OPTIONS FOR USE OF APPROPRIATE ANTICOAGULANT THERAPY IN PATIENTS WITH THERMAL INJURY WITH A HIGH RISK OF THROMBOEMBOLIC COMPLICATIONS DEVELOPMENT ASSOCIATED WITH RECURRENT INTESTINAL BLEEDING

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ABSTRACT Patients with major thermal injury require anticoagulant therapy during almost the whole period of the burn disease, forcing the physician to balance constantly between the risk of possible bleeding associated with surgical treatment and the risk of thrombosis development in patients demonstrating a number of factors predisposing to the development of VTC. We report a clinical case of appropriate anticoagulant therapy using the new oral anticoagulants in a patient with a high risk of VTC development and recurrent bleeding from the tumor of the ascending colon.

Keywords: burns, venous thromboembolic complications, heparin, oral anticoagulants, bleeding.

APTT — activated partial thromboplastin time

B.s. — the body surface

ETA — endotracheal anesthesia

FFP — fresh frozen plasma

GIB — gastro-intestinal bleeding

PE — pulmonary embolism

UH — unfractionated heparin

VTC — venous thromboembolic complications

BACKGROUND

Burn injury is one of the most common types of peacetime injuries in developed countries. The share of mortality resulted from severe thermal burns of all types of injuries reaches 9% [1]. Leading cause of death in patients with severe thermal injury is a burn shock (34.0%), pneumonia is on the second place (21.8%), and sepsis is on the third place (12.7%) [2]. Among the other most serious complications, venous thromboembolc complications (VTC) should be allocated, especially pulmonary embolism (PE), which develops suddenly and is characterized by high mortality [3-5]. It should be noted that analyzing the literature, we found controversial, sometimes conflicting reports on VTC occurrence in burn patients of different authors: from 0.25 to 23% of all observed patients with thermal injury [4-8]. According to the autopsy, the occurrence of VTC in dead burn patients increases to 65% [4]. A retrospective analysis of medical records of patients with thermal injuries treated in the burn center of Sklifosofsky Research Institute for Emergency Medicine (Moscow) showed that VTCs had been detected in 3.6 to 6.3% on the average of all patients admitted to the Burn Center [9].

Thus, the need for anticoagulation therapy in patients with thermal injury is undoubted. It is optimal for the drug for the prevention of VTC in patients with a high risk of thromboembolic complications to be clinically effective, without side effects, practical and easy to use and not requiring routine monitoring. The need for anticoagulation very often forces a physician to balance constantly between the risk of blood clots and possible bleeding. In this case, the use of modern anticoagulants may solve problems arising in the treatment course.

Clinical case:

A 58-year-old male patient P.B.S. entered the Moscow City Burn Center on 26.04.2011 on the 6th day after the injury with a diagnosis of flame burn of II-IIIAB-IV degree of 30% of the body surface (b.s.) (IIIB-IV —25% of b.s.) face, neck, forearms, hands, thighs, legs, feet. Severe burn disease, toxemia. Recent gastrointestinal bleeding (GIB). Anemia.

The history of the disease. The patient was admitted to the Moscow City Burn Center of Sklifosovsky Research Institute on 26.04.2011 from Zheleznodorozhny and was hospitalized in the intensive care unit.

The circumstances of injury: The patient got household flame burns on 20.04.2011 around 4:00 a.m. and was brought to the emergency department ofthe CRH of Zheleznodorozhny by the ambulance. He was hospitalized to have anti-shock therapy in the intensive care unit, where he had been treated for 6 days. From the report: the patient showed clinical picture of the GIB with the fall in Hb level from 130 to 80 g/l. The source of bleeding was not identified. Hemostatic therapy gave a positive effect. After recovering from the shock and stabilization of hemostasis the patient was transferred to the Moscow City Burn Center. Examination: a serious condition, conscious, adequate, hyposthenic, adynamic. Complaints of pain in wounds, significant weakness. Unaffected skin was pale. Unassisted breathing in all parts, somewhat weakened in the lower parts, isolated dry crackles, breath rate **—** 20 breaths per min. Heart sounds were muffled, rhythmic, blood pressure —160/90 mm Hg, PS — 100/min. Moist tongue. The abdomen was soft, slightly distended, and painless on palpation in all parts, with weakened peristalsis. Independent urination. ***St. localis:*** wounds total area of about 30% b.s. in the form of eroded surface with a touch of fibrin, with the presence of thin dry necrosis, dense thick wet and dry necrosis with significant perifocal inflammation, mummification of distal and middle phalanges of I, III, V finger of the right hand and II, IV, V finger of the left hand. Blood test upon arrival: **Hb — 90 g/l;** erythrocytes — **$3.18x10^{12}$**; leukocytes — $12.78x10^{9}$; myelocytes — 1%, neutrophiles: band forms — 13%, segmented forms — 73%; eozynophiles —1%; lymphocytes — 6%; monocytes — 6%; **platelets — $409.0x10^{9}$**; BSR — 74 mm/h, total protein — 45.40 g/l; urea — 2.39 mmol/l; creatinine — 73.8 mmol/l; glucose — 5.57 mmol/l; potassium — 4.10 mmol/l; sodium — 138.6 mmol/l; total bilirubin — 5.0 mmol/l. Chest X-ray on 26.04.2011: right venous plethora,

darkened lower lungs. The severity of the patient's condition was caused by severe burn disease in the stage of toxemia, long distance transportation and recent GIB (according to the discharge summary). Pathogenetic and symptomatic treatment of the severe burn disease was initiated: infusion-transfusion therapy (red blood cell transfusions, fresh frozen plasma (FFP), 10% albumin solution), antibiotic therapy (Ciplox 200 mg x 2 times i.v.), antiplatelet therapy (Trental i.v.), anticoagulant therapy (first 3 days — unfractionated heparin (UFH) 5,000 x 4 times daily s.c., then UFH 2,500 x 4 times per daily s.c.), antiulcer therapy (Aciloc 2,0 x 3 times daily i.v.), nutritional support (Nutricomp 2,000 ml per 24h) and symptomatic therapy. Dressings of burn wounds were performed regularly. After stabilization on 03.05.2011 (on the 7th day after admission to a burn center), the patient was transferred to an inpatient department for further treatment. When transferring, the patient's condition remained serious: the patient was conscious, communicative, had temperature reaction with a rise above 38.2ºC in the evening. Chest X-ray on 03.05.2011: right-sided pneumonia. Blood tests still had anemia **Hb — 90 g/l** with leukocytosis and band shift to the left. Given the high risk of VTC associated with a patient's undetected source of massive gastrointestinal bleeding, we decided to cancel the subcutaneous UFH because of its inefficiency in terms of activated partial thromboplastin time (aPTT) of 28.5 (no 1.5 times increase of aPTT from initial values) and the possible risk of heparin induced thrombocytopenia (decrease of plateletes was observed from $502.0x10^9$ (test of 01.05.2011) to $297.0x10^9$ in 1 mm^3 (test of 03.05.2011). On 05.05.2011, anticoagulation using Pradaxa was initiated in dosage of 110 mg x 2 times orally. Creatinine clearance (Cockcroft-Gault equation) was 97 ml/min. In order to monitor the status of hemostasis during of the adoption of the oral drug Pradaxa the patient underwent tromboelastography (conclusion: no abnormalities) and advanced blood coagulation on 05.05.2011 (see table).

Given that the only pathogenetic option of treatment for burn disease is an early maximum removal of necrotic tissue from wounds and closure of burn wounds of the patient, on 06.05.2011 after appropriate preparation the extensive necrectomy under the ETA of total area of 15% b.s. was performed. Blood loss during surgery was 150-200 ml and was restored with transfusion of washed red blood cells (309 ml) in the immediate postoperative period. During dressings no increased bleeding from the surgical wound was revealed. On 10.05.2011, on the background of complete well-being the patient showed clinical picture of recurrent gastrointestinal bleeding, with a gradual decline in Hb to 52 g/l. During diagnostic colonoscopy a tumor of the ascending colon was revealed, which occupied the lumen of more than 2/3, with signs of stopped bleeding. Hemostatic therapy was initiated (Etamzilatum 12.5% — 4,0 i.v., Epsilon-aminocaproic acid 5% — 100,0 i.v.), transfusion of FFP and (with the aim of substitution) erythrocyte suspension. Anticoagulation had been canceled on 10.05.2011 since the development of GIB. The hemostasis test of 16.05.2011 gave the following picture according to the coagulogram on the background of recent massive bleeding and hemostatic therapy: the fall of antithrombin III down to 60%, protein C — to 74%, plasminogen — to 47.2% (see Table). Coagulogram of 19.05.2011: aPTT fell to 22 sec, indicating the need to reinitiate anticoagulation therapy. Given the low level of antithrombin III (60%) which excluded the possibility of using heparin, it was decided to continue taking Pradaxa from 20.05.2011 under the control of coagulogram and thromboelastography. Creatinine clearance varied in the range of 88-97 ml/min over time. Against the background of ongoing therapy with *Pradaxa* the patient underwent surgeries: 26.05.2011 — I stage of autodermoplasty (ADP) of 10% b.s. under endotracheal anesthesia (ETN); 09.06.2011— II stage ADP of 10% b.s. with simultaneous amputation of III, IV and V finger of the right hand and II, IV and V finger of the left hand at the level of proximal phalanges. The postoperative period was uneventful. The coagulation findings of 23.05.2011 are presented in the table. We noted normalization of blood coagulation: aPTT (31.3 sec), antithrombin III (80%), protein C (103%) and plasminogen (75.8%). In subsequent tests of 31.05.2011, 07.06.2011 and 17.06.2011 coagulologic parameters were normal. On 08.06.2011, venous ultrasonography of lower limbs revealed no echo signs of venous thrombosis. Activation of the patient was normal. On 16.06.2011, *Pradaxa* therapy was canceled. The total duration of therapy with *Pradaxa* was 31 days. After complete restoration of the skin, the patient was transferred to the 1st surgical department of Sklifosovsky Research Institute for Emergency Medicine on 28.06.2011 for further treatment, where right-sided hemicolectomy was performed. The patient was discharged in satisfactory condition on 19.07.2011.

Table

Coagulation parameters of the patient over time

Date	APTT, sec	INR	Quick's prothrombin (%)	Thrombin time, sec	D-dimer mkg/ml	Antithrombin III,%	Protein C,%	Plasminogen, %
05.05.2011	28.5	1.20	74.2	19.5	0.30	86	122	144.8
16.05.2011	30.5	1.09	84.4	17.2	0.16	60	74	47.2
19.05.2011	22.0	1.01	99.5	-	-	-	-	-
23.05.2011	31.3	1.11	79.6	-	0.08	80	103	75.8
31.05. 2011	25.1	1.03	95.1	19.1	0.30	84	101	93
07.06. 2011	30.1	1.08	83.8	-	-	-	-	-
17.06. 2011	32.2	1.09	82.4	-	-	-	-	-

Notes: aPTT — activated partial thromboplastin time; INR — international normalized ratio

CONCLUSION

Wider use of modern oral anticoagulant agents in burn patients at high risk of VTEC (*Pradaxa, in particular*) allows adequate anticoagulation therapy to be performed, including patients with thermal injuries in the course of recurrent gastrointestinal bleeding.

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