Disseminated Intravascular Coagulation in Surgical Patients

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***Abstract*— Introduction.** Critical conditions, serious injuries, infection, trauma and major surgery are conditions that can cause significant physiological changes in response to stress. TNF-α and IL-1 are released in large quantities within one hour of stroke and have both local and systemic effects, responsible for the rise in body temperature and the release of stress hormones (noradrenaline, vasopressin, activation of the renin-angiotensin system). IL-1 and TNF-α directly act on the surface of the endothelium leading to the expression of tissue factor.

The cumulative effect of this inflammatory cascade is an unstable state dominated by inflammation and coagulation

Participants and methods. A prospective study was conducted on 60 patients undergoing abdominal surgical procedures, between January 2014 and December 2015 in the Surgery Clinic at the University Clinical Center Tuzla. Changes in coagulation with prophylactic administration of low molecular weight heparin were analyzed based on the parameters of coagulation status. To assess the increased propensity for intravascular coagulation, a DIC (disseminated intravascular coagulation) score was used.

Results. There was a statistically significant difference between the groups studied in the coagulation score ($p < 0.0001$). In the group of electively operated patients the highest value of the DIC score was 3, while in the group of urgently operated patients the highest value was 7. The highest average value of the DIC score was found in t_2. The intensity of changes in coagulation and the occurrence of disseminated intravascular coagulation affect the length and outcome of treatment for surgical patients. A good positive correlation of the DIC score was observed with the duration of hospitalization, and a negative correlation with the outcome of treatment .

Conclusion. Monitoring the coagulation parameters and evaluating the DIC score in these patients is important to assess the intensity of the coagulation cascade as part of the inflammatory response, and to make a timely diagnosis and start treatment for an eventual DIC.

Key words: disseminated intravascular coagulation,score, monitoring

INTRODUCTION

The action of various factors that threaten the integrity of the organism leads to the initiation of a number of mechanisms and the expression of appropriate reactions in the body. Critical conditions, serious injuries, infection, trauma and major surgery are conditions that can cause significant physiological changes in response to stress. The response of the organism to stress depends on the strength of the stressor and on the state of the organism before the action of the stress agent (1). Systemic response to surgical trauma involves activation of the sympathetic nervous system, endocrine "stress response" (pituitary hormone secretion, insulin resistance), immune and hematological changes (production cytokines, acute phase reaction, neutrophilic leukocytosis, lymphocyte proliferation)(2). Trauma, inflammation or infection lead to the activation of the inflammatory cascade. Tissue macrophages, monocytes, mast cells, platelets and endothelial cells can produce different cytokines. First, cytokine tissue necrotizing factor - α (TNF-α) and interleukin 1 (IL-1) are released and several cascades begin. The release of IL-1 and TNF-α (or the presence of endo or exotoxin) leads to the cleavage of nuclear factor-k B (NF-k B) inhibitors. When the inhibitor is eliminated, NF-κ B initiates the production of mRNA that induces the production of other proinflammatory cytokines. TNF-α and IL-1 are released in large quantities within one hour of stroke and have both local and systemic effects, responsible for the rise in body temperature and the release of stress hormones (noradrenaline,

vasopressin, activation of the renin-angiotensin system). IL-1 and TNF-α directly act on the surface of the endothelium leading to the expression of tissue factor. The tissue factor initiates the production of thrombin and thereby promotes coagulation and is itself a pro-inflammatory mediator. Fibrinolysis is reduced by the action of IL-1 and TNF-α on the production of plasminogen activation inhibitors. Pro-inflammatory cytokines also cleave the anti-inflammatory mediators antithrombin and activated protein C (APC), which are normally present in plasma. This coagulation cascade further leads to complications in terms of the occurrence of microvascular thrombosis, including organic dysfunction. The complement system plays an important role in this coagulation cascade. The cumulative effect of this inflammatory cascade is an unstable state dominated by inflammation and coagulation (3,4).

PARTICIPANTS AND METHODS

A prospective study was conducted on 60 patients undergoing abdominal surgical procedures, between January 2014 and December 2015 in the Surgery Clinic at the University Clinical Center Tuzla. Two groups of thirty were formed by the method of consecutive sampling. The first group (elective) consisted of subjects who were prepared for abdominal elective surgery (laparoscopic cholecystectomy), and the second group (non-elective) subjects underwent an emergency surgery due to acute abdomen (laparoscopic cholecystectomy). The subjects of both groups belonged both sexes, age from 18-70, and were the I-IV group of anesthesiologic risk according to the classification of the American Association of Anesthesiologists (ASA). They all signed informed consent to be included in investigation. Excluding factors were deep venous thrombosis (DVT) and pulmonary embolism, malignant diseases, previously coagulation disorders, oral administration of anticoagulant drugs, trauma, and the presence of infection at moment of hospitalization. As a part of the preoperative preparation of patients, in addition to the usual laboratory tests (complete blood count, blood sugar, blood gas analysis, urea, creatinine, urine), parameters of coagulation were analyzed: fibrinogen, D dimer, prothrombin time (PV), INR, activated partial thromboplastin time (aPTV). These preoperative values were signed as t0. The same parameters were analyzed 24 and 72 hours after the surgical procedure, which represents the value of t1 and t2. Blood for the analysis was taken from the peripheral vein in t o vacutainer tubes. Blood for the analysis of t0 of coagulation status was taken prior to administration of the first dose of low molecular weight heparin. Surgery was performed in general anesthesia. Introduction to anesthesia was performed by Propofol 1,5 – 2,5 mg/kg, maintence of anesthesia by Sevoflurane 1-1,5 vol%, O2, AIR, analgesia by fentanil 0,005 mg/kg and muscle relaxation by atracurium 0,4- 0,6 mg/kg. For the prevention of thromboembolism, the patients were administered reviparin sodium, in a dose that was determined according to the risk factor for deep venous thrombosis (DVT) for each patient. Changes in coagulation with prophylactic administration of low molecular weight heparin were analyzed based on the parameters of coagulation status. To assess the increased propensity for intravascular coagulation, a DIC (disseminated intravascular coagulation) score was used ((according to International Society on Thrombosis and Haemostasis - ISTH) (5), which implies:

- Platelet count: greater than 100 = 0 points; 50 - 100 = 1 point; less than 50 = 2 points

• Increased value of fibrin degradation products (D dimer): not increased = 0 points; moderately elevated = 2 points; markedly elevated = 3 points

• Extended prothrombin time: less than 3 s = 0 points; more than 3 s = 1 point; more than 6 s = 2 points

• Fibrinogen value: greater than 100 mg / dl = 0 points; less than 100 mg / dl = 1 point

A score of 5 and above indicates the presence of the DIC. Based on the data obtained, the correlation of changes in coagulation with the outcome of treatment, ie the length of hospitalization, was estimated.

The study was approved by Ethics Committee in University Clinical Center Tuzla and all the procedures used during the research were in accordance with the ethical standards of the responsible committee for human experiments based on the Helsinki Declaration. Statistical tests were done using the SPSS 19 . 0 software package. All variables were tested for the affiliation with normal distribution using the Kolmogorov- Smirnov test. Statistical data processing was done using descriptive statistic s using calculation of mean and standard deviation , and t-test, χ^2 test for calculating the significance of the determined results. Statistical analy s is was performed with a confidence interval of 95%, and the value of $p < 0.05$ was considered significant.

RESULTS

The study included two groups of 30 subjects aged 18 to 70 years. In the elective surgery group (Group 1), the average age was 47.53 ± 15.44, while the average age in the non-elective surgery group (Group 2) was 56.03 ± 20.10 years. In Group 1, the majority of subjects were 51-65 years of age, and in Group 2 they were 66-80 years old. Of the 60 analyzed patients, 26 were male and 34 were female. The majority of subjects were without co morbidities. In the elective surgery group subjects were hospitalized for 3.40 ± 1 days hospitalization, while in the non-elective surgery group subjects were hospitalized for 8.70 ± 5.88 days ($p < 0.05$). All patients from the elective surgery group were discharged home, while 25 non-elective surgery group subjects were discharged while

elderly 5 subjects died (p=0.023). There was a statistically significant difference between the groups studied in the coagulation score (p <0.0001) (Figure 1). In the group of electively operated patients the highest value of the DIC score was 3, while in the group of urgently operated patients the highest value was 7. The highest average value of the DIC score was found in t_2 (Figures 2 and 3).

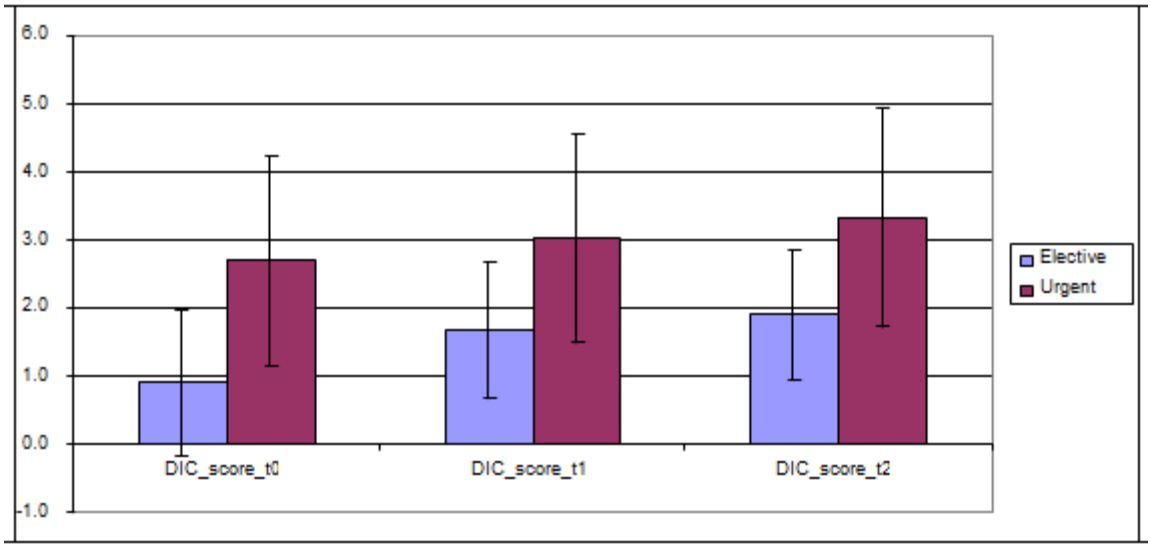

Figure 1. DIC score in both groups

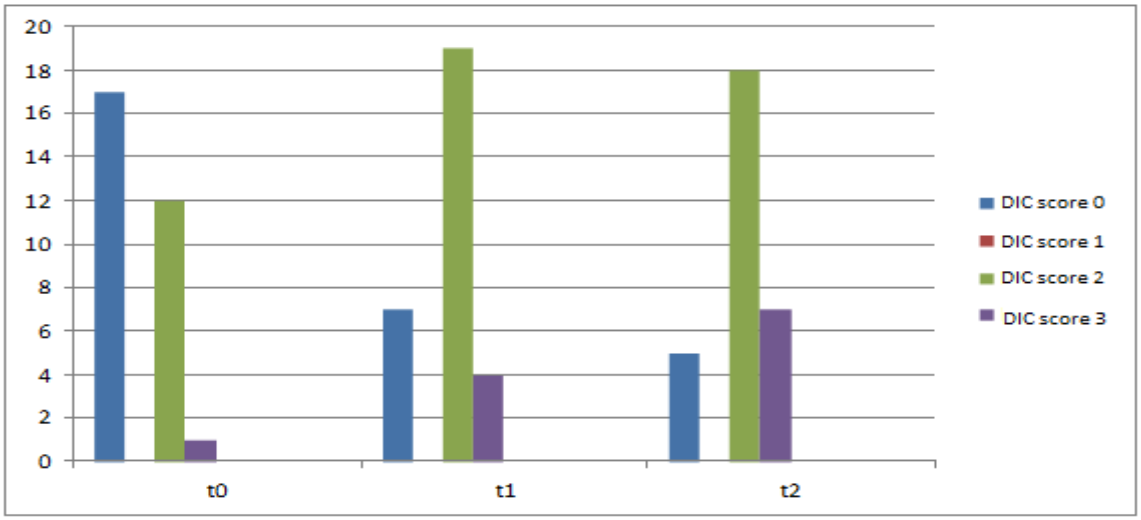

Figure 2. DIC score in group I

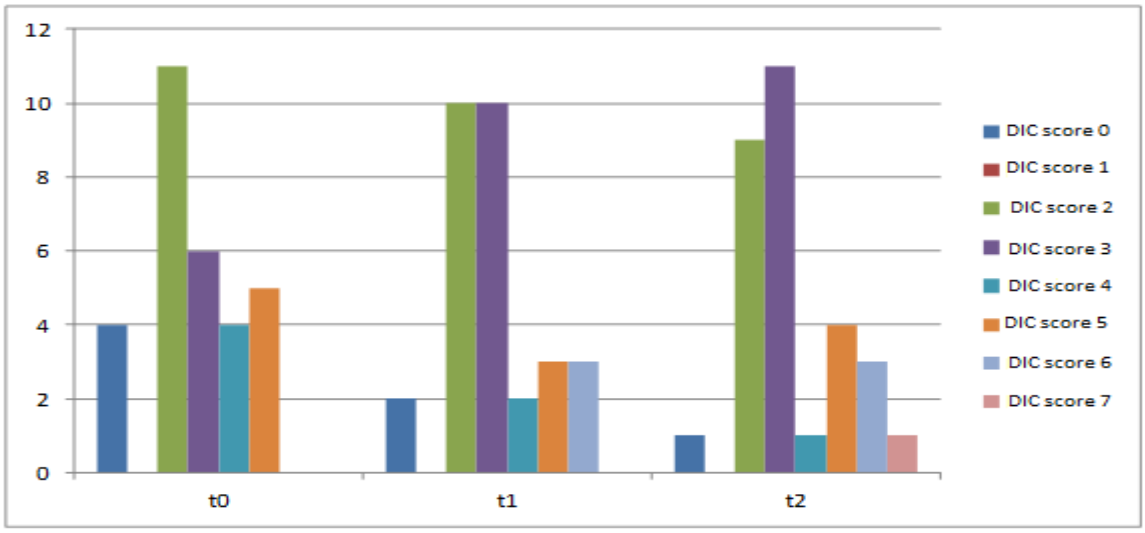

Figure 3: DIC score in group II

The intensity of changes in coagulation and the occurrence of disseminated intravascular coagulation affect the length and outcome of treatment for surgical patients.

A good positive correlation of the DIC score was observed with the duration of hospitalization, and a negative correlation with the outcome of treatment (Tables 1 and 2).

Table 1. Correlation of DIC scores and duration of hospitalization

Variable	Duration of hospitalization	
	Correlation coefficient	Significance of correlation
DIC_score_t0	.518	.000
DIC_score_t1	.398	.002
DIC_score_t2	.473	.000

Table 2. Correlation of treatment outcome with DIC score

Variable	Treatment outcome	
	Correlation coefficient	Significance of correlation
DIC_score_t0	-.420	.001
DIC_score_t1	-.385	.002
DIC_score_t2	-.362	.004

DISCUSSION

Systemic inflammation generally leads to disorders in hemostasis that can range from insignificant laboratory changes to severe disseminated intravascular coagulation. Systemic inflammation results in the activation of coagulation due to tissue factor-mediated thrombin formation, downregulation of physiological anticoagulant mechanisms, and inhibition of fibrinolysis (6). Vascular endothelial cells play a central role in all mechanisms of coagulation activation. Endothelial cells respond to cytokines released from activated leukocytes but can themselves release cytokines. They can also exhibit adhesion molecules and growth factors that can not only act on the inflammatory response but also on the coagulation response (7). An activated or damaged endothelium loses its natural anticoagulant capacity at the site of damage. In addition, activated endothelial cells and monocytes express large amounts of tissue factor, a significant trigger of the coagulation cascade. Coagulation disorders are common in critically ill surgical patients. Infection and inflammation interact with the immune and coagulation systems and promote a procoagulant state characterized by an increase in cellular tissue factor and plasminogen activator inhibitors, and reduced fibrinolysis. In addition to the traditional role in hemostasis, the onset of the coagulation cascade is an indicator of inflammation and contributes to pathogenesis through interaction with the immune system. This pleotropism of coagulation functions is nowhere near as significant as in critically ill surgical patients who may have an urgent need for postoperative haemostasis, but who also have a systemic inflammatory response with a triggered coagulation cascade. Assessment of the coagulation cascade in these patients requires careful evaluation of the patient with timely recognition of changes in coagulation parameters that may affect the patient's propensity to bleed, prognosis, and immediate therapy (8).

Critically ill surgical patients often have an increased tendency to bleed with significant changes in laboratory coagulation parameters. The causes of these disorders are multifactorial and include eating disorders, drug interaction with coagulation effects, liver dysfunction and comorbidity, and an already activated coagulation cascade by the systemic inflammatory response of the organism. Sepsa is associated with a procoagulant state that results from the induction of a cellular procoagulant response that is manifested by an increase in tissue factor and inhibitor of plasminogen activation, as well as inactivation of fibrinolytic mechanisms. With continuous systemic inflammation, there is a constant activation of the coagulation cascade, which consumes the coagulation factors and anticoagulant proteins AT III and protein C. This consumer process can lead to disseminated intravascular coagulation (DIC), which is a paradoxical combination of vascular thrombosis and hemorrhagic diathesis (9). Activation of the coagulation cascade as part of the systemic inflammatory response of the organism leads to the formation of intravascular fibrin formations that can cause microvascular thrombosis with consequent organ ischemia that can lead to necrosis and the formation of multiorgan dysfunction. Based on the pathophysiological concept and understanding of the anticoagulant and anti-inflammatory potential of coagulation inhibitors, the therapeutic application of these inhibitors in conditions of expressed SIRS and sepsis has been the subject of many studies. Disseminated intravascular coagulation, synonymous with consumptive coagulopathy, is a clinical syndrome characterized by abnormally increased activation of procoagulant mechanisms. This condition results in intravascular deposition of fibrin, and a reduced concentration of hemostasis components such as platelets, fibrinogen and other coagulation factors. DIC is characterized by pathological dysregulation of hemostatic and fibrinolytic processes as a consequence of systemic activation of coagulation and fibrinolysis. Clinical and laboratory parameters are used to diagnose DIC. The DIC scoring system established by the International Society for Thrombosis and Hemostasis (ISTH) provides an objective assessment of the DIC. In a state of consumptive coagulopathy, this scoring system correlates with clinical findings and outcome. Therefore, it is important to monitor dynamic changes based on laboratory tests and clinical evaluation of patients at risk for bleeding or thrombosis (10). Surgically critically ill patients due to a pronounced systemic response of the organism that triggers the coagulation cascade are in a procoagulant state resulting from a cellular procoagulant response manifested by increased tissue factor expression and increased activity of plasminogen activator inhibitors, as well as inactivation of fibrinolytic mechanisms, especially plasminogen activators. Continuous systemic inflammation causes continuity of the coagulation cascade and consumption of coagulation factors, but also of anticoagulation proteins AT III and protein C. This consuming process can cause disseminated intravascular coagulation. organism is of great importance (11). Bakhtiari et al published a study in 2004 exploring the application of the ISTH scoring system in the diagnosis of DIC in critically ill surgical and nonsurgical patients. They analyzed 217 patients evaluated every 48 hours for a DIC score based on platelet count, prothrombin time, D-dimer and fibrinogen values. In 34% of patients tested, DIC was diagnosed, with a higher incidence in nonsurgical patients (44%) than in critically ill surgical patients (29%). The highest score of the DIC score was related to platelet count, prolonged prothrombin time and D-dimer, while fibrinogen was generally elevated. They concluded that this scoring system was acceptable for confirming or excluding the diagnosis of DIC in critically ill patients (12). In our study, this scoring system was used to evaluate the occurrence of DIC in surgical patients. Scores of up to 5 were excluded and over 5 were confirmed by the DIC. There is a significant difference between the study groups in the value of the DIC score, which is higher in urgent

surgery patients. In the group of electively operated DIC respondents, at no stage of the trial the score had a value over five, thus excluding the existence of the DIC in this group. In the group of urgent operations in t1, 10% and in t2 13% of the subjects had a DIC score over 5, which confirmed the existence of a DIC in this group. A positive DIC score in a group of urgently operated patients is conditioned by a more pronounced inflammatory response of the organism due to acute events in the abdomen. Due to the correlation of inflammation intensity with coagulation, the more pronounced the inflammatory response, the more changes in coagulation will be more pronounced with the propensity of microvascular thrombosis and the development of DIC. As the development of the DIC increases the possibility of developing organic dysfunction, it also affects the length of hospitalization and treatment outcome.

CONCLUSION

Activation of coagulation as part of an inflammatory response caused by surgical stress and underlying surgical disease can result in microvascular thrombosis and multiorgan dysfunction in, especially critically ill patients, with pronounced systemic inflammatory response of the organism. Monitoring the coagulation parameters and evaluating the DIC score in these patients is important to assess the intensity of the coagulation cascade as part of the inflammatory response, and to make a timely diagnosis and start treatment for an eventual DIC.

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