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CLINICAL RESEARCH

Role of Thrombolestagrophy in Monitoring Perioperative Coagulation Status and Effect of Thromboprophylaxis in Bariatric Surgery

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Abstract
Background Thromboelastography is a technique that surveys the properties of viscoelastic blood clot. The purpose of this paper was to evaluate the hypercoagulability state and the effect of antithrombotic prophylaxis on thromboelastogram (TEG) results in bariatric surgery.
Methods Twenty-five patients enrolled received 0.8 ml of nodraparin starting on the day before surgery and continuing postoperatively. TEG profile was collected before induction of anesthesia, on the first and third postoperative days. Each sample was run also in a cup added with heparinase to eliminate the interference of antithrombotic prophylaxis.
Results TEG analysis with heparinase showed a tendency to reduce the r-time (rate of initial fibrin formation) and k-time (time to clot firmness) and increase the alpha angle (rate of clot growth), while an increase of maximal amplitude (MA, a measure of maximal stiffness of the clot; $p = 0.01$) and GI or shear elastic modules strength ($p = 0.03$)was observed from basal to postoperative day 3 (POD3). TEG without heparinase evidenced and increase of r-time ($p = 0.02$) and k-time ($p = 0.05$), a reduction of the alpha angle ($p = 0.03$), and an increase of MA ($p = 0.01$) and GI ($p = 0.03$) from basal to POD3. The comparison of TEG techniques showed that normal TEGs had lower values of r-time and k-time and higher values of alpha angles and MA than TEG with heparinase. No differences were evident for basal and POD1 samples and the *G* values comparing the two TEG technique. No correlation was observed between the variation of normal TEG parameters and dosage of anticoagulant used in each patient.
Conclusions Our patients presented a tendency to hypercoagulability determined most by MA and GI. Comparison between TEGs indicates that low-molecular-weight heparin not titrated on weight is able to determine a reduction of hypercoabulable tendency in the early postoperative period with few effects on increasing MA and GI.

Keywords Bariatric surgery · Thromboelastography · Antithrombotic prophylaxis · Nodraparin · Hypercoagulability

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Introduction

Each year, approximately 50,000–100,000 patients die as a result of a thromboembolic event that originated, principally, from a deep vein thrombosis of the leg, thigh, or pelvis, although it can occur from an upper extremity or cardiac thrombus [1].

The obesity condition may be a risk factor for the increased incidence of postoperative deep vein thrombosis (DVT) and pulmonary embolism (PE) [2]. Decreased fibrinolysis and increased fibrinogen concentration have been identified as the most important risk factors for thromboembolic events in obese patients. Epidemiological studies also showed an increased plasminogen activator inhibitor activity in obese patients, associated with markers of both inherited and acquired thrombophilic states,

including D-dimer, fibrinogen, factor VIII, factor IX, factor XI, and lupus anticoagulant elevation.

Postoperative deep vein thrombosis and pulmonary embolism risk are considered the most important causes of morbidity and mortality in bariatric patients [3].

The surgical stress with prolonged immobilization in association with a native hypercoagulability status typical of this kind of patients may explain the higher incidence of these events in such a population.

Although incidence of postoperative thromboembolic events does not appear increased despite the exponential growth of the number of bariatric operations performed in the last period, isolated fatal pulmonary embolism is no longer a rare event; when it does occur, it is frequently without clinical prodrome.

Diagnosing venous thrombosis in the severely obese is a sort of challenge as patients are physically difficult to visit and often have subtle signs, masked by chronic leg edema, stasis dermatitis, and vein insufficiency, meaning that minimally symptomatic deep venous thrombi can often easily progress to fatal pulmonary emboli [4].

Preventing venous thromboembolism is vital if morbidity and mortality from bariatric procedures are to be reduced. Current prophylaxis regimens use a variety of modalities, including unfractionated heparin, low-molecular weight heparin (LMWH), intermittent compression devices, elastic stockings, early ambulation, and inferior vena cava filters. All clinicians agree that prophylaxis is vital; the problem now is to determine the optimal prophylaxis regimen and how to titrate the anticoagulant therapy [5].

Thromboelastography is a technique that surveys the properties of viscoelastic blood clot, from its formation to its lysis. In the last 10 years, thromboelastography (TEG) has demonstrated its ability to highlight not only the hypocoagulability states but also the hypercoagulability states associated with significant changes in its parameters [6, 7].

The aim of this study was to evaluate whether TEG parameters are able to detect the hypercoagulability state in obese patients undergoing laparoscopic bariatric surgery (gastric bypass and sleeve gastrectomy) and to monitor the effect of the perioperative antithrombotic prophylaxis on TEG results

Methods

The study was approved by the local ethical committee and performed at IV surgical division in Pisa. Patients with severe obesity undergoing laparoscopic bariatric surgery (gastric bypass or sleeve gastrectomy) under totally intravenous anesthesia in normothermal conditions from April 2009 to February 2010 were enrolled after written consent was obtained. The following exclusion criteria were used: coagulation disorders, preoperative use of FANS, oral contraceptives or oral anticoagulants, renal disease, and liver disease. All patients received anti-thromboembolic prophylaxis with 0.8 ml of calcium nodraparin (fraxieparin) subcutaneously once daily, starting on the day before surgery and continuing in the postoperative period. Moreover, mechanical devices, such as elastic stocking and intermittent pneumatic compression of inferior limbs, were used. The dosage of nodraparin was not adjusted according to BMI or weight.

For each patient, a coagulation profile (Tables 1, 2, and 3) was collected at three successive periods:

- Baseline (before induction of anesthesia)
- POD1 (first postoperative day)
- POD3 (third postoperative day)

TEG assays have been performed with Haemoscope Thromboelasograph® Haemostasis Analyzer. A citrate-added technique has been used, removing the need for immediate processing. The coagulation process was activated using Kaolin and 20 μL of calcium chloride as described in the literature.

The thromboelastographic trace was analyzed for:

- r-time: (reaction time, in minutes) representing the rate of initial fibrin formation through enzymatic clotting activation
- k-time: (clotting time, in minutes) representing the time until a fixed level of clot firmness is reached; this value reflects thrombin's ability to cleave soluble fibrinogen.
- α-angle (degrees): closely related to K, this represents the rate of clot growth. It is affected primarily by the rate of thrombin generation.
- MA parameter (maximum amplitude, millimeters): a measurement of maximal strength or stiffness of the developed clot

Table 1 Mean ± SD of blood test values

Laboratory tests	Basal	POD1	POD3
Platelets	279.64 ± 86.87	256.76 ± 76.35	251.24 ± 76.01
Fibrinogenemia	383.04 ± 61.23	394.84 ± 57.29	474.2 ± 74.09
INR	1.01 ± 0.04	1.06 ± 0.04	1.11 ± 0.12
D-dimer	0.27 ± 0.23	0.47 ± 0.2	0.67 ± 0.21

Table 2 TEG results with heparinase

	Basal	POD1	POD3	*p* value (basal vs. POD1)	*p* value (basal vs. POD3)	*p* value (POD1 vs. POD3)
r-time (min)	8.08±2.19	7.90±2.08	7.91±3.25	0.7	0.92	0.76
k-time (min)	2.21±0.82	2.02±0.96	2.10±0.89	0.6	0.21	0.35
α angle (deg)	55.35±12.76	60.88±11.82	59.41±11.84	0.08	0.2	0.59
MA (mm)	65.64±4.06	65.83±4.69	68.12±4.89	0.83	0.01	0.01
G (dyne/cm^2)	9.69±2.09	9.9±2.1	11.06±2.6	0.46	0.03	0.002

The table shows the mean and SD and the statistical results of Wilcoxon matched-pairs signed-rank test. Level of significance, $p < 0.05$

- Shear elastic modules strength (SEMS or GI, dynes per square centimeter): a parametric measure of clot firmness expressed in metric units calculated from MA as follows: $G=(5{,}000 \times MA)/(100 - MA)$

Furthermore, each TEG sample was run also in a cup added with heparinase to eliminate the interference of the prescribed antithrombotic prophylaxis on the coagulation status of patients.

All analyses were performed as devised by the manufacturer.

Statistical Analysis

Coagulation parameters and TEG values are presented as the mean and SD. Values comparisons were made by Wilcoxon matched-pairs signed-rank test. Correlation between TEG parameters from basal to POD3 and pro/kilogram dosage of nodraparin was performed using Bravais–Pearson's correlation coefficient.

Results

We studied 25 severely obese patients, 18 women and 7 men, aged 25–60 years (mean age, 47.72±10.8 years; mean age of women, 41.3±10.1 years; mean age of men, 46.3±12.3 years) and with BMI between 36 and 82 (mean BMI, 51.21±13.3; mean BMI of men, 53.36±15.2; mean BMI of women, 50.36±11.5). The mean duration of the entire procedure has been about 120±37 min. Patients received the same amount of fluids and all were successfully extubated after the end of surgery.

The analysis of blood tests evidenced an increase of fibrinogenemia (p=2.35E−05) and D-dimer (p=1.03E−06) from basal to POD3 (Table 1).

TEG with heparinase showed:

Trend to reduction of r-time and k-time, an increase of alpha angle that did not reach statistical significance, and an increase of MA (p=0.01) and GI (p=0.03) from POD1 to POD3 (see Table 2 and Fig. 1).

TEG without heparinase evidenced a trend to increase that did not reach statistical significance of r-time (p=0.02) and k-time (p=0.05) from basal to POD3 and a significant reduction of alpha angle (p=0.03) from basal to POD3 (see Table 2). No variation of r-time, k-time, and alpha angle from basal to POD1 and an increase of MA (p=0.01) and GI (p=0.03) from basal to POD3 (see Table 3 and Fig. 1) were observed.

The comparison between TEG samples with and without heparinase showed that normal TEG analyses had lower values of r-time (p=0.01) and k-time (p=0.04) and higher values of alpha angles (p=0.02) and MA (p=0.02) than TEG with heparinase in POD3. No differences were evident for basal and POD1 samples and the G (p=0.15) values when comparing the two TEG techniques (see Fig. 1).

We did not find any correlation among variations of parameters obtained with TEG from basal to POD3 and the amount of thromboembolic prophylaxis used in each patient (Pearson coefficient for variation r-time=0.08,

Table 3 TEG results without heparinase

	Basal	POD1	POD3	Basal vs. POD1	Basal vs. Pod3	POD1 vs. POD3
r-time (min)	8.85±2.51	8.71±2.84	9.91±3.88	0.8	0.02	0.12
k-time (min)	2.25±1.04	2.21±0.77	2.65±1.36	0.3	0.05	0.14
α angle (deg)	56.32±9.99	57.76±11.03	53.10±11.82	0.6	0.03	0.09
MA (mm)	63.36±4.61	64.88±5.99	66.45±6.30	0.2	0.01	0.2
G (dyne/cm^2)	8.87±1.89	9.62±2.38	10.46±3.16	0.1	0.03	0.9

The table shows the mean and SD and the statistical results of Wilcoxon matched-pairs signed-rank test. Level of significance, $p<0.05$

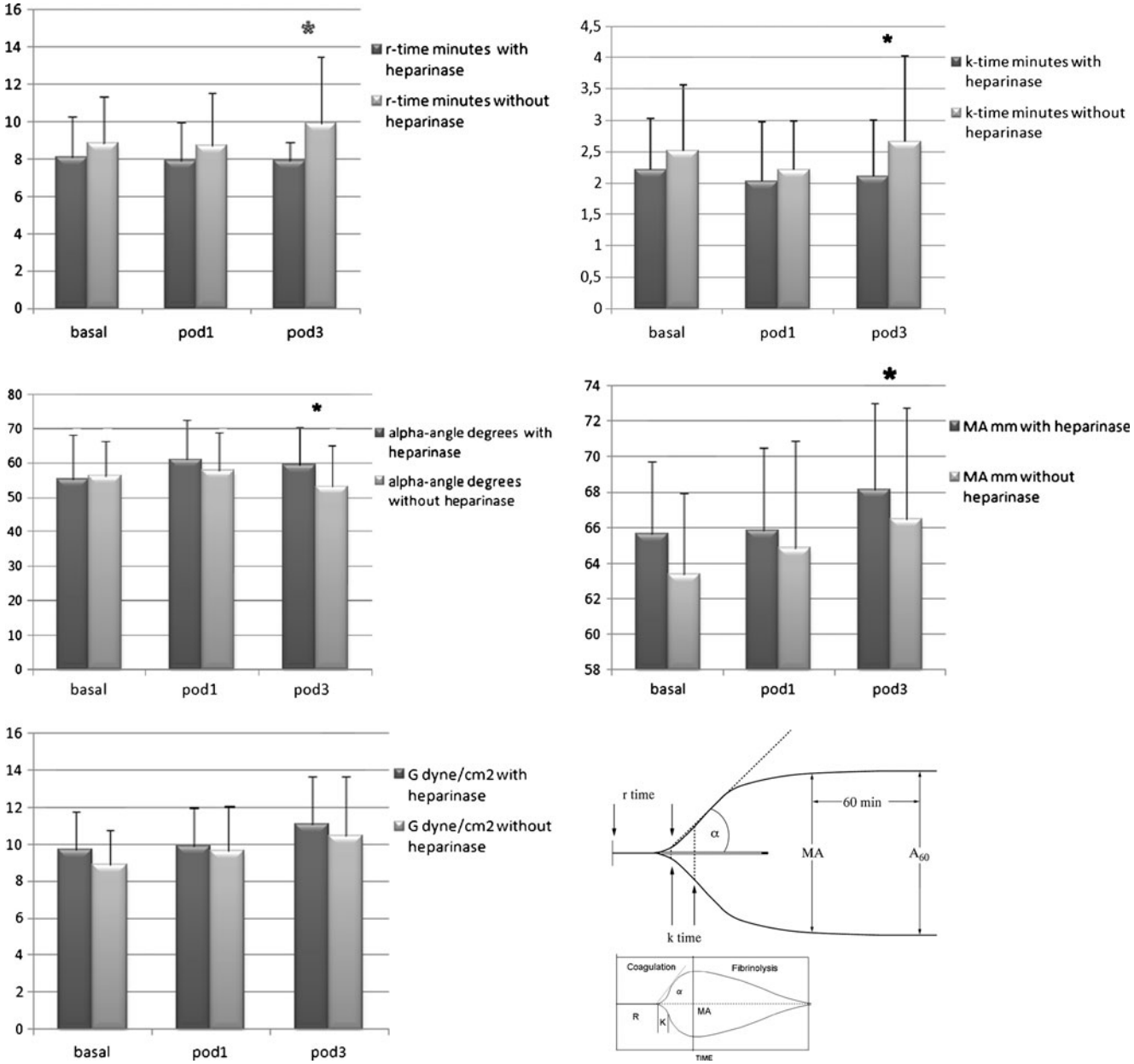

Fig. 1 Comparison of means between TEG with heparinase and without heparinase in basal, POD1, and POD3 with Wilcoxon matched-pairs signed-rank test. Level of significance, $p<0.05$. The last figure shows an example of normal trace with parameters analyzed

variation k-time=0.27, variation alpha angle=0.30, variation MA=0.14, variation GI=0.15).

No patient developed thromboembolic events during 1 year of follow-up after surgery.

Discussion

Although the exact incidence of VTE in obese patients is not known, several authors suggest that obesity represents an important risk factor for the development of VTE, particularly when these patients are hospitalized for surgical and medical reasons [8]. Overby et al. demonstrated that in bariatric surgery candidates routinely screened for serologic markers, both inherited and acquired thrombophilias occurred more frequently than in the general population, including elevation of D-dimer, fibrinogen, factors VIII, IX, and XI, and lupus anticoagulans [9]. Furthermore, increased plasma concentrations of coagulation factors, decreased concentration of coagulation inhibitors, enhanced in vitro platelet reactivity, and impaired in vitro fibrinolysis have been reported postoperatively [10]. Laparoscopic surgery causes variable serum hypercoagulability; there are data suggesting that dependent positioning in combination with pneumoperito-

neum decreases venous flow from the lower extremities and possibly increases the risk of DVT development [11].

Despite the overall consensus in using several methods of pharmacological prophylaxis to prevent thromboembolic complications, reported rates of postoperative DVT and/or PE range from 1% to 15%, and about 50% of deaths occurring in bariatric patients are attributed to a fatal PE. These considerations lead to careful monitoring of the coagulation status of patients undergoing bariatric surgery to identify hypercoagulable status. Commonly used blood tests are often aspecifics, whereas the dosage of all plasma factors involved in coagulation and platelet activity is expensive and mostly not useful to individuate the clinical risk of hypercoagulability. In our group of patients, we evidenced an increase of fibrinogen and D-dimer levels as commonly observed in the postoperative period. The modification of these values caused by the response to the surgical insult is specific and not helpful in managing the hypercoagulable state.

TEG is a technique that gives a global overview of the coagulation cascade including fibrinolysis. Used first to monitor the excessive use of anticoagulants during transplant surgery, TEG has recently played a role in the investigation of the thrombophilic status.

TEG offers the possibility to monitor the coagulative status in a rapid, repeatable, and inexpensive manner. In our study, we obtained TEG assays with and without the addition of heparinase in basal condition and during the early postoperative period.

The analysis of TEG trace with heparinase evidenced a slight reduction of r-time and k-time and an increase in alpha angle in the early postoperative period. In the normal samples analyzed where increased r and k values and reduced alpha angle were observed, we noticed a consensual increase in both analyses of MA and GI. These data suggest that the coagulation status of our patients has been characterized by a tendency to hypercoagulability mostly due to an increase of platelet activity and clot stability, as testified by MA and GI. On the contrary, we observed a minimal and not statistically significant increase of the immunoenzymatic activation measured by r-time, k-time, and alpha angle.

Recently, McCrath et al. [12] showed a major incidence of thrombotic complications in patients with increased MA (>68 mm) in the postoperative period. Furthermore, the authors showed that the percentage of those suffering postoperative myocardial infarction in the increased MA group was significantly larger than in patients with normal MA; in a multivariate analysis, increased MA was as able as the Goldman score to predict postoperative myocardial infarction.

TEG without heparinase allowed us to evaluate the effect of LMWH prophylaxis on the coagulation status. The used dosage was able to reduce the monitored TEG parameters in the early postoperative period, with a significant effect on POD3.

Interestingly, in both TEG analyses, we showed a consensual increase of MA, suggesting that prophylaxis was sufficient to reduce the activation of the coagulation system but not able to eliminate the tendency to hypercoagulability. We observed an increase in the percentage of patients with MA >68 mm in POD3 (from 20% to 50%, data not shown in tables). Considering that the parameter MA is the best prognostic index of hypercoagulability associated with thrombotic complications [15], it is possible that patients with a monitored tendency to increase MA could benefit from either an increase of dosage of LMWH or the administration of antiplatelet drugs.

Since all patients were treated with the same dosage of LMWH, we analyzed the correlation between the variation of normal TEG parameters and the amount dosage of anticoagulant therapy adjusted on body weight. We found no correlation between the variations of all screened TEG parameters from basal to POD3 and pro/kilogram dosage of LMWH administered. These suggest that LMWH prophylaxis based on weight produces a feasible but not a more efficient anticoagulation profile than standard LMWH therapy [13]. In this sense, it could be speculated to individualize anticoagulation therapy on single-patient monitoring evaluation of the coagulation system (through) TEG parameters. This goal could be achieved only after an analysis of future randomized clinical trial results built to analyze the sensitivity and specificity of TEG parameters as clinical markers of risk for postoperative thrombosis and an aid to the individualization of different anticoagulation protocols.

Despite all our samples having been analyzed within 90 min, we could not exclude any effect of delay in the processing the sample as recently investigated [14].

Our data explore the early postoperative hypercoagulability, but we could not exclude any further variation in the following postoperative days.

Conclusion

Monitoring TEG parameters can be a feasible practice to observe the coagulation status of obese patients undergoing bariatric surgery. Our patients presented a tendency to hypercoagulability determined most by the increase of MA and GI. The comparison between TEG with and without heparinase indicates that prophylaxis with LMWH not titrated on weight is able to determine a reduction of the hypercoabulable state of the early postoperative period with few effects on the increase of MA and GI.

Potential Conflicts of Interest None of the authors have conflict of interest.

References

1. Sapala JA, Wood MH, Schuhknecht MP, et al. Fatal pulmonary embolism after bariatric operations for morbid obesity: a 24 year retrospective analysis. Obesity Surgery. 2003;13(6):819–25.
2. Stein PD, Goldman J. Obesity and thromboembolic disease. Clin Chest Med. 2009;30(3):489–93.
3. Overby DW, Kohn GP, Cahan MA, et al. Prevalence of thrombophilias in patients presenting for bariatric surgery. Obes Surg. 2009;19(9):1278–85 (Epub 5 Jul 2009).
4. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation. 2010;121(17):1896–903 (Epub 19 Apr 2010).
5. Macgregor AM. Prophylaxis of venous thromboembolism in bariatric patients. Obesity Surgery. 2000;10(1):14.
6. Samama CM. Thromboelastography: the next step. Anesthesia Analgesia. 2001;92:563–4.
7. Mahla E, Lang T, Vicenzi MN, et al. Thromboelastography for monitoring prolonged hypercoagulability after major abdominal surgery. Anesth Analg. 2001;92:572–7.
8. Rocha AT, de Vasconcellos AG, da Luz Neto ER, et al. Risk of venous thromboembolism and efficacy of thromboprophylaxis in hospitalized obese medical patients and in obese patients undergoing bariatric surgery. Obes Surg. 2006;16 (12):1645–55.
9. Eriksson P, Van Harmelen V, Hoffstedt J, et al. Regional variation in plasminogen activator inhibitor-1 expression in adipose tissue from obese individuals. Thromb Haemost. 2000;83(4):545–8.
10. O'Brien JR, Tulevski V, Etherington M. Platelet function tests in pre- and post-operative patients with and without thrombosis. Acta Univ Carol Med Monogr. 1972;53:461–4.
11. Nguyen NT, Owings JT, Gosselin R, et al. Systemic coagulation and fibrinolysis after laparoscopic and open gastric bypass. Arch Surg. 2001;136(8):909–16.
12. McCrath DJ, Cerboni E, Frumento RJ, et al. Thromboelastography maximum amplitude predicts postoperative thrombotic complications including myocardial infarction. Anesth Analg. 2005;100:1576–83.
13. Rondina MT, Wheeler M, Rodgers GM, et al. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-ill patients. Thromb Res. 2010;125(3):220–3 (Epub 9 Mar 2009).
14. White H, Zollinger C, Jones M, et al. Can thromboelastography performed on kaolin-activated citrated samples from critically ill patients provide stable and consistent parameters? Int J Lab Hematol. 2010;32(2):167–73 (Epub 17 Mar 2009).
15. Dai Y, Lee A, Critchley LA. Does thromboelastography predict postoperative thromboembolic events? A systematic review of the literature. Anesth Analg. 2009;108(3):734–42.