Impact of Short-term Weight Loss on Hemostasis and Trombosis After Obesity Surgery

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Research Article

Keywords: Obesity surgery, bleeding, coagulation, thromboembolism, prophylaxis

Posted Date: March 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1430830/v1

Version of Record: A version of this preprint was published at Surgery Research and Practice on November 13th, 2023. See the published version at https://doi.org/10.1155/2023/1729167.

Abstract

Background

Metabolic disorders such as deficiency of vitamins and electrolyte imbalance may cause coagulation problems after bariatric surgery. In early postsurgical period, deplation of vitamin K dependent coagulation factors may increase the risk of hemorrhage.

Aim

We aimed to evaluate the outcomes of rapid weight loss in early period after bariatric surgery on coagulation system.

Materials & Method

This study had a prospective nature. We have enrolled 28 patients with a BMI < 40 kg/m2 who underwent bariatric surgery in our institution. Patients were discharged with vitamin K free multivitamin complex medication. Preoperative and postoperative *(at the end of first and third months)* demographic criterias – such as age, gender, weight, height, use of alcohol and/or tabacco and biochemical parameters such as PLT, PT, aPTT, INR, bleeding time, coagulation time, fibrinogen, D – Dimer, albümin, calcium, ionized calcium, vitamin D and PTH were analyzed.

Results

The success of bariatric operation has been elaborated with the weight loss in the first month compared top pre-operative period *($p < 0.001$)*, decrease in BMI in the first month compared top pre-operative period *($p < 0.001$)*, weight loss in the third month compared to pre-operative period *($p < 0.001$)*, decrease in BMI in the third month compared top pre-operative period *($p < 0.001$)*, weight loss in the third month compared to first month *($p < 0.001$)* and decrease in BMI in the third month compared to first month. The first month % EWL and % EBMIL scores were 21.7% *(ranging between 13.0–45.6%)* and 25.2% *(13.8–49.7%)* respectively. The third month %EWL and % EBMIL scores were 40.6% *(ranging between 27.1–67.5%)* and 45.5% (*ranging between 29.4–76.6%)*.

Conclusion

Tromboembolic events have crucial importance with the converse scenario of hemorrhagic diathesis during the first months of obesity surgery. In early postoperative period, vitamin support and low dose antitrombotic agents should be recommended.

Key Messages

1. *Vitamins and low dose antitrombotic agents should be recommended in early postoperative period.*
2. *The PTT in the first month was higher than pre-operative period ($p<0.011$).*
3. *INR was higher in the 1st month than pre-operative period ($p<0.001$) and in the 3rd month than the 1st month ($p=0.007$).*

Introduction

Today, the mankind has been dealing with obesity all over the globe. The reason why it has become an epidemic is fast food, which is cheap and easy to find, insufficient exercise and a sedentary life (1–3). Obesity is one of the important problems of public health due to its increasing prevalence, especially in industrialized countries (4, 5).

According to the data of the World Health Organization *(WHO)*, it has been reported that an increase of 10–30% has been detected in the prevalence of obesity in the last 10 years (6). According to the data of the Ministry of Health and the preliminary study report of "Turkey Nutrition and Health Survey 2010", the prevalence of obesity in Turkey was found to be 20.5% in men, 41.0% in women, and 30.3% in total (7).

Environmental factors and socioeconomic conditions such as behavioral disorders *(overeating and lack or lack of physical activity)* increase an individual's risk of obesity (8). In addition to environmental factors, some studies show that 40–70% of weight differences in humans can be determined by genetic factors (9, 10). In addition, the main risk factors for the development of obesity are age, female gender, low education level, marriage, number of births, excess weight gained during pregnancy, use of oral contraceptives, early periods of smoking cessation, and alcohol intake (11, 12).

Obesity increases considerably in adults, derives economic problems and premature deaths. I also caouses serious health problems in new generations with its progressive onset in children at an early age. In its studies, the Economic Assistance and Development Organization *(OECD)* determined that one out of every five children in member countries is overweight or obese with the acceleration of obesity (13). The inadequacy of diet, exercise and medical treatment, which has been utilized for many years in the struggle against obesity, and in addition to this, regaining the lost weight increases the popularity of surgical treatment day by day (2, 14).

Large-scale studies have been conduted due to the positive results of various bariatric surgery operations, which have increased significantly in recent years and are performed under the name of bariatric surgery (2). With bariatric surgery, long-term permanent weight loss can be achieved and many co-morbidities are prevented by ameliorating the metabolic effects of obesity, and hence the survival is increased. Sustainable weight loss can be achieved with the highest rate of bariatric surgery and more than 50% of excess weight can be lost (15).

Individuals who will undergo bariatric surgery are considered as risky patients. Therefore, in order to achieve successful postoperative results, extensive evaluations before and after surgery are as important as the importance of the surgical technique. According to studies, obesity patients are more frequently exposed to thromboembolic events (16, 17). Weight loss and decrease in body mass index *(BMI)* in patients undergoing bariatric surgery are expected to improve thromboembolic events (18).

On the other hand, metabolic diseases, vitamin deficiencies and electrolyte disorders that develop after bariatric surgery may cause disorders in the coagulation system (19). Subcutaneous ecchymoses and petechiae that may develop in the postoperative period are the clinical signs of this coagulation disorder (20).

Study Hypothesis

Following bariatric surgery, metabolic disorders such as deficiency of vitamins and electrolyte imbalance may cause coagulation problems. In early postsurgical period, deplation of some vitamin K dependent coagulation factors may increase the risk of hemorrhage, thus anticoagulant agents may increase the tromboembolic event rate.

The primary endpoint of this study was to examine the weight loss in the early period in patients who underwent bariatric surgery, and the secondary endpoint was to investigate whether there were significant changes in bleeding and coagulation parameters in the early period with weight loss in the first and third months after surgery. We aimed to evaluate the outcomes of rapid weight loss in early period after bariatric surgery on coagulation system.

Materials & Method

A total of 28 individuals who applied to our institution's outpatient clinic between September to December 2015 due to morbid obesity have been included in the study. The ethics committee approval has been granted at *30/09/2015* and protocole number *2011-KAEK-2015/18 – 02*. Informed consent has been obtained from all the patients before the initiation of the study, and the study has been conducted within all the regulations of declaration of Helsinky.

Inclusion Criteria

- *Patients with a BMI< 40 kg/m^2 who underwent surgery were prospectively included in the study.*

Exclusion Criteria

- *Subjects who did not volunteer to participate in the study,*
- *İndividuals who had a history of fibrinolytic, antithrombotic, anticoagulant drug (Aspirin, Coumadin) use,*

- *previous deep vein thrombosis (DVT) or thromboembolic surgery were excluded from the study.*

The following data were recorded in the pre-operative *(just before the surgery)* and post-operative 1st and 3rd month in patients who underwent bariatric surgery: age, gender, weight, height, alcohol-smoking use, laboratory results *(PLT, PT, aPTT, INR, bleeding time, clotting time, fibrinogen, D-Dimer, albumin, calcium, ionized calcium, osteocalcin, vitamin D and parathormone)*. In our pre-operative clinic, routine blood count and detailed blood analysis, hormone analysis, coagulation tests, pulmonary function test, electrocardiogram, chest x-ray, gastroscopy, endocrinology consultation, psychiatry consultation, cardiology consultation and, if necessary, dietitian consultation are performed.

Demographic information *(age, gender, weight, height)* of eligible patients and smoking and alcohol habits were recorded. Body mass index *(BMI)* was calculated by dividing the body weight in kilograms *(kg)* by the square of the height in meters *(m).* Ideal BMI was 25 kg/m^2 and ideal weight was taken as the average of the metropolitan index *(86)*. Excess weight *(EW)* was calculated by subtracting the ideal weight from the measured patient weight. Percent excess weight loss *(%EWL)* and excess body mass index loss *(% EBMIL)* were calculated according to the following formulas.

- Percent Loss of Excess Weight (% EWL) = (Preop.Weight – Postoperative Weight x 100/ Excess weight),
- Percent Excess BMI loss (% EBMIL) = [Preop.BMI – Postoperative BMI x 100/ (Preoperative BMI – 25)].

Bleeding and clotting times were evaluated manually. Hemogram and platelet count after taking into appropriate tubes *(Mindray BC-6800 Auto Hematology Analyzer, Germany)*, measurement of hormones *(Advia Cenatur xp, USA),* biochemistry values *(Mindray BS 2000 Biochemistry Analyzer, Germany)* and D Dimer *(AQT90 flex, Denmark)* devices. It was investigated whether there were significant changes in bleeding and coagulation parameters with the recorded weight loss. The data of 28 patients obtained were analyzed.

Statistical Analysis

Statistical analysis was conducted in SPSS 22.0 package program. The eligibility of the obtained data was interpreted with the Shapiro Wilk test for normal distribution. Descriptive statistics for continuous variables were given as mean±standard deviation for those showing a normal distribution, and as the median *(minimum – maximum)* for those not showing a normal distribution.

In the comparison of dependent groups, the Paired-Samples *"t"* test was used for those conforming to the normal distribution, and the Wilcoxon signed-rank test was used for those not conforming to the normal

distribution. The statistical significance was accepted as a p value of <0.05.

Results

A total of 31 patients have been operated between September and December 2015 in our institution. Of these, 3 patients were excluded because they did not meet the inclusion. Twenty-five *(89.3%)* of the operated patients included in the study were female. The mean age of the patients was 37.68 years. The smoking rate has been found as 28.6% and alcohol consumption as 10.7%.

The first month % EWL and % EBMIL scores were 21.7% *(ranging between 13.0–45.6%)* and 25.2% *(13.8–49.7%)* respectively. The third month %EWL and % EBMIL scores were 40.6% *(ranging between 27.1–67.5%)* and 45.5% (*ranging between 29.4–76.6%)*. Demographic characteristics and postoperative weight follow-ups were given in *Tables 1* and *Table 2*.

The success of bariatric operation has been elaborated with the weight loss in the first month compared top pre-operative period *($p < 0.001$)*, decrease in BMI in the first month compared top pre-operative period *($p < 0.001$)*, weight loss in the third month compared to pre-operative period *($p < 0.001$)*, decrease in BMI in the third month compared top pre-operative period *($p < 0.001$)*, weight loss in the third month compared to first month *($p < 0.001$)* and decrease in BMI in the third month compared to first month.

The first month platelet levels was significantly different ftom the pre-operative values *($p < 0.001$)*. The prothrombin time in the first *($p < 0.001$)* and third month *($p < 0.009$)* was also comparable. The PTT in the first month was higher than pre-operative period *($p < 0.011$)*. During the analysis of INR the first month value *($p < 0.001$)* was higher than the pre-operative period and the third month *($p = 0.007$)* value was higher than the first month. In terms of fibrinogen levels all parameters indicated statistical significance within each other; pre-operative to first month *($p < 0.001$)*, first month to third month *($p < 0.016$)*. Third month D – Dimer levels were lower than the first month values *($p = 0.032$)*. These parameters are elaborated in *Table 3*.

Discussion

Weight loss following bariatric surgery was evaluated by various methods. Total weight loss compared to the patient's weight before surgery, decrease in BMI, weight loss according to standard weight and BMI, loss of excess weight relative to standard weight *(EWL)* based on age and height, or loss in excess BMI based on BMI 25 kh/m^2 *(EBMIL)* are some of these assessment methods (21). The rate of weight loss *(% EWL)*, which has been popularly used recently, showed a success target of 50 and above in the first 1–2 years (22). In our study, % EWL and % EBMIL achieved in the first 3 months were calculated as 40.6 kg/m^2 and 45.5 kg/m*2* respectively, and no study in the literature has interpreted weight loss in the first 3 months. The previously published data focused on the 1-year results.

By virtue of heomeostasis there exists a delicate balance between coagulation and fibrinolysis in the vascular system and the disruption of this balance leads to pathological events. The increase in obesity

in coronary heart diseases, peripheral vascular diseases, stroke, arterial and venous thrombosis (23) shows that this balance increases in favor of coagulation. Various clinical and epidemiological studies argue that there is a strong link between obesity and thrombosis (24, 25).

Increased fat mass in obesity is not only an increased fat tissue energy store, but also an increase in the secretion of a metabolically active fat cell and an increased autocrine, paracrine and endocrine effect with it. Leptin secreted from fat cell, adeponectin, resistin, plasminogen activator inhibitor – 1 *(PAI – 1)*, tissue factor *(TF)*, tumor necrosis factor alpha *(TNF – α)*, transforming growth factor beta *(TGF – β)* and interleukin – 6 *(IL – 6)* all play an active role in thrombosis. (18). Increasing leptin in obese causes an increase in insulin resistance and increases the incidence of stroke and myocardial infarction (26). Hyperfibrinogenemia found especially in obese women increases the risk of developing coronary and peripheral artery diseases, stroke and venous thrombosis. Increased fibrinogen indicates the risk of developing arterial and venous thrombosis with fibrin formation, platelet aggregation, deterioration of blood viscosity, and atherosclerosis (26).

In recent years, many studies have been carried out especially on TF, Factor VII and PAI – 1. PAI – 1, a serine protease inhibitor and one of the most important coagulating agents providing the balance against the fibrinolytic system, has been shown to have a significant effect on the increase in morbidly obese patients and in the increase in thrombotic events in obesity (27). Along with it, an increase is detected in FVII, thrombin, thrombin-antithrombin complex *(TAT)* and TF activities, which have a significant role in thrombotic events (26, 27).

There are different and sometimes contradictory studies in the literature on the role of thrombocyte in obesity. The most important risk factors for increased venous thromboembolism in obese patients are inflammation, decreased fibrinolysis and increased thrombin formation, as well as increased platelet activation (17).

A significant improvement has been detected in morbid obese patients in hematological changes in blood flow, such as increased blood and plasma viscosity (27). Morbid obese patients, with either low-calorie diet (28) or weight loss after bariatric surgery operations had improvement in increased erythrocyte aggregation that appears in morbid obesity and impairs blood flow, and an improvement in the impaired lipid profile in hyperlipidemia have also had been found (24). Weight loss associated with obesity surgery and thromboembolic mediators such as PAI – 1 and TF reduction, chronic inflammation, metabolic changes, and provides improvement in platelet dysfunction (28). In the literature, long-term weight loss achieved by bariatric surgery and thromboembolic events that improve with it show that obesity is a thrombosis risk factor that can change and improve (18).

Lupoli et al. (29) reported improvement in impaired fibrinolytic activity in patients after bariatric surgery. In this study, while they recorded a 20% decrease in PAI – 1 in the first months, they found a 10% decrease in t-PA. However, decreases were found in FVII, Protein C and S (29). These factors were related to vitamin K. The rapidly decreasing fat mass with weight loss may also be the cause of the fat-soluble vitamin K deficiency, and it also explains the increased bleeding risk in the early period (29). The decrease

in PAI – 1 was found to be between 75–80% at 12 months in other studies. In this study by Ferrer et al., it was determined that the platelet volume, not the platelet count, changed in the postoperative 12th month. However, a significant PT, CT prolongation and fibrinogen change were also noted (30).

Pulmonary embolism (1%) and deep vein thrombosis of obesity surgery of surgery and deep vein thrombosis *(DVT)* (1%) is a significant cause of mortality (31). In a comprehensive 8-year review of 4293 patients at the Cleveland Clinic by Jamal et al., they found that laparoscopic bariatric surgery and/or postoperative prophylactic anticoagulant therapy did not change the risk of DVT. This risk is average diagnostic time post-operative was 24th day. In the study, they showed that the conversion, increased age and high BMI increased this risk (31). In the study of Carmody et al. although routine heparin prophylaxis does not reduce this rate, the authors recommend more aggressive prophylaxis (32).

As we stated in our study, patients were discharged with a multivitamin supplement that did not contain vitamin K in the post-operative period. The significant decrease in fibrinogen and platelet in the 1st month we recorded may be associated with an increase in consumptive coagulopathy and accompanying enhanced micro-embolic events. Prolongation in PT and aPTT and elevation in INR may suggest that intrinsic and extrinsic coagulation pathways are affected. These changes may have resulted from the decrease of coagulation factors that depend on hemostasis parameters. The increase in D – Dimer in the 3rd month compared to the 1st month may be due to the partial decrease in consumption.

When these results are evaluated together, in the middle and long term of bariatric surgery, improvement and improvement in hypercoagulopathy, but in the short term, an increase in bleeding diathesis due to some factor deficiencies and an increase in thromboembolic events due to various post-operative reasons are detected.

According to the different data we recorded in our study and obtained from the literature, bleeding diathesis is also important along with thromboembolic events in the first months of bariatric surgery. The increase in the PT, aPTT and INR values in the first and third months compared to the pre-operative values, which we stated in the results of our study, was thought to indicate the bleeding diathesis occurring in this period. At the same time, considering the increase in D – Dimer values and the subsequent regression in the third month, the risk of early bleeding and simultaneous thromboembolism can be considered in these patients. Therefore, it is important to carry out close follow-up and laboratory screenings regularly in the first months (33). Particular attention should be paid to bleeding that may occur in the stapler line after surgery. It may be recommended to use *low-molecular weight heparin (LMWH)* for a long time in the early post-operative period together with vitamin support (34, 35).

The main limitation of the study could be attributed comorbidities. Some of the patients included in the study used antihypertensive and antidiabetic drugs. It is not known whether these drugs will have a different effect on bleeding and coagulation parameters.

The strength of this study could be ealborated as: the study was performed at a designated time interval, in a single center, with the same devices. The patients were followed up closely in the preoperative and

postoperative period. Individuals with fibrinolytic, antithrombotic, anticoagulant use, previous deep vein thrombosis (DVT) or thromboembolic surgery were excluded from the study.

Conclusion

Obesity is a public disease that has increased recently, has serious health problems, and will create greater medical and economic problems in the future. Tromboembolic events have crucial importance with the converse scenario of hemorrhagic diathesis during the first months of obesity surgery. In early postoperative period, vitamin support and low dose antitrombotic agents should be recommended. Considering the results of our study, it is obvious that there are still aspects of this issue that need to be clarified. There is a need for new prospective, randomized, large-scale case studies about surgery, which is one of the most successful methods against obesity.

Abbreviations

aPTT
activated partial thromboplastin clotting time
BMI
body mass index
DVT
deep vein thrombosis
EBMIL
excess body mass index loss
EW
excess weight
IL – 6
interleukin – 6
INR
international normalized ratio
OECD
Economic Assistance and Development Organization
PAI – 1
plasminogen activator inhibitor
PT
prothrombin time
SPSS
Statistics Package for the Social Sciences
TAT
thrombin, thrombin-antithrombin complex
TE

thromboembolic events
TF
tissue factor
TGF –β
transforming growth factor beta
TNF –α
tumor necrosis factor alpha
WHO
World Health Organization

Declarations

Funding

There is no specific funding related to this research.

Editorial Support

The editorial support of this article has been conducted by QA Executive Consultancy, Ozan Batigun MD, MBA in 2021. www.QAexeutiveconsultancy.com

Competing interests

The authors declare that they have no competing interests.

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Tables

Table – 1: *Baseline Demographics of the Study Population*

Gender (Female), (%)	25 (89.3)
Age, Mean ± SD, years	37.68±9.69
Height, Median (min-max), cm	160 (150-188)
Pre-operative weight, Mean ± SD, kg	123.38 ± 20.50
Smoking	8 (28.6)
Alcohol consumption	3 (10.7)

Table – 2: *Loss of excess weight and body mass index in the first and third months*

	End of First Month	End of Third Month
% EWL, Median (min- max)	21.7 (13.0 – 45.6)	25.2 (13.8 – 497)
% BMIL, Median (min- max)	40.6 (27.1 – 67.5)	45.5 (29.4 – 76.6)

Table – 3: *Comparison of treatment group parameters with pre-operative values*

	(n=28)	Pairwise Comparisons	
Preoperative kg (Mean±SD)	123.38±20.50	Preoperative kg – First Month kg	**p<0.001***
First Month kg (Mean±SD)	109.07±18.62	Preoperative kg – Third Month kg	**p<0.001***
Third Month kg (Mean±SD)	97.77±15.68	First Month kg – Third Month kg	**p<0.001***
Preoperative BMI (Mean±SD)	46.86±5.70	Preoperative BMI – First Month BMI	**p<0.001***
First Month BMI (Mean±SD)	41.46±5.66	Preoperative BMI – Third Month BMI	**p<0.001***
Third Month BMI (Mean±SD)	37.26±5.05	First Month kg – Third Month BMI	**p<0.001***
Preoperative PLT Median (min-max)	286 (128-393)	Preoperative PLT – First Month PLT	**p<0.001#**
First Month PLT Median(min-max)	216 (139-349)	Preoperative PLT – Third Month PLT	ns**#**
Preoperative PT (Mean±SD)	12.37±1.07	Preoperative PT – First Month PT	ns*****
First Month PT (Mean±SD)	12.53±0.71	Preoperative PT – Third Month PT	**0.001***
Third Month PT (Mean±SD)	13.10±0.94	First Month PT – Third Month PT	**0.009***
Preoperative PTT (Mean±SD)	32.26±3.80	Preoperative PTT – First Month PTT	**0.025***
First Month PTT (Mean±SD)	34.86±5.46	Preoperative PTT – Third Month PTT	**0.011***

Third Month PTT (Mean±SD)	35.24±4.93	First Month – Third Month PTT	ns*
Preoperative INR (Mean±SD)	0.98±0.10	Preoperative INR – First Month INR	ns*
First Month INR (Mean±SD)	1.01±0.07	Preoperative INR – Third Month INR	**p<0.001***
Third Month INR (Mean±SD)	1.06±0.09	First Month INR – Third Month INR	**0.007***
Preoperative KZ (Mean±SD)	82.25±15.39	Preoperative KZ – First Month KZ	ns*
First Month KZ (Mean±SD)	77.56±11.94	Preoperative KZ – Third Month KZ	ns*
Third Month KZ (Mean±SD)	83.07±15.75	First Month KZ – Third Month KZ	ns*
Preoperative PZ Median(min-max)	300 (4-361)	Preoperative PZ – First Month PZ	ns#
First Month PZ Median(min-max)	326.50 (280-400)	Preoperative PZ – Third Month PZ	ns#
Third Month PZ Median(min-max)	340 (240-450)	First Month PZ – Third Month PZ	ns#

Preoperative FIB (Mean±SD)	365.36±55.60	Preoperative FIB – First Month FIB	**0.001***
First Month FIB (Mean±SD)	313.01±42.30	Preoperative FIB – Third Month FIB	**0.016***
Third Month FIB (Mean±SD)	325.90±47.35	First Month FIB – Third Month FIB	ns*
Preoperative D – Dimer Median (min-max)	409 (267-1170)	Preoperative D – Dimer – First Month D – Dimer	ns#
First Month D – Dimer Median (min-max)	489.5 (211-4530)	Preoperative D – Dimer – Third Month D – Dimer	ns#
Third Month D – Dimer Median (min-max)	409 (162-1170)	First Month D – Dimer – Third Month D – Dimer	**0.032#**

***** *Paired-Samples "t" test,* ***#*** *Wilcoxon signed-rank test*