artricular instability and reduced mobility, until total ankylosis, with invalidating potential and decrease of patient's life quality. From the orthopaedic perspective, the treatment of hemophilia arthropathy can be done by conservative methods or surgery. The conservative methods are orthoses, joint evacuatory puncture, intra-articular injection of anti-inflammatory drugs, intra-articular corticosteroid therapy, injections of hyaluronic acid and chondroitin sulfate, radiosynoviorthesis, gradual corrective straightening of ankylosis in flexion. A complex multi-disciplinary team is required, made of a hematologist, an orthopedic surgeon, medical restoration physicians, physical therapist for optimal results. These orthopaedic procedures must be carried out in hospitals by experimented teams [5-7].

Hemophilic patient's preoperative balance presents some particularities (table 2).

The main objectives of the multi-disciplinary team are improving the functionality and the life quality of the haemophilic patient.

The indications of the orthopaedic surgery are represented in table 3 [4].

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Preoperative balance	Objectives
Severity and type of haemophilia	-estimating the substitutive treatment; -requirement of factor concentrate being dependent also on the scale of intervention and restoration
Determination of the presence of circulating inhibitors	• Crucial to avoid some potentially lethal complications; • Even low level of inhibitors can increase spectacularly after giving high doses of factors immediately before and after surgery.
Exploring the viral status	It is necessary to repeat the serologic tests to find any infection with VHB, VHC, HIV before surgery, if they were not done during the last 3 months (active hepatitis is a contraindication for surgery)
Complete clinic and imagistic evaluation	▪ in view of carrying out multiple correcting surgeries, so that the same consumption of coagulation factor could solve more orthopaedic problems.

Table 2
HEMOPHILIC PATIENT'S PREOPERATIVE BALANCE

Indications of orthopaedic surgery
a.chronic sinovitis – cannot be controlled in a conservative way, with recommendation of synovectomy
b. bone and joint deformations, muscular contractions with recommendation of osteotomy and arthroscopic arthrolysis
c. degenerative joint modifications with recommendation of prosthesis or arthrodesis
d. haemophilic pseudo-tumours with recommendation of excision
e. open fractures
f. invalidating pain

Table 3
INDICATIONS OF ORTHOPAEDIC SURGERY – ADAPTED FROM [4]

In cases of severe haemophilic artropathy, it is approached through basic surgery, represented by total arthroplasty, radiosynovectomy, chemical synovectomy, arthroscopic synovectomy and arthrodesis [5,6,8,9].

Severe hip artropathy is much less frequent than that of the knee, elbow or ankle. The radiologic image can have the aspect of a juvenile arthritis or coxarthrosis. Increased pressure in the intra-articular space can determine the appearance of the aseptic necrosis of femoral tip. In patients with important destruction of coxo-femural articulations, total hip arthroplasty was very efficient, with significant improvement of articular amplitude. Knee artropathy is the most frequent cause of pain and invalidity in patients with haemophilia [5,9,10].

Indications for arthroplasty are represented by: articular pain and invalidity, which does not respond to conservative treatment, as well as advanced radiologic modifications. The objectives of this surgery consist in diminishing pain, improving articular amplitude and correcting deformation [3-6].

Total endoprosthesis, in their cemented version, are indicated in major articular destructions, which lead to important functional deficit. Indication of total endoprosthesis remains to be evaluated from the point of view of the remote prognostic. The main risks consist in infection and aseptic enlargement of bone structures, which influence the stability of the endoprosthesis. The major indication of endoprosthesis aims mainly the hip and knee joint, and it is done with prudency at young ages. They are currently improved a lot, both from the point of view of the surgery technique and the material of the prostheses, so that the indications of usage have extended when it comes to the age and articulations targeted (including ankle articulations) [3,5,8,11].

Post-surgery bleeding is the main complication that can appear in haemophilic patient who underwent total arthroplasty [5,11].

More observational studies associated the post-surgery blood transfusion with a longer hospitalization period, higher costs, frequent infections, and mortality in some cases. [4-6,8,9] Taking into consideration the major risk of bleeding in the haemophilic patient, mainly by coagulopathy but also the type of surgery, most endo-prostheses are scheduled to assure the necessary quantity of coagulation factor for substitutive treatment, and another haemostatic adjuvant, such as tranexamic acid as an antifibrinolytic agent [5,8,10,12-17].

Currently, the standard protocols of treating the patient plead for the necessity of using a haemostatic product that, once administered, can perform an efficient haemostasis. In this sense, anti-fibrinolytic drugs such as tranexamic acid, researched in numerous studies, have proved their safety and efficiency in orthopaedic surgery [5,12-17].

The tranexamic acid was initially used about 40 years ago in cardio-thorax surgery, in controlling gynecological bleeding and in bleedings secondary to major traumas. Apart from its use in surgery (orthopaedic, cardio-thorax surgery, gynaecology, gastroenterology and hepatology, urology, ENT), efficiency of tranexamic acid was also studied in some hematologic pathologies such as deficiency of factor von Willlebrand, in hemophilia or thrombocytopenia [13]. It is frequently and successfully used in orthopaedic to reduce the perioperative bleeding events, especially in patients with total hip or knee arthroplasty [13,16,17].

Tranexamic acid

The tranexamic acid, discovered in 1960, is a synthetic derivative of lysine with antifibrinolytic action; it prevents

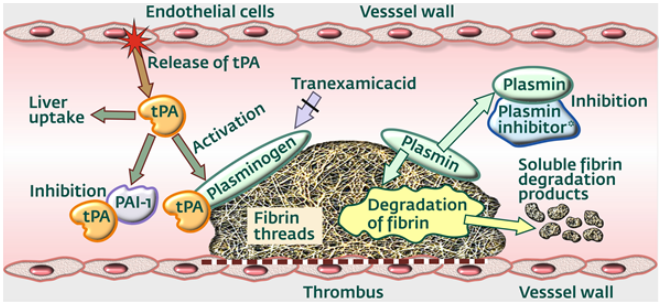

Fig.1 Schematic view of the fibrinolytic system - adapted from Lilian Tengborn et al. [18]

the degradation of fibrin, by reversible inhibition of plasminogen. This mechanism prevents the conversion of plasminogen into plasmin and to exercise its fibrinolytic action (fig.1). The halving period of the tranexamic acid is 2 h, and its excretion is through kidneys [13,18-21].

From the chemical point of view, it is a trans-4-aminometylcyclohexancarboxylic acid, corresponding to the chemical formula $C_8H_{15}NO_2$ with molecular mass of 157.213g/mol (fig. 2). In the haemophilic patients, administration is on short term (2-8 days) to reduce or prevent minor bleeding (for example tooth extraction), but it can be extended to 14 days according to the protocols in case of hip or knee arthroplasty [22].

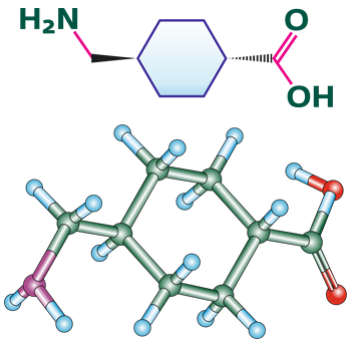

Fig. 2 Chemical structure of the tranexamic acid

Experimental part

Material and method

Two patients with severe form of haemophilia A were evaluated from the orthopaedic point of view (factor VIII < 1%) with present inhibitors, with chronic haemophilic arthropathy algically and functionally decompensated, with severe motor deficit, who presented indication of endoprosthesis and to whom total arthroplasty of left hip, respectively total arthroplasty of left knee was performed by a complex multidisciplinary team (involving haematology – orthopaedics – intensive care specialists). The orthopaedic surgery benefited from hematologic support well set by specialized protocols (protocol Giangrande) [22], the necessary quantity of coagulation factor for the substitutive treatment being assured. At the same time, tranexamic acid 25 mg/Kg i.v. was given every 6-8 h according to the protocol mentioned. During the orthopaedic surgery, as well as after surgery, the level of hemoglobin and hematocrit, coagulation profile parameters, transfusion requirements, and any complications in the orthopaedic field that could have interfered were carefully monitored. Haemostasis was perfect, and the evolution after surgery regarding bleeding was very good; paraclinically, the decrease of the level of haemoglobin did not impose transfusion treatment. Bleeding after surgery was minimal in both cases, of about 400 mL, similar to that of a patient without haemophilia (fig. 3). Due to the normalized coagulation profile after the replacement therapy, an anticoagulant treatment with low molecular weight heparin (Enoxaparin) was administered

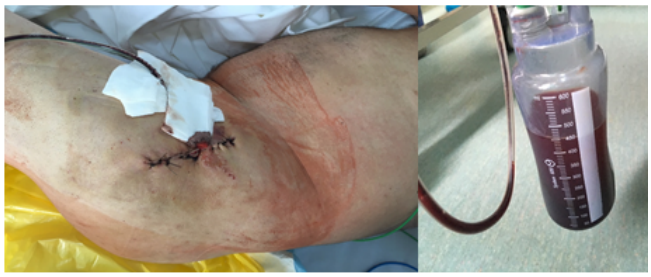

Fig. 3. Aspect of blood drainage (400ml) at 48h postoperative after a total left hip replacement in a patient with type A Hemophilia with inhibitors

to prevent any thromboembolic complication that could have extended the hospitalization period. From the orthopaedic point of view, in both cases, the patients' evolution after surgery was favourable, with significant reduction of pain in hip and knee, improvement of the joint functionality and an the increase in life quality.

Results and discussions

The tranexamic acid is an antifibrinolytic agent that inhibits the activation of plasminogen in plasmin. The recent meta-analyses of some controlled, randomized trials, as well as several reviews that involve studies of cohort type, present the tranexamic acid as being efficient in reducing bleeding both in total hip and knee arthroplasty, without presenting any thrombogenic risk. [12,20] Hallstrom et al. carried out a study on about 35,000 patients, having as main objective the association of the tranexamic acid in the standard haemostatic protocol in the patients where it was practised total hip or knee arthroplasty; the results underlined a reduction of the postoperative bleeding phenomena and, implicitly, the necessary quantity of transfusion for both types of arthroplasty, without increasing the rate of thromboembolic complications. [20] The absence of secondary thromboembolic events, after administration of tranexamic acid, was also supported by Sukeik et al., in their study [23].

Orthopaedic surgery in the haemophilic patient with inhibitors is complex and presents major risk of bleeding, mainly by hematologic disease, and also by surgery. In the recent decades, numerous studies have been published, assessing the efficiency of the tranexamic acid in reducing bleeding and the transfusion requirements in elective patients for total hip and knee arthroplasty. The results of these studies showed that the tranexamic acid proved to be efficient and safe in orthopaedic surgery [12-18,20,21,23-26]. The two cases of endoprosthesis carried out in our service of orthopaedics have confirmed this hypothesis also in the case of the haemophilic patients, who were administered in the hemostatic protocol tranexamic acid in association with the substitutive factor of coagulation. Also in this sense, Benone et al. concluded that the minimum concentration for an efficient therapeutic level is 10 mg/ Kg body, repeated every 8 h [27].

In a meta-analysis, Sukeik et al. [23] identified at 11 eligible studies with 505 patients undergoing endoprosthesis, where the tranexamic acid was used to carry out hemostasis, and two years later, Zhou et al. [29] added another 8 studies, including 525 patients who underwent the same type of surgery and were administered the same haemostatic. The tranexamic acid was administered in dose of 10-15 mg/kg i.v., underlining the direct proportion between the doses administrated and the hemorrhagic phenomena, bleeding being lower in patients with higher administrated doses [28].

Also in order to evaluate the efficiency of the tranexamic acid, Tan et al. carried out a meta-analysis on 1114 patients

and noticed that its administration reduces post-surgery bleeding and the necessary transfusion amount; also, in the lot of patients studied, there were not thromboembolic events or other side effects of the tranexamic acid treatment [29].

Yang et al. studied the relation between the tranexamic acid and aPTT, but without underlining the relation in this sense, because the aPTT value is not influenced by the use of tranexamic acid [14].

According to the research, the i.v. administration of the tranexamic acid seems to be the most efficient method of administration for the tranexamic acid, because it can enter relatively fast in large joints. In a study of meta-analysis it was proved that one topic administration is much inferior to the i.v. one, in total knee arthroplasty, and there is a risk of severe bleeding that imposes secondary transfusion treatment with red blood cells [13,30,31]. In the haemophiliac patients with endoprosthesis in our hospital, the i.v. administration of the tranexamic acid has proved to be efficient, the post-surgery values of the haemoglobin not imposing transfusion treatment.

Conclusions

Hemofilia is a chronic hereditary coagulopathy that requires treatment of substitution with lifelong haemophilic factor. The main chronic complication of this disease, the haemophilic arthropathy, causes disabling sequelae, requiring surgical orthopaedic treatment.

In orthopaedic surgery of the haemophilic patient, the tranexamic acid, as antifibrinolytic agent, has proved its efficiency in reducing the bleeding events and the necessity of transfusion in patients with indication of total hip or knee arthroplasty, without generating thromboembolic events, fact confirmed also by the two cases of endoprosthesis in our hospital.

All these effects of the tranexamic acid improve the patient's safety and decrease the costs related to the medical care.

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