Scientific Research Publishing

Journal of Biosciences and Medicines, 2023, 11, 17-23
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Assessment of Fibrinolytic Activity in Gastric Cancer

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How to cite this paper: Wu, D., Zheng, H., Bao, F. and Huang, Y. (2023) Assessment of Fibrinolytic Activity in Gastric Cancer. *Journal of Biosciences and Medicines*, **11**, 17-23.
https://doi.org/10.4236/jbm.2023.113003

Received: January 31, 2023
Accepted: March 6, 2023
Published: March 9, 2023

Abstract

Objectives: To explore the relationship between thrombin-antithrombin complex (TAT), plasmin—α plasmin inhibitor complex (PIC), thrombomodulin (TM), tissue plasminogen activator/plasminogen activator inhibitor-1 complex (t-PAIC) and Gastric cancer. **Methods:** The plasma levels of TAT, TM, t-PAIC and PIC in patients with gastric cancer (40 in the initial diagnosis group and 35 in the post-treatment group) and 40 healthy controls were measured by chemiluminescent enzyme immunoassay. Then analyze the differences between these indicators in different stages of gastric cancer patients and healthy controls. **Results:** 1) The plasma levels of TAT, TM, t-PAIC and PIC in the newly diagnosed gastric cancer group were higher than those in the control group and the post-treatment group ($P < 0.05$). After treatment, the plasma levels of TAT, TM, t-PAIC and PIC in patients with gastric cancer have no significantly different than those in healthy controls ($P > 0.05$). 2) The plasma levels of TAT, TM, t-PAIC and PIC were not significantly different among the effective treatment group, the ineffective treatment group and the healthy control group. **Conclusion:** The changes of TAT, TM, t-PAIC and PIC levels are closely related to the development of patients with gastric cancer, and their increase may indicate that patients have a high risk of thrombosis.

Keywords

TAT, TM, t-PAIC, PIC, Multiple Myeloma, IMiDs

1. Introduction

In recent years, the annual incidence rate of thrombotic diseases accounts for 0.5% of tumor patients and 0.1% of the general population. The risk of throm-

bosis in tumor patients is five times higher than that in normal people [1]. Gastric cancer is one of the most common malignant tumors in the world [2]. Current research shows that patients with gastric cancer have a higher risk of venous thromboembolism [3]. Therefore, it is necessary to explore the mechanism of thrombosis and prevent thrombosis in patients with gastric cancer.

Exploring the changes of coagulation and fibrinolytic system function in tumor patients can help to analyze the mechanism of thrombosis in patients, while detecting the markers of coagulation, fibrinolysis and vascular endothelial function changes can better assist tumor patients in early diagnosis of thrombosis, and understand the relationship between the progression, stage, prognosis, survival rate and hypercoagulable state of tumor patients. With the progress of detection technology, thrombin-antithrombin complex (TAT), plasmin—α plasmin inhibitor complex (PIC), thrombomodulin (TM), tissue plasminogen activator/plasminogen activator inhibitor-1 complex (t-PAIC) and other indicators have been more widely used in clinical practice. These indicators are molecular markers of thrombosis and activation of fibrinolytic system. They are all detected by a new type of high-sensitivity chemiluminescence instrument. The detection results are more accurate and the detection speed is faster.

In this study, a new automated technology was used to detect the levels of TM, TAT, PIC, t-PAIC in plasma and comprehensively evaluate the relationship between them and gastric cancer.

2. Materials and Methods

2.1. Patients and Controls

Select 40 patients with gastric cancer from January 2018 to July 2022 as the observation group, including 22 males and 18 females. The age ranged from 52 to 79 years, with an average of (66.23 ± 5.87) years. Another 40 cases of healthy control group matched with the observation group were selected as the control group, including 21 males and 19 females. The age ranged from 50 to 79 years, with an average of (65.86 ± 5.51) years. There was no significant difference in sex, age between the two groups (both $P > 0.05$).

Inclusion criteria: 1) age 18 - 80. 2) The patients in the observation group met the diagnostic criteria of gastric cancer. The participants in the control group had normal physical examination results, knew the content of the study, volunteered to participate in the study, and signed the informed consent form. Exclusion criteria: Patients with infection, trauma, surgery, thrombotic disease, hypertension, diabetes, chronic renal failure, chronic metabolic disease and other diseases affecting coagulation indicators are excluded.

After treatment, the gastric cancer group was divided into effective group and ineffective group according to the curative effect after treatment to evaluate whether the remission was obtained (complete remission plus partial remission). There was no significant difference in sex and age between these groups (all $P > 0.05$).

This study was approved by the Medical Ethics Committee of The Second People's Hospital of Hefei, and all subjects signed the informed consent form.

2.2. Experimental Method

TAT, PIC, TM, t-PAIC are detected on the HISCL automatic analyzer using the principle of enzymatic chemiluminescence. In a certain external environment, specific antigen-antibody binding reaction is carried out by using biotinylated antibodies and substances in the tested samples, and then combined with streptomycin magnetic particles for demagnetization, cleaning and separation. Then the monoclonal antibody labeled with ALP reacts with the specific antigen antibody of the substance to be tested on the magnetic bead again. After demagnetization, cleaning and separation, buffer solution and high sensitive luminescent substrate CDP-Star are added to emit light under the catalysis of ALP, its luminous intensity is measured and the content of this substance in the sample to be tested is calculated. Japan HISCL 800 TM test kit, Japan HISCL 800 TAT test kit, Japan HISCL 800 t-PAIC test kit and Japan HISCL 800 PIC test kit were used for the test.

2.3. Statistical Analysis

SPSS 18.0 statistical software was used to process the experimental data. The measurement data conforming to the normal distribution and the homogeneity of variance are expressed in ($x \pm s$). The comparison between the two groups uses the t-test, and the comparison between multiple groups uses the analysis of variance. $P < 0.05$ indicates statistically significant.

3. Results

3.1. The Plasma Levels of TAT, TM, t-PAIC and PIC in the Newly Diagnosed Gastric Cancer Group and the Healthy Control Group (See Table 1)

The plasma levels of TAT, TM, t-PAIC and PIC in the newly diagnosed gastric cancer group were higher than those in the control group and the post-treatment group ($P < 0.05$). After treatment, the plasma levels of TAT, TM, t-PAIC and

Table 1. The plasma levels of TAT, TM, t-PAIC and PIC study group and the healthy control group.

Group	n	TAT (ng/mL)	TM (IU/mL)	t-PAIC (ng/mL)	PIC (μg/mL)
Newly diagnosed	40	11.26 ± 2.48*#	19.22 ± 6.23*#	22.48 ± 7.22*#	1.72 ± 0.62*#
post-treatment	35	3.72 ± 1.38	12.26 ± 4.98	14.24 ± 6.12	0.70 ± 0.29
Healthy controls	40	3.22 ± 1.11	11.11 ± 5.62	13.22 ± 5.13	0.63 ± 0.24
P	-	<0.05	<0.05	<0.05	<0.05

*$P < 0.05$ compared with the after treatment group. #$P < 0.05$ compared with healthy controls.

PIC in patients with gastric cancer has no significantly different than those in healthy controls ($P > 0.05$).

3.2. Plasma Levels of TAT, TM, t-PAIC and PIC in Effective and Ineffective Groups after Treatment (See Table 2)

The plasma levels of TAT, TM, t-PAIC and PIC were not significantly different among the effective treatment group, the ineffective treatment group and the healthy control group ($P > 0.05$). The plasma levels of TAT, TM and PIC in the treatment effective group and the treatment ineffective group were significantly lower than those in the newly diagnosed group ($P < 0.05$).

4. Discussion

Gastric cancer is in a state of easy thrombosis, and there is a clear correlation between the treatment of gastric cancer and the formation of thrombus [4]. Therefore, in terms of treatment, we should select the appropriate scheme for patients, evaluate the risk of thromboembolism events, and timely give anticoagulants to prevent the formation of thrombus. Therefore, it is particularly important to accurately evaluate the risk factors of thrombosis in gastric cancer patients, and timely anticoagulation to prevent thrombosis.

TAT is an inactive irreversible complex formed by the covalent bond of thrombin and antithrombin in plasma 1:1 after the formation of thrombin in the body, thus inactivating thrombin. The increased concentration of plasma TAT complex indicates that the concentration of thrombin is increased, the blood is in hypercoagulable state, and the risk of thrombosis is increased. Therefore, TAT is regarded as a sensitive molecular marker reflecting the activation of coagulation, and is also the direct evidence of the massive production of thrombin, which can be significantly increased even in the early stage of coagulation activation or before thrombosis [5]. Our study found that the plasma TAT level of newly diagnosed patients with gastric cancer was higher than that of the healthy control group, and the TAT level decreased after treatment. It shows that there is a certain degree of coagulation activation in patients with gastric cancer, and this hypercoagulable state can be partially relieved after tumor control.

Table 2. Plasma levels of TAT, TM, t-PAIC and PIC in effective and ineffective groups after treatment.

Group	*n*	TAT (ng/mL)	TM (IU/mL)	t-PAIC (ng/mL)	PIC (μg/mL)
Newly diagnosed	40	11.26 ± 2.48	19.22 ± 6.23	22.48 ± 7.22	1.72 ± 0.62
effective	25	3.55 ± 1.26*	13.27 ± 4.78*	13.57 ± 5.36*	0.67 ± 0.25*
ineffective	10	3.83 ± 1.55*	11.52 ± 4.86*	14.74 ± 4.75*	0.77 ± 0.38*
Healthy controls	40	3.22 ± 1.11*	11.11 ± 5.62*	13.22 ± 5.13*	0.63 ± 0.24*

*$P < 0.05$ compared with the newly diagnosed group.

TM is a single-chain transmembrane glycoprotein with a relative molecular weight of 75,000. It is generally expressed on the surface of vascular endothelial cells. Immunohistochemical staining confirmed that more than 99% of vascular endothelial cells express TM. TM exists in two forms, membrane type and dissolved type. Damage to vascular endothelium caused by malignant tumor can lead to release of TM on cell membrane into blood and increase the level [6] [7]. This study found that the plasma TM level of patients with gastric cancer was higher than that of healthy controls, and the TM level decreased after treatment. It shows that there is obvious vascular endothelial injury in lung cancer patients, and the degree of injury is related to the severity of the disease.

T-PAIC is a complex formed by the rapid combination of tissue plasminogen activator (t-PA) released from vascular endothelium into blood and physiological inhibitor plasminogen activator inhibitor-1 (PAI-1) in the ratio of 1:1. PAI-1 and other components of its fibrinolytic system, such as urokinase-type plasminogen activator and receptor (uPA, uPAR), play an important role in the physiological process of cell migration and proliferation, tissue remodeling, and participate in the occurrence, development, invasion, angiogenesis and fibrosis of tumor [8]. When vascular endothelial injury occurs, PAI-1 and t-PA are released simultaneously in the blood, resulting in the increase of t-PAIC concentration. It is suggested that the increased concentration of t-PAIC is not only a marker of vascular endothelial injury, but also a marker of the activation of fibrinolytic system, and that t-PAIC is more reliable than PAI-1 when reflecting the fibrinolytic function of the body [9] [10]. This study found that the plasma t-PAIC level of patients with gastric cancer was higher than that of healthy controls, and the TM level decreased after treatment. It is suggested that the detection of plasma t-PAIC level has certain significance for the early diagnosis, curative effect judgment and prognosis of gastric cancer complicated with vascular endothelial injury and/or fibrinolytic dysfunction.

PIC is fibrinolytic enzyme and its representative inhibitor α2-Antifibrinolytic enzyme (α2-PI) complex formed by 1:1 combination. Fibrinolytic enzyme α The fibrinolytic system composed of anti-fibrinolytic enzyme and other fibrinolytic activators or inhibitors has important physiological and pathological functions. It has a contradictory and unified dynamic balance relationship with the blood coagulation system. Once the body produces blood coagulation reaction, it also activates the fibrinolytic system almost at the same time. The latter will dissolve the fibrin deposited in the blood vessels and interstitium to keep the blood vessels and glands smooth, angiogenesis, prevent thrombosis, or dissolve the formed thrombus. Since the blood half-life of fibrinolytic enzyme is very short and cannot be directly measured, while the blood half-life of PIC is 6 hours, the appearance of PIC can directly reflect the activation of fibrinolytic enzyme. The increase of plasma PIC concentration indicates hyperfibrinolytic activity and increased bleeding risk [11] [12] [13]. This study found that the plasma PIC level of patients with gastric cancer was higher than that of healthy controls, and the PIC level decreased after treatment. It shows that the fibrinolytic function of pa-

tients with gastric cancer is enhanced while coagulation is activated.

However, due to the limited number of cases, the results of this study may have some limitations. In the future, we will continue to expand the sample size and strive for more accurate conclusions.

5. Conclusion

The changes of TAT, TM, t-PAIC and PIC levels are closely related to the development of patients with gastric cancer, and their increase may indicate that patients have a high risk of thrombosis, so it is necessary to consider the use of antithrombotic drugs.

Acknowledgements

The authors thank the patients and their families and all the investigators, including the physicians, nurses, and laboratory technicians in this study.

Consent

Written informed consent was obtained from the patient for publication of this article and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Conflicts of Interest

The authors declared that they have no competing interests.

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