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D-DIMER AND FIBRINOGEN IN MALIGNANT AND BENIGN OVARIAN TUMOR PATIENTS UNDERGOING SURGERY

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ABSTRACT

An ovarian tumor ranks second in gynecology tumor cases and ranks second in gynecology tumor death in Indonesia. Tumour causes hypercoagulable that increase the risk of thrombosis by the procoagulant mechanism. Tumor cells also can cause hyperfibrinogenemia that can cause bleeding. The aim of the study was to know D-dimer and fibrinogen value to investigate primary hyperfibrinolysis on a malignant and benign ovarian tumor, and to know whether operation procedure on malignant and benign tumor change D-dimer and fibrinogen value. Prospective analysis study was performed. Subjects were malignant and benign ovarian tumor patients underwent surgery in the Adam Malik Hospital, Medan. Oneway ANOVA test dan Wilcoxon Sum-Rank test was performed. Statistical differentiation was indicated with $p<0.05$. Study subjects were 16 patient; 8 malignant and 8 benign ovarian tumor patient respectively. Malignant ovarian tumor D-dimer values were higher than benign ovarian tumor ($p<0.01$) that indicate fibrinolysis increase in a malignant ovarian tumor. Malignant ovarian tumor fibrinogen values were the same as the benign ovarian tumor ($p>0.05$) that indicated that the fibrinolysis in an ovarian tumor was not primary hyperfibrinolysis. Surgery procedure didnot influence D-dimer and fibrinogen values. Primary hyperfibrinolysis was not occurred in the ovarian tumor.

Key words : Ovarian tumor, malignant, benign, D-dimer, fibrinogen

INTRODUCTION

The ovarian tumor is the most deadly gynecological malignancy type.[1] In developing countries, ovarian cancer is considered as a neoplasm positioning the top seven for its incidence and the top six for its mortality effect.[2] Benign ovarian tumors attack in all age groups, while malignant ovarian tumors are more common in older females.[1]

The hemostatic system is known to be involved in the growth and spread of malignancies. During the development of cancer, coagulation activation is often in the form of Disseminated Intravascular Coagulation (DIC). Coagulation factors released by tumor cells then activate the coagulation pathway and fibrinolysis system. Thrombin causes fibrin formation which acts as a growth factor for tumor cells and facilitates angiogenesis. Ovarian cancer cells can influence thrombin formation and induce fibrin degradation, useful for the spread of cancer. Thus, the hemostatic system is considered to be involved in the growth and spread of malignancy.

Hemostatic abnormality associated with cancer, however, is considered as a major challenge for clinicians because they can cause excessive thrombosis and bleeding. Even though there are abnormalities without excessive clinical symptoms, carcinoma patients usually experience abnormalities in their blood coagulation. Abnormalities in blood coagulation have been found in 92% of cancer patients. The most frequent abnormality is an increase in the value of clotting factors, such as fibrinogen as well as factors V, VII, IX and X, and also an increase in fibrinogen/fibrin degradation products, D-dimer, and thrombocytosis.[3]

D-dimer is the final product and a specific fibrinolysis marker widely evaluated in thromboembolism studies but still investigated in studies of progressive systemic inflammatory responses and multi-organ dysfunction in critical illness and assessment of carcinoma progression. Endothelial dysfunction in thrombosis, inflammation, and malignancy has the same pathophysiology, namely, thrombin formation induction by tissue factor, coagulation dysfunction, and fibrinolysis.[4]

Moreover, most tumors in humans and experimental animals contain some fibrinogen-related products, generally cross-linked fibrin, so it is thought that fibrin or fibrinogen are very important in the formation of tumor stroma. Fibrin matrix encourages the

migration of certain types of cells, such as endothelial cells, macrophages, and fibroblasts. The fibrin matrix also promotes neovascularization, which facilitates the formation of tumor stroma with a mechanism analogous to wound healing. Besides, Fibrin Degradation Products (FDPs) have strong chemotactic, immune-modulatory and angiogenic abilities. All of them play an essential role in the progression of the tumor.[5]

Surgery, on the other hand, is a technique of physical intervention in tissues and muscles. Surgical procedures are often categorized by their urgency, the type of process, the body system involved, the level of invasiveness, and unique instruments needed. Post-operative complications due to general or specific surgery must be treated based on the patient's disease history. The postoperative complications that often occur are postoperative fever, atelectasis, wound infection, embolism, and Deep Vein Thrombosis (DVT).[6]

Changes in the hemostasis system during surgery vary greatly from disseminated intravascular coagulation to deep venous thrombosis. These changes are in the form of an increase caused by neoplasm or the effect of surgery itself. Although careful surgical examination of the hemostasis system is critical to prevent hematoma, abnormalities of coagulation activation and/or increased fibrinolytic activity still can cause postoperative bleeding. Therefore, standard coagulation tests on partial Thromboplastin Time (PTT), Prothrombin Time (PT), fibrinogen, and platelet count as important parameters can monitor perioperative hemostasis capacity concerning fibrin clot formation.[7] For those reasons, this research aimed to evaluate the perioperative and postoperative patterns of D-dimer and fibrinogen in malignant and benign ovarian tumor patients undergoing surgery.

METHODS

This research was conducted in May-August 2016 using a prospective analysis study design with samples taken sequentially. This research was approved by Health Research Ethical Committee Medical Faculty of Universitas Sumatera Utara / H. Adam Malik General Hospital No. 407/TGL/KEPK/FK USU-RSUP HAM/2016. Subjects of this research consisted of patients with malignant and benign ovarian tumors undergoing surgery at the Adam Malik General Hospital in Medan. Exclusion criteria for the research subjects were patients who received anticoagulant and antithrombotic therapies, had sepsis, and were a coma.

Next, D-dimer and fibrinogen examinations were carried out on the subjects of this research before having surgery, one day after surgery, and before leaving the hospital. Malignant and benign ovarian tumors then were assessed histopathologically. Afterward, laboratory tests were carried out at the Clinical Pathology Laboratory of Adam Malik General Hospital in Medan. D-dimer and fibrinogen collected then were examined using Coatron A4 Automated Coagulation Analyzer.

Subsequently, statistical analysis was performed using Oxstat V, Version 5.01.02. Differences in D-dimer and fibrinogen between before having surgery, one day after surgery, before leaving the hospital were analyzed using the ANOVA test. The differences in D-dimer and fibrinogen between malignant and benign ovarian tumors were then analyzed using the Wilcoxson Sum-Rank Test with a p-value of <0.05 and a confidence interval of 95%.

RESULTS AND DISCUSSION

The total number of ovarian tumor patients treated and underwent surgery at the Adam Malik General Hospital in Medan following the inclusion and exclusion criteria was as many as 16 patients. Those patients consisted of 8 patients with malignant ovarian tumors and 8 patients with benign ovarian tumors.

Table 1 illustrates that there was no trend of change in the median levels of D-dimer in malignant ovarian tumors during the surgical procedure.

Similarly, Table 2 depicts that there was no trend of change in the median (ranges) levels of D-dimer in benign ovarian tumors during the surgical procedure.

Moreover, Table 3 demonstrates that there was no trend of change in the median (ranges) levels of fibrinogen in malignant ovarian tumors during the surgical procedure.

Table 1. The median (ranges) levels of D-dimers in malignant ovarian tumors

	Median	Ranges	ANOVA
Before the surgical procedure	1365	(385 - 2618)	
After the surgical procedure	1625	(765 – 2971)	p > 0.05
Before leaving the hospital	1349	(631 - 2137)	

Table 2. The median (ranges) levels of D-dimers in benign ovarian tumors

	Median	Ranges	ANOVA
Before the surgical procedure	570	(285 – 834)	
After the surgical procedure	741	(525 – 944)	p > 0.05
Before leaving the hospital	545	(266 – 852)	

Table 3. The median (ranges) levels of fibrinogenin malignant ovarian tumors

	Median	Ranges	ANOVA
Before the surgical procedure	349	(225 -687)	
After the surgical procedure	588	(308 – 854)	p > 0.05
Before leaving the hospital	402	(238 – 735)	

Table 4. The median (ranges) levels of fibrinogen in benign ovarian tumors

	Median	Ranges	ANOVA
Before the surgical procedure	402	(198 – 527)	
After the surgical procedure	543	(304 – 669)	p > 0.05
Before leaving the hospital	393	(175- 557)	

Like in malignant ovarian tumors, there was also no trend of change in the median levels of fibrinogen in benign ovarian tumors during the surgical procedure (Table 4).

Furthermore, the Wilcoxon Sum-Rank test was performed with the following steps: Compare the D-dimer values in malignant ovarian tumors to the D-dimer values in benign ovarian tumors. Next, based on the results of the ANOVA test carried out, the p-value obtained was less than 0.01; Compare the fibrinogen values in malignant ovarian tumors to the fibrinogen values in benign ovarian tumors. Subsequently, based on the results of the ANOVA test, the p-value obtained was higher than 0.05.

Based on the results of the ANOVA test, it is clear that the surgical procedure did not affect the trend of the presence or absence of changes in both D-dimer and fibrinogen levels. In other words, both of these markers in ovarian tumors are completely independent both during the post-operative period and when going home. These findings eliminate the impression that surgery on ovarian tumors will increase the productivity of fibrinolysis derived from X-linked fibrin, a product of thrombus formation, reinforced by clotting factor XIII activated by thrombin.

Also, based on the results of the Wilcoxon Sum-Rank test on D-dimer, there was a very significant difference between malignant ovarian tumors and benign ones with a p-value of <0.01. This result indicated that in malignant ovarian tumors the results (products) of fibrinolysis breaking down X-linked fibrin were much higher than in benign ovarian tumors. It means that malignant ovarian tumors have higher fibrin formation results and are strengthened by clotting factor XIII compared to benign tumors. Indirectly this shows that in malignant tumors there is a tendency to hypercoagulability and higher thrombosis formation. In other words, malignant tumors have risk factors for the greater side effects of thrombogenesis.

Another interesting finding is the appearance of higher D-dimers dragging towards fibrinolysis which occurred in malignant ovarian tumors due to secondary hyperfibrinolysis, the process of fibrinolysis triggered by the formation of X-linked fibrin. Until now, many kinds of research have assumed that some types of tumors can trigger a process, called as primary hyperfibrinolysis, where the tumor itself produces "plasmin-like-substance" purely excreted by tumor cells rather than plasmin products produced by the presence of X-linked fibrin. As a result, primary hyperfibrinolysis will cause direct digestion in fibrinogen and will result in hypofibrinogenemia.

Moreover, 90% of ovarian cancers are carcinomas (malignant epithelial tumors). Based on histopathology, immunohistochemistry and molecular genetic analysis, there are five types of ovarian cancers, namely High-Grade Serous Carcinoma (HGSC, 70%), Endometrioid Carcinoma (EC, 10%), Clear-Cell Carcinoma (CCC, 10%), Mucinous Carcinoma (MC, 3%), and Low-Grade Serous Carcinoma (LGSC, <5%). These tumor types (about 98% of all ovarian carcinomas) can be diagnosed with a light microscope and come from different diseases, influenced by epidemiological factors, genetic risk, precursor lesions, spread patterns, molecular events during oncogenesis, as well as response to chemotherapy and prognosis.[8]

The biology of ovarian carcinoma, furthermore, is different from hematogenous tumors since ovarian cancer cells mainly spread in the peritoneal cavity and are only superficially invasive. But, when tumors that proliferate rapidly suppress the visceral organs and only chemosensitivity is temporary, ovarian carcinoma becomes a deadly disease with a cure rate of only 30%. There are some genetic and epigenetic changes causing transformation of ovarian carcinoma cells. Ovarian carcinoma can come from three potential locations, namely the surface of the ovary, fallopian tube, or mesothelium-lined peritoneal cavity. Sixty-nine percent of all ovarian carcinoma patients will give up their disease compared with 19% in breast cancer. The high mortality of these tumors is based on a fact that most (75%) patients come at an advanced stage with extensive metastases in the peritoneal cavity. This cancer grows and metastasizes quickly. Hence, it is considered a very aggressive disease. Unlike most other cancers, ovarian carcinoma rarely spreads through blood vessels. But, the pelvic lymph glands and/or para-aortic can be involved.[9]

The latest treatment strategy for advanced ovarian carcinoma is aggressive surgery ("cytoreduction" or "tumor debulking"). Surgery often involves en bloc resection of ovarian tumors, reproductive organs, and sigmoid colon with a primary bowel reanastomosis ("posterior exenteration") to remove cancer from the pelvis. This procedure is technically possible because ovarian tumors grow in the peritoneal cavity, only invade the mesothelium-lined surface, and develop above the peritoneal reflection in the pelvis. Even large tumors attack only the superficial bowel serosa and never invade deeper layers, so removal of the transverse colon is very rare. The purpose of surgical therapy, consequently, is to remove as much as possible the tumor since some previous researches argue that results of cytoreduction can improve patient survival. The effect of cytoreduction is differences in the biological behavior of ovarian cancer compared to other malignancies. The removal of metastatic tumors does not improve survival in most other carcinomas.[9]

The history of the knowledge of the relationship between coagulation and cancer began in 1865 when Armand Trousseau found that patients who suffered from idiopathic venous thromboembolism often had underlying diseases that are cancer and vice versa. Different mechanisms can activated the blood coagulation cascade, and be used to differentiate the patient's cancer level. Changes occurred are usually from small abnormalities in laboratory tests to overt thrombosis and disseminated intravascular coagulation.[10]

Cancer, moreover, is also known to trigger blood coagulation activation by the appearance of a hypercoagulable state with chronic DIC in cancer patients. Abnormalities in one or more coagulation tests often occur in cancer patients, even in the absence of overt thrombosis and/or bleeding manifestations. Laboratory test results show that the process of fibrin and fibrinolysis formation is parallel to the development of cancer, more increased in metastatic one. Cancer can also affect the hemostasis system, and the hemostasis system at the same time affects cancer.

Consequently, in cancer patients, there is a coagulation abnormality which can underlie the increasing tendency of thrombosis and bleeding in cancer patients. The cause of this coagulation disorder is due to common risk factors that commonly occur in other patient categories, and other cancer-specific factors, such as the type of tumor and stage of the disease. In venous tissue, Deep Venous Thrombosis (DVT) in the lower limbs is the most common manifestation, followed by upper limb DVT, Pulmonary Embolism (PE), cerebral sinus thrombosis, and migratory superficial thrombophlebitis. Significant retrospective researches and prospective population researches even show the incidence of VTE ranges from 0.6% to 7.8%. This wide range is because many different factors contribute to the risk of VTE, and the most important one is the type of cancer.[11]

The high number of researches has recently improved our understanding of cancer-associated thrombosis as a significant cause of morbidity and mortality in cancer patients. The significant number of investigations even has been followed by an increase in clinical events with the most contemporary reports displaying an "unacceptably high" incidence rate. For instance, the venous manifestations of cancer-associated thrombosis are known to be DVT and PE, visceral or splanchnic vein thrombosis, also known as Venous Thromboembolism (VTE). Meanwhile, its arterial manifestation can include strokes and myocardial infarction.[12]

Besides, tumor mass is known to become stasis by infiltrating blood vessel walls, endoluminal growth, and vascular compression. Tumor cells then can directly trigger clotting through procoagulant secretions, such as TF procoagulant cancer. Therefore, it can be said that there is a two-way relationship between the hemostasis system and malignancy. First, malignancy itself promotes hypercoagulable state through secretion of procoagulant substances, then interferes with endothelial homeostasis, and increases blood flow. Second, the hemostasis system with its components and interactions facilitates cancer

progression-related processes, such as tumor growth, invasion, and neoangiogenesis.[13]

The D-dimer antigen, moreover, is a unique marker of the degradation of fibrin by the sequential action of three enzymes, namely thrombin, factor XIIIa, and plasmin. First, thrombin breaking down fibrinogen produces fibrin monomers, which polymerize and become templates for the formation of factors XIIIa and plasmin. Second, thrombin activates factor XIII plasma to bind to fibrin polymer to produce active transglutaminase, factor XIII. Factor XIII then catalyzes the formation of covalent bonds between d-domains in fibrin polymerized. And third, plasmin degrades cross-linked fibrin to release fibrin degradation products and exposes D-dimer antigen. The D-dimer antigen, thus, can be present in fibrin degradation products derived from soluble fibrin before binding into a fibrin gel, or after the fibrin clot are degraded by plasmin.

In general, the D-dimer test can be requested to as certain how far fibrin formation has begun or to determine whether there is a change in this process during a particular therapeutic process or disease process. In practice, D-dimer measurements have been most comprehensively validated in excluding VTE in specific patient populations, and diagnosing and monitoring coagulation activation in DIC. Recently, the D-dimer test has also begun to find clinical utility in predicting recurrent VTE and patient risk stratification for VTE recurrence. Several factors influenced the validity of the DVT diagnostic algorithm in patients with cancer. First, the level of D-dimer can be increased in patients with cancer without thrombosis. Second, there is no diagnostic algorithm designed for the diagnosis of DVT that has been validated in cancer patients.[14]

Patients with ovarian cancer actually have a high risk of DVT. Symptomatic venous thromboembolism has been reported to correlate with the prognosis in ovarian cancer. Hence, an accurate diagnosis of DVT is needed to treat patients with this disease appropriately. D-dimer is known as a useful molecular marker of blood coagulation and fibrinolysis. D-dimer is a specific degradation product derived from cross-linked fibrin processing by plasmin. High D-dimer values are thought to occur due to increased fibrin formation and efficient fibrinolytic system.[15]

Furthermore, fibrinogen, synthesized by hepatocytes, is a glycoprotein that is converted into fibrin insoluble by active thrombin. Fibrinogen is also known to be a critical protein in the coagulation pathway, interacting in various platelet aggregation processes, clot formation, and wound healing, as well as contributing to the final step of the coagulation cascade. Fibrin, fibrinogen, and other coagulation factors actively play a role in tumor cell growth, invasion, and metastasis by promoting tumor neoangiogenesis and by supporting continuous tumor cell adhesion.

Besides, fibrinogen is considered as one of the leading acute phase proteins, and its biosynthesis increases as inflammation and stress occur. It has been discussed that the development and growth of various tumors, including ovarian cancer, is closely related to the inflammatory process. Microenvironment tumor inflammation actively influences the proliferation, survival, and migration of tumor cells. And, fibrinogen itself can directly bind inflammatory cells or tumors, inducing the synthesis of proinflammatory cytokines.[16]

Hence, it can be said that the increased blood fibrinogen levels in cancer patients are not triggered by the increased production of fibrinogen in patients, but are more likely caused by tumor growth. This finding is also supported further by a reduction in the level of fibrinogen in the blood of patients having tumor surgical procedure, while in the blood of patients having no tumor surgical procedure, the concentration of fibrinogen will increase. The escalation of fibrinogen seems to be related to the presence of a tumor rather than the characteristics of the patients themselves. As a result, it can be assumed that tumor may produce factors that inhibit the speed of degradation or cross-linking of fibrinogen in the blood and also affect the transformation of fibrinogen to fibrin (antithrombin activity, etc.).[17]

Moreover, it can also be said that the increase in the levels of D-dimer found after the various surgical procedures are independent of the occurrence of VTE. Because the kinetics of D-dimer during the postoperative period is still unknown, it cannot be ascertained in which D-dimer time points can be used again after the surgical procedures as part of the diagnostic algorithm in the case of suspected VTE. The kinetics of D-dimer is mostly unknown in limiting the use of the D-dimer test to exclude VTE after the surgical procedures. Similarly, Dindo *et al*. also finds that the levels of D-dimer are above the normal ones before surgical procedures.

In this research, malignancy and age were also significantly associated with the increased D-dimers levels before the surgical procedures (P ¼= 0.01 and 0.02, respectively). After the surgical procedures, the D-dimer levels increased postoperatively reaching a peak on day seven and then taking the same points as those before the surgical procedures. After entering the peak, the levels of D-dimer usually decrease at a rate of 6% per day.[18]

Like in this research, Kodama *et al*., also revealed

that the D-dimer level was above the normal one before surgical procedures for gynecological cancer. In their study, after the surgical procedures, the level of D-dimer increased and reached a peak on day ten as high as an increase in the level of D-dimer during the pre-operative period. After reaching the peak, the level of D-dimer then decreased.[19]

Similarly, Prell *et al*. found that the D-dimer level was above the normal one before craniotomy. After the surgery, the level of D-dimer increased postoperatively and reached a peak on day three as high as an increase in the level of D-dimer during the pre-operative period. After reaching the peak, the level of D-dimer then decreased.[20] Gerlach *et al*. also found that the D-dimer level increased postoperatively.[7]

A Primary Hyperfibrinolysis State (PHS) is over expression of fibrinolysis without compensation. The name itself is impropriated because it is a secondary process in genetic diseases or some disorders, such as chronic liver failure or malignancy. Besides, this condition is related to hematological malignancies as well as solid tumors, such as prostate carcinoma and breast carcinoma. In this case, DIC is more common with features of hyperfibrinolysis than PHS. Also, there is a current opinion that when the hyperfibrinolytic condition occurs in solid tumors, this condition is more related to DIC than PHS. Thus, this condition is considered as a paraneoplastic expression of metastatic carcinoma, which treatment response depends on the evolution of the tumor. Because natural history underlying this condition often results in a fatal outcome, the overall prognosis will become poor.[21]

CONCLUSION AND SUGGESTION

In conclusion, the results of this research indicate that there is no difference in fibrinogen levels between malignant and benign ovarian tumors. Besides, the results of the ANOVA test also demonstrated that there was no change in fibrinogen levels either before the surgery, after the surgery, or when the patients were going home. This means that fibrinolysis occurred in ovarian tumors is due to secondary fibrinolysis, not because of primary fibrinolysis.

Cancer can confer a prothrombotic or hypercoagulable state through an altered balance between the coagulation and fibrinolytic systems, which can be related to long-term prognosis and treatment. Cytotoxic chemotherapy or other cancer therapies initiate additional mechanisms of clotting activation. D-dimer and fibrinogen testing can prevent thromboembolic complications in ovarian cancer patients, in particular when surgical treatment is involved.

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