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Stoma takedown after Hartmann's procedure in a patient with hemophilia A complicated with production of inhibitor to FVIII (review and case report)

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ABSTRACT One of the specific manifestations of hemophilia A is the spontaneous abdominal hematoma mimicking the clinical picture of acute abdominal disease. The appearance of auto-antibodies to FVIII leads to a loss of response to replacement hemostatic therapy and requires an individualized approach as well as highly sensitive laboratory monitoring to reduce the risk of uncontrolled bleeding. The paper presents the case of multi-stage surgical treatment of this complication.

KEYWORDS: Hemophilia, inhibitor form of hemophilia, colorectal anastomosis, anastomosis failure

CONFLICT OF INTEREST: The authors declare no conflict of interest

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INTRODUCTION

Hemophilia A is one of the most common hereditary diseases of the blood coagulation system with a recessive X-linked type of inheritance. Clinical manifestations of hemophilia A are associated with a deficiency of blood clotting factor VIII (FVIII), caused by a mutation of the gene encoding FVIII (Xq28) [1, 2]. The severity of the disease determines the degree of FVIII deficiency. Severe forms account for 60–70% of all diagnosed cases of hemophilia.

A feature of the clinical manifestations of hemophilia A are spontaneous bleeding, hemarthrosis and hematomas of various sites. The average life expectancy in hemophilia A before the early 1960s was about 30 years [2]. The development of agents that replace the deficiency factor and an effective therapy strategy allowed not only to increase the duration and improve the quality of life of patients, but

also to perform surgeries of any degree of complexity if necessary [2].

Hemophilia A refers to orphan diseases, its prevalence is estimated as 1:10000 for the male population [3]. For this reason, both the approach to urgent surgical diseases and the possibilities of elective surgery of diseases requiring surgical care in patients with hemophilia are not well known. Spontaneous or induced abdominal and retroperitoneal bleeding occurring in patients with hemophilia are diverse in their clinical manifestations and can mimic various acute diseases — appendicitis, intestinal obstruction, cholecystitis, renal colic. Erroneous diagnosis, untimely and insufficient hemostatic therapy in some cases lead to aggressive surgical approach and further deterioration — compression and dislocation of the abdominal cavity and retroperitoneal space, followed by the formation of a so-called pseudotumor or a breakthrough of a hematoma into the peritoneal cavity [4].

In the perioperative period in patients with hemophilia A, the goal of hemostatic therapy is to replace the missing FVIII and maintain the procoagulant activity of FVIII at the level of 80–100%, which is achieved by the introduction of concentrate FVIII. Nevertheless, the rate of postoperative hemorrhagic complications during elective surgery in patients with hemophilia reaches 25–30% of all postoperative complications [4]. In addition, the use of modern concentrated coagulation factor agents can cause the formation of auto-antibodies (inhibitor) to FVIII, which aggravates the course of the disease and requires a different protocol of hemostatic therapy [2]. The development of an inhibitor to FVIII is associated with the introduction of large doses of FVIII concentrate, with a significant wound surface and a large volume of blood loss and leads to the ineffectiveness of replacement therapy and the occurrence of uncontrolled bleeding. In patients with an inhibitory form of hemophilia, hemostasis is carried out by drugs with shunting mechanisms of action — anti-inhibitory coagulant complex (AICC) and recombinant activated FVII (rFVIIa). In the inhibitory form of hemophilia, bleeding often becomes uncontrolled, and ensuring hemostasis is quite a difficult task [5, 6].

For an adequate selection of the hemostatic therapy scheme (dose and frequency of administration of agents), as well as control of the hemostasis system in real physiological conditions, it is necessary to evaluate the results of all possible hemostatic tests before surgery and during the perioperative period, both routine (chronometric indicators, procoagulant activity of coagulation factors) and integral — thromboelastography (TEG). The use of the TEG technique allows real-time assessment of the hemostasis system and response to hemostatic replacement therapy, which leads to a reduction in the risk of hemorrhagic complications [7].

This article, using the example of a clinical case of performing reconstructive surgery in a patient with hemophilia A complicated by the production of an FVIII inhibitor, demonstrates the possibility of performing extensive surgery and the features of the course of the perioperative period.

Clinical Case

Patient B., 43 years old. Diagnosis of hemophilia A in a moderate form. The diagnosis of hemophilia was established in early childhood. Family history: hemophilia in the maternal grandfather. The disease occurred with damage to the musculoskeletal system, hemorrhages in the ankle and knee joints (the incidence of hemarthrosis is up to 3–4 times a year). In addition, there is a history of soft tissue hematomas, hematuria. He was observed for hemophilia A since 2005 and received hemostatic therapy with plasma concentrate of blood clotting factor VIII on demand.

On 30.04.2020, he was hospitalized in a Moscow city hospital with symptoms of “acute abdomen”. Laparotomy was performed urgently. The surgery revealed an intrahepatic hematoma of the distal sigmoid and proximal rectum. Hematoma drainage and suturing of superficial defects of the sigmoid colon were performed. The blood loss was 2000 ml, reinfusion was performed with the Sell Saver device. Three days later, a hematoma of the rectal wall was detected, narrowing the lumen. In order to drain the hematoma, the rectal mucosa was dissected through a rectoscope. The patient was discharged the next day.

On the seventh day after discharge, being in a serious condition with a clinical picture of intestinal bleeding, he was hospitalized again in an emergency in one of Moscow clinical hospitals. The examination revealed a rupture of the rectal wall, a tense infected hematoma of mesorectum and sigmoid mesentery. He was urgently operated on 12.05.2020. Obstructive resection of the colon with end descendostomy was performed. The early postoperative period was complicated by the diffuse peritonitis, the rectal stump leakage, which required a series of program wash out of the abdominal cavity (on 16.05.20, 18.05.20 and 19.05.2020). The patient was under hematologist control as well; replacement therapy with concentrate FVIII was performed. The patient's condition stabilized, peritonitis was resolved. However, in the postoperative period, a total postoperative ventral hernia developed.

The presence of a colostomy, a total ventral hernia was the reason for the patient's appeal to the National Medical Research Center of Hematology of the Ministry of Health of the Russian Federation

in order to perform the reversal of Hartmann's procedure. Upon admission, the condition was satisfactory, the body mass index was 20 kg/m². During the examination, attention was drawn to the presence of a total defect of the anterior abdominal wall from the xiphoid process to the pubis with a maximum diastasis of the rectus abdominis muscles up to 12 cm. Hernial protrusion measuring 15 × 10 cm contained loops of the colon and small intestine. An end colostomy was in the left mesogastric region.

Moderate anemia was detected in blood tests (hemoglobin: 93 g/l). In the hemostasis test, there was an extension of the APTT 86.9 s (norm 25.1–36.5 s); a decrease in the activity of factor VIII 4.6% (norm 50.0–150.0%); the prothrombin index according to Quick 89%.

According to the results of the preoperative check-up (abdominal CT, pelvis MRI), signs of a massive adhesive process were revealed.

In order to examine the rectal stump, a rectoscopy was performed. The length of the stump was 7 cm. The walls were fixed, the lumen was deformed, the proximal part was narrowed (Fig. 1).

Taking into account the technical complexity of the surgery, severe concomitant pathology, high risks of intraoperative complications, a consultation was held to resolve the issue of the possibility of reconstructive surgery, together with specialists of the RNMRC of Coloproctology of the

Health Ministry of Russia. It was decided to perform a combined surgery in the volume of reversal of Hartmann's procedure and hernioplasty. The patient was informed about the risks and possible impairment of the sphincter function associated with low colorectal anastomosis.

On 03.02.2021 the patient was operated on. During the surgery a total median laparotomy was performed. The loops of the colon and small intestine were separated in an acute way. An abscess (5 ml in volume) was found and drained in the area of the rectal stump; the source of the abscess was the fistula of the rectal stump.

In order to mobilize the rectal stump, the middle rectal arteries and veins were controlled. The rectal stump was mobilized to the pelvic floor. Transanally, a circumferential incision of the rectal wall was made 2 cm above the dentate line. The rectal stump was mobilized and removed.

The left colon was mobilized using the LigaSure® device with the intersection and ligation of the left colon artery of the inferior mesenteric vein. A stapler supra-anal colorectal anastomosis without tension was formed. A preventive Turnbull ileostomy was formed in the right iliac region. The next stage was TAR hernioplasty with a Symbotex mesh with a partial sub lay bridge. The operative time was 9 hours, the total blood loss was 1100 ml.

Hemostatic replacement therapy in the perioperative period was carried out by intravenous

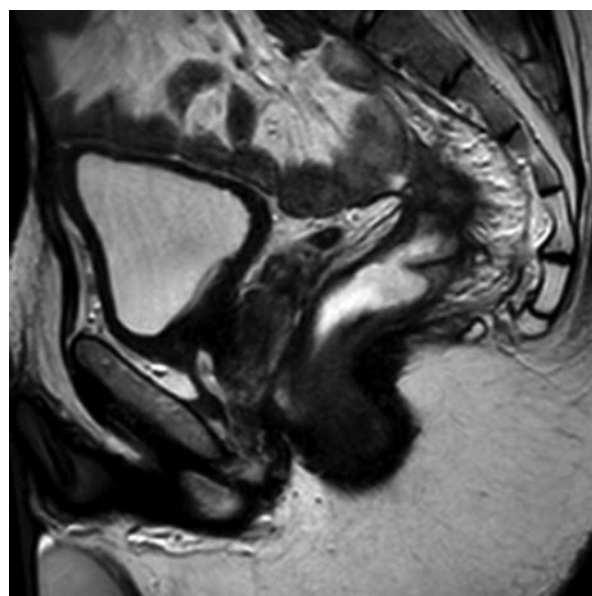
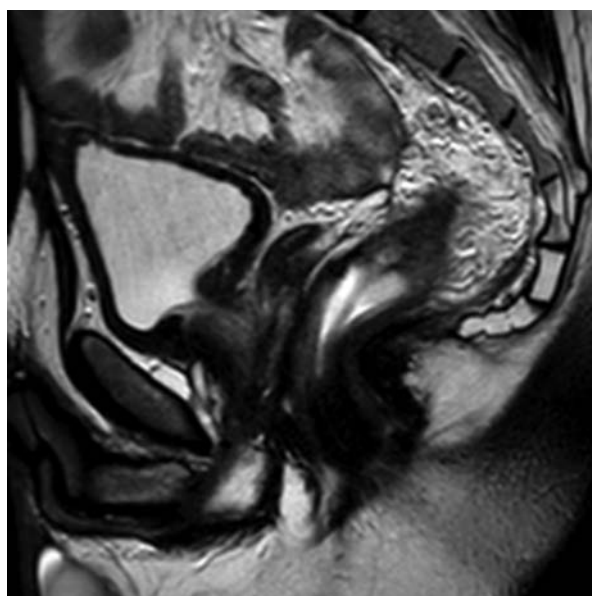


Figure 1. MRI of the pelvic organs. Rectal stump. Inflammation in the adjacent tissues. Fixation of the loops of the colon in the small pelvis

administration of recombinant FVIII concentrate. The target value of the deficiency factor activity in the perioperative period was 90–100%. The calculation of a single dose was carried out according to the formula:

dose (IU) = body weight (kg) × (required activity — basal activity) × 0.5.

Taking into account the time of excretion, the drug was administered 2 times a day. In the preoperative period (30 min.), FVIII was administered at a dose of 3000 IU. The concentration of factor VIII was reached — 94% (Fig. 2, 3).

On the 1–4 postoperative days, factor VIII was administered every 12 hours at a total daily dose of 6000 IU. Further, the dose of the drug was reduced, from 6 to 13 days, 4000 IU/day was administered. Laboratory control was carried out daily using the standard clotting method and thromboelastography (TEG). The APTT indicator varied from 30 to 50 seconds. There were no clinical signs of hemorrhagic syndrome. From the 1st to the 7th day after the surgery, antibacterial therapy of cefoperazone/sulbactam 4 g/day; metronidazole 1.5 g/day was performed. On the 5th day after the surgery, ultrasound control of the abdominal cavity was performed, no fluid accumulations were found in the abdominal cavity and in the area of the anterior abdominal wall.

Thus, the postoperative period proceeded smoothly. On the 13th day, the patient was discharged in a satisfactory condition.

After discharge, the patient continued hemostatic therapy prescribed at the prehospital stage.

On the 15th day (18.02.21), he noted a sharp deterioration in his condition: cold sweat, sharp weakness, rapid heartbeat. For the next two days, weakness increased, abdominal pain appeared, but he did not seek medical help. He applied to the NMRC of Hematology of the Health Ministry of Russia on 22.02.21 and was urgently hospitalized. Upon admission, the picture of acute posthemorrhagic anemia (weakness, dizziness, heart rate 180 beats / min, Hb 59 g/l), due to acute massive blood loss. During the examination, attention was drawn to the increase in volume and asymmetry of the abdomen. According to the results of CT of the abdominal organs in the central parts of the abdominal cavity, from the edge of the xiphoid process to the level of the pubic articulation, along the large omentum, a massive hematoma, inhomogeneous density (from 22 HU to 75 HU), max transverse dimensions at the level of the wings of the iliac bones — up to 186.5 × 72 mm, vertical length — about 305 mm. The loops of the small and large intestines were pushed back (Fig. 4).

Thus, it was established that the bleeding site is the preperitoneal space. Hemostatic therapy with the drug FVIII was started. However, there was negative dynamics of the response to the therapy characterized by an increase in APTT to 68 c (2.5 norm), signs of hypocoagulation according to the TEG data and a decrease in the concentration

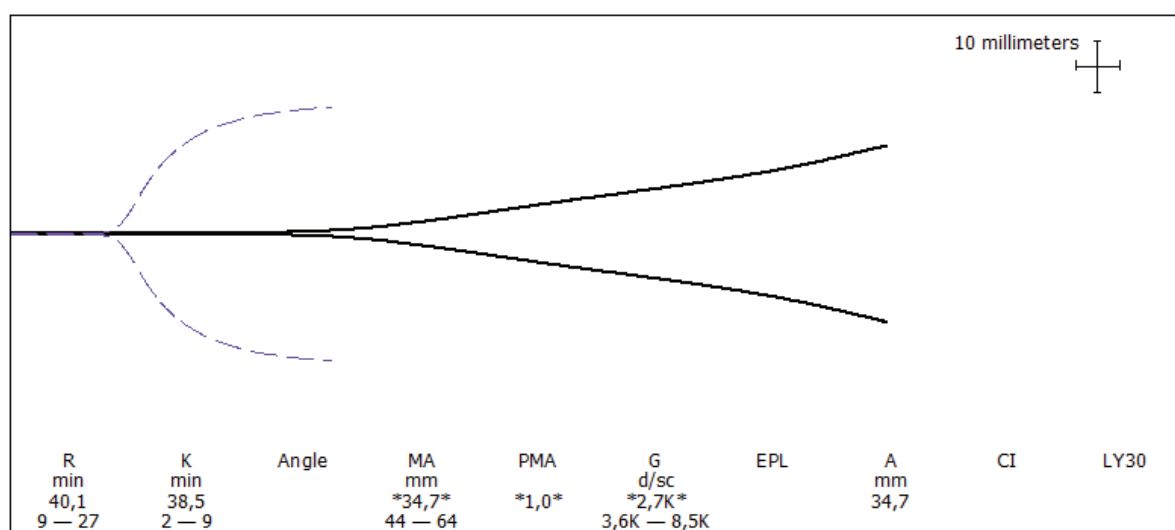


Figure 2. The TEG diagram demonstrates the initial state of hemostasis before the introduction of the factor: severe hypocoagulation along the plasma link of hemostasis

of FVIII to 6%. For the first time, an inhibitor to FVIII was detected at a titer of 4.3 BE (Fig. 5). Due to the initial detection of an inhibitor to FVIII in the patient's blood serum, the therapy with a drug with a shunting mechanism of action was initiated: recombinant activated coagulation factor VII (rFVIIa) 120 mcg/kg every 2 hours. However, according to thromboelastography, there was no effect from the therapy, and therefore rFVIIa concentrate was replaced with an anti-inhibitory coagulant complex — AICC at a dose of 150 Units/kg per day with an interval between injections every 12 hours. After the first administration of the drug, there was pronounced positive dynamics in the form of normalization of coagulation hemostasis. Figure 2 shows thromboelastograms demonstrating the response to rFVIIa and AICC therapy.

After achieving hemostasis of AICC at a dose of 4000 Units on days 2, 4 and 6, the patient underwent hematoma drainage and a number of program rehabilitation with the installation of the VAC system. The postoperative period proceeded without hemorrhagic complications.

The second stage of reconstruction was completed in 4 months. On 17.05.21 the ileostomy closure was performed. An ileostomy was excised from local access, an antiperistaltic ileo-ileoanastomosis "side-to-side" was formed with the help of the EndoGIA apparatus. The postoperative period was complicated by hematoma at

the level of the anastomosis, sized ~ 64 × 34 × 31 mm and a flat hematoma around the cecum, the initial sections of the ascending colon and intestinal obstruction phenomena. Hemostatic therapy with bypass drugs was carried out: eptacog-alpha activated (120 mg/kg every 2 hours), AICC (FABA 12000 U/s) sequentially. Against this background, the hematoma regressed, intestinal function restored, on day 11 the patient was discharged with a self-controlled act of defecation.

From 25.06.2021, the patient noted the formation of a fistula on the anterior abdominal wall in the right iliac region in the area of the scar from a drainage puncture with a purulent discharge. The patient independently took NSAIDs 3 times a day for the purpose of anesthesia. He was hospitalized in the NMRC of Hematology on 30.06.21. An abscess of the anterior abdominal wall was diagnosed. On 01.07.2021 revision of the fistula in the right iliac region and opening of the abscess in the mesogastric region was performed. Rejection of the mesh endoprosthesis site in the wound of the mesogastric region was revealed. The VAC-therapy started, against which the postoperative wound healed by secondary tension.

DISCUSSION

The strategy of providing surgical care to patients with hemophilia with specific hemorrhagic

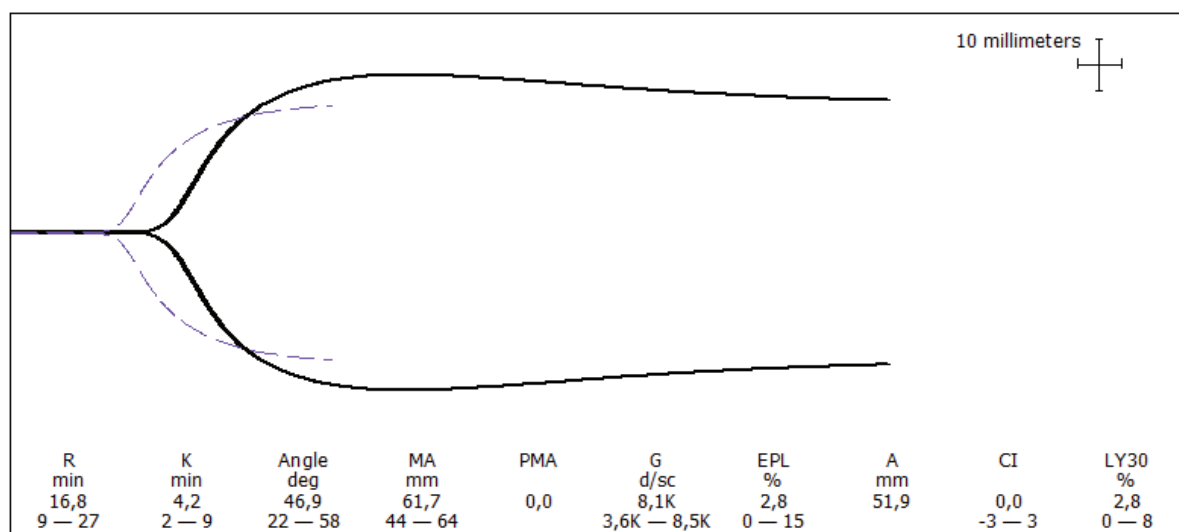


Figure 3. The TEG diagram reflects normocoagulation in all parts of hemostasis in 40 minutes after factor VIII concentrate injection, indicating an adequate matching dose of the drug



Figure 4. CT scan of the abdominal cavity organs. Massive hematoma of the abdominal cavity

manifestations of hemophilia (spontaneous bleeding and hematomas of the abdominal and pleural cavities) should be rationally conservative [3, 4]. Acute spontaneous hematoma of the abdominal cavity or retroperitoneal space in patients suffering from hemophilia is the most common complication with which it is necessary to differentiate diseases requiring urgent surgery. In particular, hematomas of the intestinal wall and/or mesentery are manifested by a clinical picture of dynamic intestinal obstruction. The method of choice in the diagnosis of hematoma is ultrasound

(ultrasound) and magnetic resonance imaging (MRI). In challenging situations, diagnostic laparoscopy is possible [4]. In a study representing the experience of treating 366 patients with hemophilia, it was shown that the introduction of hemostatic replacement therapy drugs and maintaining the activity of the missing coagulation factor at the level of 80–100% is a decisive factor in recovery. The clinical effect is manifested by a decrease in the size of the hematoma and restoration of intestinal motility. Operations in such cases only aggravated the condition of patients and were risk factors for hemorrhagic complications, abdominal adhesions, and the formation of ventral hernias [4].

In the presence of comorbidities (emergency and elective), in patients suffering from hemophilia, surgeries should be performed in full volume [4, 8]. Reconstructive colorectal surgery refers to high volume procedures. The widespread use of staplers of the appropriate diameter allows to make ultra-low anastomoses (at the level of the pelvic floor) and the reconstruction of the bowel with a short rectal stump. However, such procedures are associated with a significant risk of intra- and postoperative complications, the rate of which increases significantly with coagulopathies. The

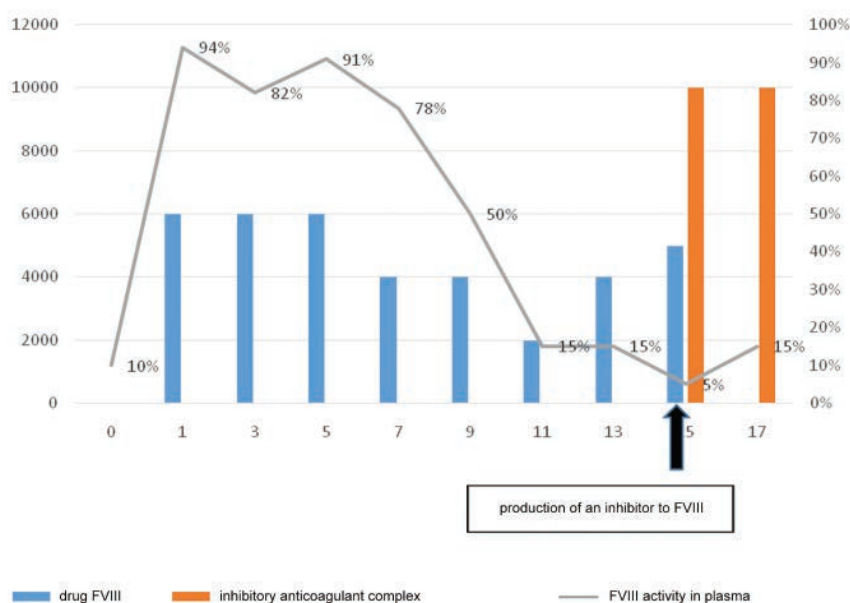


Figure 5. Dynamics of FVIII activity in serum in response to hemostatic replacement therapy with FVIII preparations before and after production of inhibitor to FVIII

incidence of low colorectal anastomoses leakage remains high and reaches 17% [9].

Tekkis P., et al. analyzed the experience of the coloanal anastomoses in a large sample ($n = 71$). Anastomosis leakage was noted in 8.5% ($N = 6$) of cases, the hematoma/seroma of the pelvis — in 7% ($N = 5$) of cases [10]. It is worth noting that with coagulopathies, including hemophilia, the rate of complications associated with the risks of anastomosis leakage increases significantly, which actualizes the problem of preventive stomas. Preventive stoma does not prevent the leakage, but reduces the severity of complications to which it leads, and also reduces the rate of re-operations [11]. In a meta-analysis performed by a group of researchers Gavriilidis P., et al. in 2018, a comparative assessment of preventive loop colostomy and ileostomy demonstrated a smaller number of events associated with wound infections and postoperative hernias ($p < 0.001$), stoma prolapse was significantly less common during ileostomy ($p < 0.001$), which demonstrates some advantages of using ileostomy over colostomy in patients with coagulation pathology. However, there was no convincing evidence of the superiority of one procedure over another in the total population of patients in the meta-analysis [12].

One of the most serious complications of the postoperative period in patients with hemophilia is the occurrence of an inhibitor to FVIII, which is directly related to the volume and trauma of surgery, as well as intensive hemostatic replacement therapy with FVIII concentrates. The appearance of an inhibitor leads to the ineffectiveness of hemostatic therapy and the development of uncontrolled postoperative bleeding [5, 13]. Such patients require a specific, individual approach to hemostatic replacement therapy. Correction of the hemostasis system with shunting drugs (rFVIIa and AICC) makes it possible to effectively cope with bleeding under the condition of adequate laboratory control [6, 14, 15]. The most significant test for laboratory control of the hemostasis system in hemophilia, including those associated with a factor VIII inhibitor, is thromboelastography (TEG). The TEG technique allows to collectively analyze all the links of the blood coagulation system (plasma, platelet and

fibrinolysis system) in real time and in a short time to evaluate the effectiveness of the hemostatic [7, 16]. So, a group of researchers Fisher, S. et al. demonstrated high sensitivity of thromboelastography (TEG) in the diagnosis of hemorrhagic conditions and response to therapy in a patient with extensive bleeding secondary to the acquired FVIII inhibitor.

Comparable with the clinical case described in this article, the use of the TEG technique made it possible to modify therapy in the shortest possible time to ensure adequate hemostasis against the background of bypass therapy, which significantly led to minimizing the risks of death from bleeding in the postoperative period [17].

A group of domestic researchers Galstyan G., et al. confirmed the undeniable advantages of using the TEG technique, which is one of the most accepted methods of monitoring rFVIIa therapy in patients with an inhibitory form of hemophilia, which allows not only monitoring therapy with shunting drugs, but also detecting resistance to one of them, contributing to the timely modification of hemostatic therapy [18].

CONCLUSIONS

1. Currently, there are no contraindications for performing surgery of any degree of complexity in patients with hemophilia with the right choice of surgical aid and adequate hemostatic replacement therapy.
2. Constant and full-fledged monitoring of the hemostasis system is necessary throughout the perioperative period in patients with hemophilia in order to prevent life-threatening hemorrhagic complications.

AUTHORS CONTRIBUTION

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Collection and processing of the material: Pavel A. Batrov

Writing of the text: Pavel A. Batrov, Svetlana V. Shtyrkova

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