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SPECIFICITIES OF HEMATOLOGY LABORATORY FINDINGS IN MAJOR OPERATIONS FOR HEAD AND NECK TUMORS

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SUMMARY – The aim of the study was to determine the incidence of coagulation disorders and possible differences between patients operated on for head and neck tumors with and without blood transfusion treatment. The study included 31 patients divided into two groups: 16 patients with and 15 patients without intraoperative administration of blood transfusion. The following laboratory parameters were monitored: leukocyte count, erythrocyte count, hemoglobin, hematocrit, platelet count, activated partial thromboplastin time, prothrombin time, fibrinogen, thrombin time, and fibrinolysis. Data were statistically analyzed by Student's t-test for dependent and independent samples, and by simple correlation. The results showed prothrombin time to be statistically significantly reduced postoperatively in both patient groups, while fibrinolysis was statistically significantly accelerated in the group of patients who received intraoperative blood transfusion. Accordingly, in patients administered blood transfusion during the surgery, fibrinolysis was statistically significantly accelerated in comparison with their preoperative values. In the group of patients who did not receive intraoperative blood transfusion, fibrinolysis remained within the physiological range.

Key words: *Head and neck neoplasms, surgery; Neoplasms, blood; Fibrinolysis, physiology*

Introduction

Radical operative procedure for extirpation of the larynx and pharynx as well as radical operations of the neck with partial removal of the mandible are basic therapeutic methods for malignant tumors of the neck and jaws. The patients undergoing such operations mostly are at an advanced age and suffer from many concomitant chronic diseases, primarily chronic obstructive lung disease, liver impairment, ischemic heart disease, and alcoholic and nicotinic dependence. According to the estimated risk, they belong to ASA II and ASA III groups. Besides preoperative examination and routine laboratory tests, pulmonary function tests, arterial blood gases, cardiac function tests, proteinogram, coagulation tests and others are included, depending on the coexistent chronic disease[1]. Analysis of the laboratory findings thus obtained revealed precipitated fibrinolysis in some patients, while the concentration of plasma fibrinogen was elevated in a majority of patients. Increased concentration of fibrinogen and accelerated fibrinolysis were most commonly observed, and led to the introduction of mandatory monitoring of basic coagulation tests in 31 patients. In addition to coagulation tests, the levels of erythrocytes, leukocytes, hemoglobin, hematocrit and platelets were also observed. These parameters were preoperatively and postoperatively monitored and statistically analyzed.

The aim of the study was to determine the incidence of coagulation disorders in patients operated on for malignant diseases of the head and neck, and to assess changes in laboratory findings of patients with and without intraoperative blood transfusion.

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Patients and Methods

The study included 31 patients divided into two groups of 16 and 15 patients who did and did not receive intraoperative blood transfusion, respectively. The following laboratory parameters were preoperatively and postoperatively monitored: leukocyte count (L), erythrocyte count (E), hemoglobin (Hb), platelets (Plt), active partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen, thrombin time (TT), and fibrinolysis. The values of L, E, Hb and Plt were determined on an automated Counter Micro Diff 2 (Miami, FL, USA), while APTT, PT and TT were determined by standard methods on an automated ALC 2000 coagulometer (IL-Instrumentation Laboratory). Fibrinogen was determined on the same device by the method of Clauss. The test of euglobulin fibrinolysis was performed in water bath at 37 °C by use of standard methods. Analyses were performed on citrated plasma samples. The values thus obtained were statistically analyzed by Student's t-test for dependent and independent samples, and by simple correlation.

Thirty minutes before the operation, the patients were premedicated with 5 mg midazolam and 0.5 mg atropine sulfate intramuscularly. Thiopental, etomidate or propofol was used for general anesthesia induction, and anesthesia was maintained by the administration of midazolam and fentanyl, with ventilation with a mixture of oxide and nitrous oxide (FiO_2 0.33). The use of general anesthetics (halothane and isoflurane) was restricted to a small number of patients with specific respiratory disorders. Anesthesia was controlled by a Dräger Sulla 808V device (Dräger, Lübeck, Germany), and duration of anesthesia was between 3 and 8 hours.

Results

Laboratory test findings obtained before and after the surgery in 31 patients operated on for planocellular carcinoma of the head and neck are presented in Table 1. Postoperatively, a statistically significant increase in L, and statistically significant decrease in E, Hb, Htc and Plt were recorded, whereas APTT showed no statistically significant alteration. Postoperative PT values were statistically significantly decreased in comparison with preoperative findings. No statistically significant change was recorded for the values of fibrinogen and TT. Postoperatively, fibrinolysis was found to be statistically significantly precipitated, however, the mean values of fibrinolysis were slightly below the normal physiological values and caused no clinically relevant hemostatic disturbances such as hemorrhage. Analysis of statistical results for 16 patients with and 15 patients without intraoperative blood transfusion (Tables 2 and 3) revealed a statistically significant increase in L and a statistically significant decrease in E, Hb and Htc in non-transfused patients. On the other hand, no stastistically significant change was recorded for E, Hb and Htc in transfused patients, i.e. their postoperative values remained almost unchanged, which was attributed to the good anesthesiologist's assessment of the blood loss and replacement.

Table 1. Preoperative and postoperative values (mean ± SD) of laboratory parameters in 31 patients obtained by Student's t-test for dependent samples

Parameter	Preoperative	Postoperative	p
L	7.6±1.9	14.3±4.7	<0.0001
E	4.2±0.5	3.96±0.5	<0.005
Hb	131.9±14.4	122.8±12.2	<0.0002
Htc	0.40±0.05	0.38±0.04	<0.001
Plt	250.5±84.7	220.2±78.9	<0.003
APTT	35.0±4.3	32.7±5.4	NS
PT	104.2±15.8	92.2±14.9	<0.0001
Fibrinogen	4.7±1.5	4.8±1.5	NS
TT	17.8±2.0	17.7±2.3	NS
Fibrinolysis	185.3±37.0	140.6±74.0	<0.003

NS=non-significant

Table 2. Preoperative and postoperative values (mean ± SD) of laboratory parameters in 16 patients receiving intraoperative blood transfusion, obtained by Student's t-test for dependent samples

Parameter	Preoperative	Postoperative	p
L	7.25±2.12	14.86±5.0	<0.00002
E	4.03±0.38	4.02±0.41	NS
Hb	129.81±15.1	126.13±11.2	NS
Htc	0.39±0.04	0.38±0.04	NS
Plt	230.1±80.1	204.6±49.4	<0.04
APTT	33.9±3.7	32.2±4.0	NS
PT	109.3±16.2	96.0±15.3	<0.002
Fibrinogen	4.9±1.7	4.7±1.5	NS
TT	118.0±1.8	17.3±1.8	NS
Fibrinolysis	192.2±36.0	122.2±76.8	<0.01

NS=non-significant

Platelets showed a statistically significant decrease in both groups of patients, as the result of intraoperative di-

Table 3. Preoperative and postoperative values (mean ± SD) of laboratory parameters in 15 patients not receiving intraoperative blood transfusion, obtained by Student's t-test for dependent samples

Parameter	Preoperative	Postoperative	p
L	7.97±1.72	13.63±4.23	<0.00008
E	4.4±0.5	3.91±0.53	<0.0003
Hb	134.07±3.71	119.2±12.67	<0.00001
Htc	0.42±0.05	0.37±0.04	<0.0003
Plt	272.3±86.6	236.9±100.7	<0.04
APTT	36.1±4.7	33.3±5.9	NS
PT	98.8±14.1	88.1±13.7	<0.02
Fibrinogen	4.5±1.2	4.8±1.6	NS
TT	17.5±2.2	18.1±2.7	NS
Fibrinolysis	178.0±38.2	160.3±67.7	NS

NS=non-significant

lution and hemostatic consumption[4]. Eight non-transfused and four transfused patients had basal values of fibrinolysis below the normal limits. Statistical analysis of correlation for individual parameters pointed to differences between the transfused and non-transfused patients. Positive correlation in transfused patients (Table 4) and negative correlation in non-transfused patients (Table 5) was found for all parameters except for postoperative fibrinogen and fibrinolysis, which yielded positive correlation.

Table 4. Simple correlation of laboratory findings in 16 patients receiving intraoperative blood transfusion

Parameter	r	p
L 0 – Plt 1	0.86	0.0002
Plt 0 – Plt 1	0.85	0.00003
Plt 0 – Fibrinogen 0	0.77	0.0005
PT 0 – PT 1	0.62	0.01
Fibrinogen 0 – Fibrinogen 1	0.50	0.05

0=preoperative value; 1=postoperative value

Table 5. Simple correlation of laboratory findings in 15 patients not receiving intraoperative blood transfusion

Parameter	r	p
L 2 – Htc 2	-0.82	0.0002
L 3 – Fibrinolysis 3	-0.53	0.04
E 3 – Fibrinolysis 3	-0.53	0.04
Fibrinogen 2 – Fibrinolysis 2	-0.53	0.04
Fibrinogen 3 – Fibrinolysis 3	0.52	0.05

2=preoperative value; 3=postoperative value

Discussion and Conclusion

The results obtained were expected and could be explained by metabolic, endocrinologic, neurologic and immunologic response of the body to the operation, and intraoperative dilution, blood loss and hemostatic consumption[2-4]. The reduced postoperative PT values could be interpreted as intraoperative hemostatic consumption of the prothrombin complex factors. The basal values of fibrinogen were elevated due to malignant disease, its growth and central tumor necrosis activating considerably more macrophages and enhancing the fibrinogen response and its serum concentration increase. Elevated fibrinogen concentrations are found in smokers and in mild liver impairment, because in these conditions the liver produces more fibrinogen as a compensation. Most of our patients were smokers and consumed more or less alcohol until the diagnosis of malignoma. Thrombosis and microembolism associated with malignancy lead to hypercoagulability and increased fibrinogen concentrations[2,4]. In our patients, the following clinical parameters could have contributed to the laboratory impairment of hemostasis: advanced age, fear from the disease and operation, general condition (e.g., hypoventilation, liver diseases, etc.), length of operation (major surgery), depth and type of anesthesia, intraoperative hypothermia, size and type of tumor, number and dissemination of metastases, tumor relation with the adjacent tissue, blood transfusion, amount of transfusion, type and storage of blood preparations, thrombocytopenia in some patients, etc.[5,6].

Interactions between the neoplasm and hemostatic system have long been known and numerous mechanisms of this interaction have been investigated. The vascular system within the tumor mass undergoes active rearrangements with time, usually resulting in the formation of irregular blood compartments, frequently lacking endothelium, which leads to direct contact between the blood and basal membrane. Hemodynamically, the geometric resistance frequently increases in intratumorous blood vessels, thus hampering the blood flow[3]. Tumor cells may release procoagulant activators such as tissue factor (TF), tumor procoagulant CP, prothrombin activators, thrombin activators, tissue specific proteases, cytokines and plasminogen activator inhibitors[5]. On the other hand, the concentration and synthesis of coagulation inhibitors (AT III,

protein C, protein S) and increased activity of plasminogen activators may also cause hemostatic impairments in these patients. These activities are most commonly induced by tumors of the pancreas, gastrointestinal tract, ovary, prostate, breast, lungs and liver[5-7].

From the clinical viewpoint, the hemostatic impairments associated with neoplasia include a wide range of manifestations, from mild biological coagulation activity through thrombosis, thromboembolism and hemorrhage. No major coagulation disturbances in patients with and operated for planocellular carcinoma of the head and neck have been described in the literature. Betlejewski et al. investigated the effect of laryngectomy on the process of fibrinolysis in the blood of patients with laryngeal neoplasm. Their study has demonstrated that the increased values of tissue plasminogen activator (t-PA) and fibrin and fibrinogen breakdown products (FDB), decreased values of plasminogen activation inhibitor 1 (PAI-1), and low values of fibrinogen along with reduced euglobulin lysis test (ELT) lead to the activation of fibrinolysis during the procedure of laryngectomy[8].

During the surgery, the patients received one or two blood doses. No major hemorrhage or replacement of blood or blood products were recorded in the patients. According to current concepts, an acute blood loss of 10% of the total volume of circulating blood and replacement of this blood volume should not be expected to cause any impairments in primary hemostasis dependent on platelets, coagulation and fibrinolysis[9]. According to the reports from animal experiments (rabbits), acute losses of 20% of total volume of circulating blood produce significant clotting time reduction without any discernible changes in primary hemostasis and fibrinolysis. However, if these losses are accompanied by blood transfusion, the coagulation time and time to the formation of the first hemostatic clot occur without any change in the fibrinolysis[10]. In our patients, enhanced hemorrhage and, consequently, intraoperative blood transfusion were most probably caused by lower basal values of E, Hb and Htc; major surgery implying prolonged duration of the procedure; tumor size and localization; number and dissemination of metastases; and surgeon's skill, rather than by a coagulation system impairment. In the patients with intraoperative blood transfusion, the precipitated fibrinolysis probably resulted from higher fibrinolytic activity, elevated fibrinogen concentration, or >14-day storage of the transfused blood with an increased content of platelet, leukocyte and fibrin degradation.

The results of the study pointed to the following conclusions: 1) basal values of precipitated fibrinolysis do not appear to predict for enhanced intraoperative hemorrhage and transfusion; 2) planocellular carcinomas of the head and neck induce mild hypercoagulation; 3) the hypercoagulant changes did not cause any severe clinical complications of coagulation such as thrombosis, thromboembolism, or hemorrhage; 4) elevated concentrations of fibrinogen might correlate with advanced disease, thus also likely with further prognosis; and 5) precipitated fibrinolysis in transfused patients was probably due to the transfused blood storage of >14 days.

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Sažetak

SPECIFIČNOSTI HEMATOLOŠKIH LABORATORIJSKIH NALAZA KOD VELIKIH ZAHVATA TUMORA GLAVE I VRATA

J. Kovač, M. Perić, S. Martinac-Djulepa, M. Ivkić, V. Stančić, B. Raić, D. Tonković, S. Krapinec i M. Novkoski

Cilj ispitivanja bio je utvrditi učestalost poremećaja zgrušavanja krvi u bolesnika operiranih zbog tumorskog procesa glave i vrata, te moguću razliku između bolesnika koji su tijekom operacije primali transfuziju i onih koji to nisu. Ukupno je 31 bolesnik bio obuhvaćen ispitivanjem. Bolesnici su bili podijeljeni u dvije skupine: 16 bolesnika je primalo transfuziju tijekom operacijskog zahvata, a 15 bolesnika nije primalo transfuziju. Praćeni su sljedeći laboratorijski parametri: broj leukocita, broj eritrocita, hemoglobin, hematokrit, broj trombocita, aktivirano parcijalno tromboplastinsko vrijeme, protrombinsko vrijeme, fibrinogen, trombinsko vrijeme i fibrinoliza. Podaci su bili statistički obrađeni Studentovim t-testom za zavisne i nezavisne uzorke, te jednostavnom korelacijom. Rezultati su pokazali statistički značajno skraćenje protrombinskog vremena nakon operacije u objema skupinama, dok je fibrinoliza bila statistički značajno ubrzana u skupini bolesnika koji su primali transfuziju. Dakle, u skupini bolesnika koji su primali transfuziju zabilježeno je statistički značajno ubrzanje fibrinolize nakon operacije u usporedbi s prijeoperacijskim vrijednostima. U bolesnika koji nisu primali transfuziju fibrinoliza je ostala u fiziološkim granicama.

Ključne riječi: *Neoplazme glave i vrata, operacija; Neoplazme, krv; Fibrinoliza, fiziologija*