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Original Research

Evaluation of the hypercoagulable state of gynecologic cancer patients by thromboelastography: a prospective pilot study and a review of the literature

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Summary

Objective: Cancer patients are at risk for developing venous thromboembolism (VTE). The present authors assessed the value of using thrombelastography (TEG) to evaluate the coagulation state of women with various forms of gynecological disorders. *Materials and Methods:* Surgical patients with gynecological malignancy (study group, n = 65, 71%) were prospectively compared to patients with premalignant and benign disease (control group, n = 19, 29%). Routine blood tests and TEG results were collected one day prior to surgery. Clinical and laboratory data were collected from the medical charts. Univariate and multivariate analyses were performed to determine group differences. *Results:* The study patients included 15 (23%) women with endometrial, 22 (33.8%) with ovarian, and nine (13.8%) with uterine cervical cancer. They were significantly older, had a higher body mass index, and more comorbidities, all known risk factors to develop VTE, compared to the control group. Surprisingly, TEG parameters were similar for both groups except for the α angle (time of clot formation), that was wider in the study group (76.6 ± 3.43º *vs.* 74.66 ± 3.66º, $p = 0.044$, non-significant on multivariate analysis). *Conclusions:* The pre-surgical/basal TEG profile is similar for gynecological patients with malignant and benign disease and therefore does not differentiate between them in terms of greater risk of VTE.

Key words: Thrombelastography; Hypercoagulability; Gynecologic cancer.

Introduction

Cancer patients have a seven-fold higher risk to develop venous thromboembolism (VTE) than patients without cancer [1]. VTE is common among patients with gynecologic cancer [2], with a 5.2% prevalence in those with ovarian cancer and 1.5% to 10.5% occurring within 24 months of diagnosis among women with uterine cancer [3]. Patients with gynecological cancer possess various risk factors for VTE, such as the malignancy itself, advanced age, vascular compression by a pelvic mass, lengthy surgery, vascular injury, and treatment with thrombogenic chemotherapy [4]. Anticoagulant treatment may be beneficial in preventing VTE in patients with cancer, however, it may cause severe bleeding, especially in those undergoing a major surgical procedure. To date, it is difficult to predict the occurrence of VTE and thereby identify the patients that will benefit from perioperative anticoagulation.

Conventional coagulation tests, such as activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen level, and platelets number, can only partially analyze the coagulation cascade and cannot reliably reflect the dynamics of clot formation, particularly in hypercoagulable states [5]. A viscoelastic test of blood coagulation, such as thrombelastography (TEG) generates a complete analysis of the clotting mechanisms, from thrombin activation to fibrinolysis. It generates a real-time image of in vitro clot formation, which is sensitive to all of the interacting cellular and plasmatic components of a blood sample and their effects on clot formation, strength and eventual lysis [6]. These instruments have been traditionally utilized within surgical and anesthesiology departments as point-of-care tests for determining the risk of bleeding and as a guide to transfusion requirements. It has been recently shown that TEG can be used to predict trauma patients at high risk for pulmonary emboli [7], and to predict thromboembolism in surgical and oncology patients [8, 9]. However, there is scant information on the efficacy of TEG specific to gynecologic oncology.

The purpose of this study was to assess the use of TEG to evaluate whether there are different coagulation profiles among women with benign gynecological disease versus women with various types of gynecological cancer.

Materials and Methods

This prospective case–control study was conducted from December 2016 until May 2017. The study received the institutional

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Table 1. — *General demographic and clinical data of study and control groups.*

Parameter	Total $n = 65$	Benign disease $n = 19$	Uterine cancer $n = 15$	Ovarian cancer $n = 22$	Cervical cancer $n = 9$	*p-value total	All cancers $n = 46$	p-value Benign *vs.* all cancers
Age (years), mean (SD)	57.1±13.1	54.2±13.7	65±9.5	59.1±10.8	45.1±12.9	0.001	58.3±12.7	0.261
BMI (kg/m^2), median (IQR)	27.17 (21.6-31.7)	25.2 (20.3-31)	31.1 (28.3-39.3)	24 (21.8-31.6)	24.2 (18.5-29)	0.013	27.2 (22.5-32.6)	0.301
DM, *n* (%)	10 (15.4%)	2 (10.5%)	7 (46%)	1 (4.5%)	0 (0%)	0.003	8 (17.4%)	0.71
HTN, *n* (%)	23 (35.4%)	6 (31.6%)	8 (53.3%)	8 (36.4%)	1 (11.1%)	0.207	17 (37%)	0.68
IHD, *n* (%)	3 (4.6%)	0	2 (13.3%)	1 (4.5%)	0	0.319	3 (6.5%)	0.55
ASA, *n* (%)	1 15 (24.6%)	8 (47.1%)	0	2 (10%)	5 (55.6%)	0.001	7 (15.9%)	0.013
	2 37 (60.7%)	9 (52.9%)	10 (66.7%)	14 (70%)	4 (44.4%)		28 (63.6%)	
	3 9 (14.8%)	0	5 (33.3%)	4 (20%)	0		9 (20.5%)	
Stage, *n* (%)	1 22 (47.8%)	0	12 (80%)	2 (9.1%)	8 (88.9%)	<0.001	22 (47.8%)	N/A
	2 1 (1.5%)	0	1 (6.7%)	0	0		1 (1.5%)	
	3 21 (32.3%)	0	1 (6.7%)	19 (86.4%)	1 (11.1%)		21 (32.3%)	
	4 2 (3.1%)	0	1 (6.7%)	1 (4.5%)	0		2 (3.1%)	
Grade, *n* (%)	1 9 (13.8%)	0	4 (26.7%)	3 (13.6%)	2 (22.2%)	<0.001	9 (13.8%)	N/A
	2 13 (20%)	0	7 (26.7%)	1 (4.5%)	5 (55.6%)		13 (20%)	
	3 24 (36.9%)	0	3 (26.7%)	18 (81.8%)	2 (22.2%)		24 (36.9%)	

*SD: standard deviation; BMI: body mass index; IQR: interquartile range; DM: diabetes mellitus; HTN: hypertension; IHD: ischemic heart disease; ASA: American Society of Anesthesiologists; N/A: not applicable. *p-value total represents differences between benign and individual cancer groups. Data presented as mean (standard deviation) for normally distributed variables and median (interquartile range) for non-normally distributed variables.*

review board approval (# 0016-12-TLV). All the participants signed an informed consent form prior to enrollment into the study. The study group included patients with confirmed pathological diagnosis of ovarian, endometrial or cervical cancer admitted for a non-urgent surgical intervention. The control group included patients with premalignant and benign conditions admitted for the same purpose. Patients with diseases of the hematological system and recurrent gynecological cancer were excluded.

Patient data were collected from computerized medical charts. Demographic and clinical data included age, gravidity, current body mass index (BMI), current diseases, medications, and personal or family history of coagulopathy. Perioperative data included stage of malignancy, postoperative histological diagnosis, and surgical procedure. Routine coagulation function tests and TEG profiles were carried out on the day prior to surgery. All patients underwent combined thromboprophylaxis with low molecular weight heparin administered six hours prior to surgery and pneumatic compression devices that were initiated at the induction of anesthesia.

A blood sample for TEG was collected into a citrated blood tube for coagulation. One mL of citrated whole blood was gently mixed with kaolin, and 360 mL of this preparation was pipetted into a TEG cup containing 20 mL calcium chloride and prewarmed to 37°C. Measurements were performed within two hours using a TEG hemostasis analyzer 5000, which is calibrated daily using the controls supplied by the manufacturer before running the study samples. Analysis of TEG parameters was performed by TEG analytical software. The following TEG parameters were analyzed: 1) R-time: the time interval from the beginning of the test until initial fibrin formation, 2) K-time: the time interval until a 20-mm amplitude has been achieved on the graph, 3) α angle: the rate of clot formation, 4) maximum amplitude (MA): the strength of the fibrin clot (fibrinogen and platelets contribute 20% and 80% of clot strength, respectively), 5) coagulation index (CI): calculated overall indicator of coagulation, which takes into account the relative contribution of each of the four parameters that are measured, and 6) LY30 (a measurement of the fibrinolytic system): the percentage decrease in graph amplitude 30 minutes after MA has been achieved.

Categorical variables were described using frequency and percentage. Continuous variables were evaluated for normal distribution using histograms and Q-Q plots. Normally distributed continuous variables were described as mean and standard deviation, and skewed variables were expressed as median and interquartile range. ANOVA, independent sample *t*-test, Kruskal Wallis test, and Mann Whitney test were used to compare continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. Multivariate linear regression was used to evaluate associations between TEG components and cancer. The multivariate linear regression consisted of two blocks: the first block included cancer and age and the second block included variables that were selected using the forward method. Diabetes mellitus, ischemic heart disease, dyslipidemia, peripheral vascular disease, atrial fibrillation, cerebral vascular accident, BMI, hemoglobin, fibrinogen, American Society of Anesthesiologists (ASA) score, uterus weight, and grade were considered for inclusion in the second block. The linear regressions were evaluated to meet the assumptions. All statistical tests were two tailed. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software.

Results

Sixty-five patients were enrolled into the study, 22 (33%) with ovarian, 15 (23%) with endometrial, and nine (14%) with cervical cancer (study group), and 19 (29%) with premalignant and benign gynecological disease (control group). Their demographic and clinical data are presented in Table 1. The patients with cervical cancer were on average the youngest (mean age 45.1 ± 12.9 years) and the uterine cancer patient group were the eldest (mean age 65 ± 9.5 years, $p = 0.001$). The mean BMI of the patients with uterine cancer was the highest, with an average of 31.1 (range 28.3-39.3, $p = 0.013$). Uterine cancer patients also had the

Table 2. — *Complete blood count, conventional coagulation tests, and TEG parameters for patients diagnosed with gynecologic cancer and benign disease.*

Parameter	Normal range	All combined	Benign disease	Uterine cancer	Ovarian cancer	Cervical cancer	*p*-value Total	All cancers	*p*-value Benign *vs.* all cancers
Hematocrit, %	35 - 45	36.185±5.24	39.263±4.43	35.667±4.9	36.185±5.24	36.185±5.24	0.008	34.913±5.05	0.002
Hemoglobin g/dL	11.7 - 15.5	11.87±1.72	12.853±1.53	11.78±1.66	11.06±1.74	11.96±1.22	0.009	11.47±1.64	0.003
WBC, X 10^3/mm^3	4 - 11	6.9 (5.4-8.7)	7.8 (6.9-8.7)	7 (5.5- 10.2)	6.15 (4.57-7.52)	8.1 (6-9.4)	0.072	6.7 (4.67-8.72)	0.116
Platelets, X 10^3/mm^3	150 - 450	251 (190-349)	239 (200-278)	265 (203-298)	249.5 (209.5-304.5)	251 (200.5-297)	0.92	255 (202-299.25)	0.498
Conventional coagulation tests									
PT, seconds	10.03 - 12.43	10.95±0.54	10.8±0. 57	10.94±0.54	11.054±0.45	11.06±0. 58	0.454	11.01±0.52	0.14
APTT, seconds	25 - 34	27.77±2.89	27.31±2.63	27.06±3.31	28.01±2.98	29.38±2.01	0.228	27.97±2.99	0.406
Fibrinogen, mg/dL	190 - 470	335.55 (269.07- 405.1)	302 (264-389)	389.1 (288- 492.9)	352 (297.45- 405.1)	326.3 (239.75- 356.9)	0.282	349.45 (289.5-410.47)	0.205
PT, INR	0.97 - 1.19	0.99±0.054	0.97±0.057	0.99±0.054	1.0064±0. 049	1.0044±0. 055	0.276	1.001±0.051	0.074
TEG parameters									
R time, minutes	2 - 8	5.08±1.11	5.35±0.99	4.67±1.41	4.85±0.97	5.74±0.83	0.064	4.972±1.15	0.214
K time, minutes	1 - 3	1.3 (1-1.4)	1.3 (1.1-1.8)	1 (0.9-1.3)	1.3 (0.97-1.425)	1.3 (1.05-1.4)	0.172	1.25 (0.975-1.4)	0.073
α degree	55 - 78	76.03±3.52	74.66±3.66	77.32±3.7	76.45±2.95	75.74±3.78	0.155	76.6±3.43	0.044
Maximal amplitude (MA)	51 - 69	66.24±6.96	64.25±7.92	69.06±6.17	66.46±5.41	65.18±8.81	0.239	67.06±6.44	0.14
Coagulation index (CI)	-3 - 3	2 (2-4)	2 (1-3.25)	3 (1.75-4)	2 (2-3)	2 (0-3.5)	0.316	2 (2-4)	0.281
LY30, %	0 - 8	0.4 (0-1.8)	0.5 (0.1-1.8)	1.3 (0-2.9)	0.25 (0-1.87)	0.1 (0.05-0.65)	0.569	0.3 (0-1.825)	0.63

*WBC: white blood cells; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; TEG: thromboelastography. *p-value total represents differences between benign and individual cancer groups.*

highest rate of comorbidities as well as a higher average ASA score ($p = 0.001$), while those with ovarian cancer presented at a more advanced stage ($p < 0.001$) and grade of disease ($p < 0.001$). Noteworthy, no cases of thromboembolism were recorded during the study period.

The mean hematocrit at the time of TEG measurement in the study group was 34.9 ± 5.0%, which was significantly lower compared to the control group (39.2 ± 4.4%, $p = 0.008$). No differences were found between the groups in the assessment of the coagulation system by means of conventional coagulation tests (PT and APTT). There was no group difference in the mean fibrinogen level, and it was not above the upper normal limit of the laboratory range (470 mg/dL, Table 2).

All the coagulation parameters assessed by TEG with the exception of the α angle, were not significantly different among the groups. The α angle was significantly higher in the study group compared to the control group ($p = 0.044$) (Table 2). The LY30 level, which measures fibrinolysis, was also similar among the groups. Multivariate linear regression was used to evaluate the association between TEG components and cancer, and an elevated α angle was not found to be an independent factor associated with any type of gynecologic cancer (Table 3). The maximum amplitude and the coagulation index, which have been suggested to predict the risk of thromboembolic events in patients admitted to intensive care, as well as in patients with cancer [7, 10, 11], were within the normal range for all of the present patients (Table 4).

Discussion

This prospective pilot case-control study evaluated the use of TEG, a comprehensive clinical assessment tool of coagulopathy, and the findings give some perspective to the risk of thrombosis in women diagnosed with various types of gynecologic cancer. They showed that women with cervical, endometrial, and ovarian cancer shared the same level of risk of thrombosis as the women diagnosed with non-malignant gynecologic conditions.

Cancer is a common cause of VTE, and the impact of VTE in patients with gynecologic cancer is considerable in terms of morbidity, mortality, and cost. The identification of tests able to predict the occurrence of VTE or hypercoagulability would be of great value, particularly in those patients undergoing surgery or chemotherapy [12], but current diagnostic tests do not reliably identify hypercoagulable states. Although TEG was developed for assessing

Table 3. — *Multivariate linear regression analysis for the α angle and cancer.*

	Parameter	B (95% CI)	*p*-value
Basic model	Cancer	1.802 (-0.191-3.79)	0.75
	Age	0.029 (-0.04-0.097)	0.407
	Parameter	B (95% CI)	*p*-value
Final model	Cancer	0.505 (-1.133-2.143)	0.537
	Age	0.036 (-0.031-0.103)	0.285
	Fibrinogen	0.2 (0.012-0.029)	<0.001
	HTN	-3.74 (-5.66-1.81)	<0.001
	Hg	-5.88 (-1.02-0.15)	0.01
	BMI	0.128 (0.012-0.244)	0.031

CI: confidence interval; HTN: hypertension; Hg: hemoglobin; BMI: body mass index.

Table 4. — *Maximum amplitude and coagulation index cutoff values and hypercoagulability for the study and control groups.*

	Benign	Malignancy	*p*-value
MA ≤ 68	12 (63.2%)	24 (52.2%)	0.418
MA > 68	7 (36.8%)	22 (47.8%)	
CI ≤ 2.6	12 (66.7%)	23 (51.1%)	0.262
CI > 2.7	6 (33.3%)	22 (48.9%)	

MA: maximum amplitude; CI: coagulation index.

patients in grave traumatic hemostatic states, it has reportedly detected changes in coagulability regardless of the etiology by assessing the interactions between coagulation factors, inhibiting factors, platelets and fibrinolysis, in addition to measuring the clotting cascade from the time when fibrin strands are formed to fibrinolysis [5].

The ability of TEG to detect hypercoagulable states has been reported in patients with cancer, however, most reports include patients with advanced disease who are receiving systemic chemotherapy [9, 13, 14]. Data on the use of TEG to assess hypercoagulability in gynecologic malignancies are scarce [12, 15, 16]. The present review of the literature is presented in Table 5. One early report describes a heterogeneous cohort of 198 patients with different gynecologic cancers, at different stages of disease and remission, as well as those with recurrent disease. Aznar *et al.* reported a trend towards hypercoagulability using celite-activated TEG, and concluded that more data are needed to validate their results [16]. Wehrum *et al.* examined specimens of 25 women with newly diagnosed gynecologic malignancies and from 21 age-matched controls that were analyzed using a TEG coagulation analyzer. Patients with gynecologic malignancies were found to have a short R value (7.1 ± 2.1 *vs.* 11.8 ± 1.8 min; $p < 0.001$), a short K value (3.1 ± 0.9 *vs.* 4.6 ± 0.9 min; $p < 0.001$), a prolonged maximum amplitude value (64.7 ± 5.4 *vs.* 58.8 ± 6.1 mm; $p = 0.001$), and a greater α-angle (70.6 ± 5.3 *vs.* 61.6 ± 4.9°; $p < 0.001$) compared with age-matched controls [12]. A retrospective study from Liu *et al.* included 376 patients with gynecological cancers that were inspected for deep vein thrombosis and pulmonary embolism by venous ultrasonography and computerized tomography. Thirty-nine (10.37%) patients were diagnosed as having VTE. Logistic regression multivariate analysis revealed that the TEG CI value, D-dimer, arrhythmia, coronary heart disease, surgery within four weeks, and chemotherapy within four weeks were independent risk factors for VTE. The TEG CI cutoff value was 2.55, which had a 53.8% sensitivity and a 75.4% specificity for VTE [15].

In the present study, the authors aimed to assess the coagulability state of patients hospitalized prior to surgical intervention for different types of gynecologic cancer in comparison to patients with benign or premalignant gynecologic conditions. None of the patients developed VTE during the study period. Although the study group was significantly older, had higher BMI levels, and more comor-

Table 5. — *Literature review of TEG studies for patients with all types of gynecologic cancer.*

Study	TEG analyzer	Number of patients	Type of gynecologic cancer	Stage of disease	Controls	Methods	Significant TEG results
Anzar *et al.*	Celite-activated	198	All	Diagnosis, remission recurrence	None	Retrospective	Trend toward hypercoagulability
Wehrum *et al.*	Celite-activated	25	All	Newly diagnosed	Age-matched controls	Prospective	Short R value Short K value Prolonged MA value Greater α angle
Liu *et al.*	TEG 5000 Thromboelastograph	376	All	Diagnosis, remission recurrence	Patients without VTE	Retrospective	Coagulation index value
Current	TEG 5000 Hemostasis analyzer	65	All	Newly diagnosed	Patients with benign or premalignant conditions	Prospective	Greater α angle

TEG: thromboelastography; VTE: venous thromboembolism; MA: maximum amplitude.

bidities, all known risk factors for developing VTE, compared to the control group, there were no detectable significant differences on TEG among the groups. The α angle was significantly elevated in the gynecologic cancer group versus the control group ($p = 0.044$) but the significance was lost on multivariate linear regression analysis. Previous studies suggested that both MA and CI may be useful for identifying cancer patients at high risk for thrombotic complications [10, 15]. In the current study, however, both the MA and CI were within the normal range in both the study and control groups. Noteworthy, the present authors could not find a significant correlation between a specific type of cancer or an advanced stage (increased tumor burden) and a hypercoagulable state as identified by the TEG.

This study has several limitations that bear mention. The study sample is relatively small and it comprises a combination of disease sites and stages. However, the patients in this cohort were treated by the staff of a single department with a strict preoperative protocol. The blood specimens of the control group were handled in the same manner as the study group. Previous reports have warned that the TEG profile of specimens stored in citrated containers for extended periods of time may tend towards hypercoagulability [17, 18]. The blood collected in the present study was analyzed immediately and stored in citrated tubes for no longer than two hours until analyzed. Another limitation is the variation in the definition of "hypercoagulability" using TEG parameters and thresholds that are not well defined. Studies comparing the changes in the coagulable state by means of TEG have not produced outstanding data [19]. TEG is a viscoelastic hemostatic assay that measures the global viscoelastic properties of whole blood clot formation under low shear stress. TEG was developed to monitor hemodynamics of trauma patients and to manage the administration of blood products [20]. It can detect the interaction of platelets with the coagulation cascade (aggregation, clot strengthening, fibrin cross-linking, and fibrinolysis), but it does not necessarily correlate with blood tests, such as INR, APTT, and platelet count. Studies on TEG showed cost-effectiveness and reduction of blood products use in patients undergoing liver transplant and cardiac surgery [21-24]. It was also found to be useful for the administration of blood products transfusion under extreme hemodynamic conditions, such as trauma and obstetric care, and in the early detection of dilutional coagulopathy [25-28].

In conclusion, changes in TEG parameters are small and not well resolved in patients that are not hemodynamically destabilized. From the findings of other studies as well as the current one, it would appear that TEG testing is not suitable for detecting subtle hypercoagulable changes, at least not in the preoperative setting, and a valid conclusion would be the limited knowledge about the potential value of TEG in risk management of patients with gynecologic malignancies and the need for better designed studies, especially because the parameters and thresholds of TEG are not well defined.

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