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Clinical experience

Changes of coagulation factors in patients with carcinomas and carcinomas of the breast; perioperative influence of local anesthetics

DINKO BAGATIN[1]
DEANA ŠTURM[2]
TOMICA BAGATIN[1]

[1]Polyclinic Bagatin for maxillofacial, general and plastic surgery, Zagreb, Croatia

[2]Department of Transfusion Medicine and Coagulation in Oncology Patients, University Hospital for Tumors
Department of Transfusion Medicine, Sestre milosrdnice
University Hospital Center, Zagreb, Croatia

Correspondence:
Dinko Bagatin,MD
Department of maxillofacial, general and plastic surgery
Polyclinic Bagatin, Zagreb,
Kneza Višeslava 14, Croatia
Email: dinko.bagatin@poliklinikabagatin.hr

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After Croatian Register for Cancer there are approximately 2300 new cases diagnosed each year in Croatia. Breast cancer is the most common cause of death in women and accounting for more than 800 deaths a year. In 2010. in University Hospital for Tumors 600 patients had breast biopsy for suspicious breast tumors and afterward therapy after protocol for breast cancer. Patients with carcinoma are at risk of coagulopathy which can be first sign of malignant disease. Trombelastometry (TEG) is fast diagnostic method for differentiation hypercoagulation and hyperfibrinolytic conditions and their causes. TEG allow the dynamic assesment of haemostatic profile and in that way can be early predictor of breast carcinoma,differentiation between benign and malignant breast tumors and provide early therapy for carcinoma.

Breast cancers are the second most common cancer in women immediately after skin cancer. In the U.S. the 2010th estimated number of new cases of breast cancer was 207 090 (women) and 1970 (men) to the annual fatal: 39 840 (women) and 390 (men) (www.cancer.gov). In the last 20 years there has been a significant increase in the incidence mainly due to increased detection with screening mammography. Patients with breast cancer have been treated by resection of breast tissue with preservation of the rest of the breast *(1-7)*.

Abbreviations:

TEG	– Thrombelastography
DVD	– deep venous thrombosis
FXII	– Factor 12
FVIII	– von Willebrand factor
u-PA	– urokinase plasminogen activator
PAI-1	– plasminogen activator inhibitor 1
t-PA	– tissue plasminogen activator
VTE	– thromboembolism
TAT	– thrombin-antithrombin complexes
AT	– antithrombin
ALL	– acute lymphoblastic leukemia
PC	– protein C
PC	– protein S
NKT	– natural killer T cells.
IL-1	– interleukin-1
VEGF	– Vascular endothelial growth factor
VPF	– vascular permeability factor
TNF-α	– tumor necrosis factor-alpha
LA	– local anesthetics

Cancer patients are at increased risk of developing venous thromboembolism (VTE). Studies have shown that the risk is up to 6 times greater in patients with cancer. Tumor cell alters both host immunocompetent cells and activation of coagulation through a series of activations and secretions. Tumor itself gives rise to transformation of the host immunocompetent cells. Macrophages transform to so-called M2 cells characterized by lower antigen presenting ability. These alterations result in suppression of T cell response and immunosuppression. M2 cells enhance angiogenesis and tumor tissue proliferation. Vascular endothelial growth factor (VEGF) and inflammatory cytokines (TNF-α and IL-1β) from tumor cell stimulate tissue factor secretion by the macrophages and endothelium, as well as platelet adhesion to vascular endothelium and cell tumor-endothelium interaction resulting in FXII activation. The fibrinolytic system balance is severely impaired by the increased synthesis of urokinase plasminogen activator (u-PA) and plasminogen activator inhibitor 1 (PAI-1), and a decreased synthesis of tissue plasminogen activator (t-PA) *(8)*.

Thrombelastography (TEG) is a fast diagnostic method for differentiation hypercoagulable and hyperfibrinolyric states and its causes. TEG takes into account interreaction between fibrinogen, platelet and protein coagulation cascade. Using whole blood give us information about cumulative effect of various parameters of plasma factors, platelets, white blood cells at all stages of the coagulation process and fibrinolysis. In addition to the quantitative data we get also graphic presentation of clot formation and its decomposition. TEG is a dynamic evaluation of hemostatic profile in contrast to the static conventional coagulation parameters *(9)*.

In patients with malignant disease frequent clotting disorders may be the first manifestation of their malignancy. These disorders can be the result of pathophysiological events in the growth of malignant tumors and the consequences of their treatment. Venous thrombo-embolism (VTE) is a common complication in patients undergoing surgery. Cance rsurgery seems to have at least twice the risk of postoperative deep vein thrombosis (DVT) and more than 3 times the risk of fatal pulmonary embolism (PE) than similar procedures in non cancer patients *(10)*. In the study of Robert H. I. Andtbacka et alt., 3898 patients with breast cancer underwent 4416 surgical procedures. Seven patients with postoperative VTE within 60 days were identified, for a rate of 0.16% per procedure *(11)*. In Paulo Prandoni *et al.* study of the 842 includedpatients, 181 had known cancer at entry. The 12-month cumulative incidence of recurrent thromboembolism in cancer patients was 20.7% (95% CI, 15.6%–25.8%) versus 6.8% (95% CI, 3.9%–9.7%) in patients without cancer, for a hazard ratio of 3.2 (95% CI, 1.9–5.4) *(12)*.

During the growth tumors produce proteolytic enzymes that degrade the surrounding tissue and thus allow propagation of the malignant process. The most important is the matrix metalloproteinases (collagenase type 4), which allows the destruction of the basement membrane, which is necessary for the process neoangiogenesis, formation of new blood vessels of the tumor. Tumor blood vessels are anatomically imperfect, have numerous defects in the endothelium, what at the same time leads to bleeding and clotting activation process, and will therefore in most patients with malignant diseases be present in the laboratory findings as activated clotting process. Clinically visible clotting disorders do not perceive it in all patients with laboratory markers of activated clotting process. Their frequency have been increased during invasive diagnostic and therapeutic procedures, radiotherapy, surgery, use of central venous catheters or during the administration of chemotherapy. The occurrence of thromboembolism (TE) in patients with cancer is one of the indicators of their poorer outcomes *(12)*.

Tumor cells during growth release proteases, collagenase type 4, known as matrix metalloproteinases, which is released on intraluminal surface of endothelial cells and have been involved in direct fibrinolytic activity, which leads to destruction of the basement membrane of blood vessels, a process that is essential for the formation of new capillaries and tumor growth. Tumor cells release stimulatory factors, such as growth factors (vascular endothelial growth factor, VEGF) and core permeability factor (vascular permeability factor, VPF). VEGF stimulates the proliferation of endothelial cells in the extracellular space. VEGF / VPF increase microvascular permeability, induces migration of endothelial cells, enhance their proliferation and survival. While covering the endothelium of blood vessels in the area there are many gaps, and the relationship between endothelial cells and pericytes are much looser, endothelial cells are not tight to the basement membrane and in some places are accumulated in multiple layers *(13)*. These blood vessels have increased permeability, and through them have been increased release of plasma proteins, including prothrombin and fibrinogen in the extracellular matrix. Prothrombin is converted into thrombin and leads to activation of the clotting process, the conversion of fibrinogen to fibrin with formation of fibrin degradation products (FDP).

Activation of platelets within the anatomical imperfect vessels will lead to the expression of GPIIb / IIIa (or $\alpha_{11b}\beta_3$, from the group of integrins), the complex of two platelet glycoprotein involved in platelet adhesion to the vessel wall *(14)*. After activation platelets release growth factors and produce aggregates within which are linked fibrin network. Because of this process in patients with tumor disease there is an increased consumption and reduced life span of platelets. In the early stages of tumor disease platelet count can therefore be increased. Kuenen *(15)* has noted increased platelet counts in 40% of patients with malignant diseases. In advanced stages of malignant diseases commonly have been observed decreased platelet count, which is associated with poor prognosis. Decrease in the number of platelets occurs as a result of consumption of platelets due to bleeding in the tumor and surrounding tissue.

Anomalies in tumor microvasculature promote activation of clotting process externally in circulation to relieve clotting factors, the concentration of which is proportional

to the stage of the tumor, the intensity of angiogenesis and metastasis. Therefore, in malignant disease usually have been found increased concentration of clotting factors, particularly tissue factor (TF), a proteolytic enzyme synthesized by different bodies. Elevated levels of soluble tissue factor in the circulation have been increased with increased thrombogenic potential of tumors. Activation of the extrinsic pathway of coagulation in tumors leads to the activation cascade of proteolytic enzymes and the conversion of prothrombin to thrombin, which is the strongest procoagulable enzyme in the body. Its performance leads to the degradation of fibrinogen in fibrin monomers and creating extracellular fibrin network. In this process the resulting degradation are products: prothrombin fragments 1 and 2, fibrin degradation products of D-dimers. Immunohistochemical staining of these degradation products have been proven in extacellular matrix, and their concentration is higher in large tumors, malignant tumors with deep infiltrate of surrounding tissues and metastases in the lymph nodes. Studies have shown a significant correlation of these degradation products and tissue factor *(16)*.

FVIII / von Willebrand factor are two different glycoproteins that circulate in the plasma as a complex of FVIII / VWF. VWF is synthesized by endothelial cells and megakaryocytes, and it helps the adhesion of platelets to activated endothelium and maintain links between platelets during thrombus formation. VWF plays a significant role in the creation, operation and stabilization of FVIII, serves as his carrier and as a cofactor for FVIII in plasma. Factor VIII acts as a cofactor that accelerates the activation of FX by activated FIX in the clotting process. Increased synthesis of VWF, which correlated with tumor grade observed in the majority of cancers, including breast cancer *(17)*.

Counterbalance procoagulable processes in malignant diseases are natural anticoagulants: protein C, protein S and antithrombin. Antithrombin is the most important natural inhibitor of thrombin. He inactivate the irreversiable reaction that generates thrombin-antithrombin complexes (TAT). Higher TAT values that reflect the activation of the clotting process and increased consumption of AT were observed in acute lymphoblastic leukemia (ALL) *(18)*. Because consumer activation clotting process, the value of AT, protein C and protein S in the circulation are usually reduced. To hypercoagulability also contributes acquired and acquired resistance to the effect of protein C (APC-resistence), a disorder that is often observed in malignant disease, and disappears after the removal or cure of malignant diseases *(19)*.

In patients with breast cancer will be changes in trombelastogram (abbreviated coagulation time and formation of a clot with increased á angle and maximum clot firmness) and coagulation factors system (increased platelets, increased platelet aggregation, prolonged PT and APTT, fibrinogen, D-dimer, VWF, PAI-1, and decreased AT, PS, PC and plasminogen) in terms of diathesis, while we do not expect such changes in benign changes

SURGERY AND REGIONAL ANESTHESIA

Coagulation disorders may have a significant impact on the clinical perioperative outcomes in cancer population as a consequence of tumor growth, chemotherapy, radiotherapy or due to the surgical trauma. Surgery promotes the formation of fibrin and platelet clots around tumor cell emboli, thereby impairing natural killer cell--mediated tumor cell clearance, whereas perioperative anticoagulation attenuates this effect *(20)*. Undergoing surgical procedure presents an additional stress for the organism. Coagulation and anticoagulation inhibitor values analysis of perioperative measurements should have answered questions about a pathophysiological processes that are activated during the operation, but which are also blocked by applied Low molecular weight heparines, which has an antithrombin, profibrinolytic and antiaggregational effect *(21)*. Changes in coagulation and fibrinolysis inhibitor activity can perioperatively cause trombosis and/or bleeding *(22)*. Awareness of underlying mechanisms should point to preventive strategies, early diagnostics, and appropriate treatment of cancer and coagulation disorders associated. By activating t-PA and blocking PAI-1, thromboprophylaxis with LMW Heparin creates a stable and balanced perioperative system of haemostasis. Those may have a significant impact on the clinical outcomes in this suspectible population.

It is known that hematogenous dissemination of cancer cells occurs during the surgical resection of a tumor *(23)*. Recent studies confirmed that the circulating tumor cells were detected in the blood 24 h postoperatively, and there are an independent prognostic marker for cancer recurrence because of the ability of these cells to extravasate and metastasize (24). Also, It has been shown that opioids even at clinically useful concentrations might promote migration and proliferation of tumor cells, *e.g.*, in breast cancer *(25, 26)*. Authors with the results of study, suggest that the perioperative administration of local anesthetics(LA) may have the potential added benefit of attenuating extravasation and metastasis of circulating tumor cells *(27)*. The potential beneficial effect of regional anesthesia to improve long-term outcome after cancer surgery has been attributed to inhibition of the surgical stress response and to the decrease in opioid requirements. At the recent knowledge exert a possible mechanism by which local anesthetics might be beneficial in patients with cancer and/or undergoing cancer surgery and that this mechanism may be because of, at least in part, inhibition of Src tyrosine kinase, a key enzyme in cancer growth and metastasis *(27)*.

The benefit of paravertebral block with local anaesthetics to be proven in major breast procedures, and the pain relief was superior compared to general anesthesia. It is left to investigate place of regional anestehsia in minor breast surgical procedures *(28)*.

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