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The Effect of Laparoscopic Sleeve Gastrectomy Applications on Coagulation in Morbidly Obese Patients: Clinical Research

Morbid Obez Hastalarda Laparoskopik Sleeve Gastrektomi Uygulamalarının Koagülasyona Etkisi: Klinik Araştırma

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ABSTRACT Objective: Obese patients have an increased predisposition to thrombosis and are at a high risk for thrombotic complications associated with bariatric surgeries. This study aimed to evaluate the effect of laparoscopic sleeve gastrectomy (LSG) on coagulation parameters in morbidly obese patients. **Material and Methods:** This prospective study was performed with 40 American Society of Anesthesiologists II-III morbidly obese patients with a body mass index of ≥40 kg/m² who underwent LSG. Anaesthesia was maintained with sevoflurane after anaesthesia induction. Haemoglobin, haematocrit, platelet, D-dimer and fibrinogen levels as well as prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalised ratio (INR) were compared in blood samples taken before the operation and at 1, 24 and 48 hours after the operation. In addition, duration of operation, length of hospital stay and the presence of symptomatic thromboembolic complications within 7 days after the operation were examined. **Results:** A significant increase was observed in PT and INR in all postoperative periods ($p<0.001$). Although a significant decrease was observed at the 1st hour, a significant increase was observed at the 24th and 48th hours in aPTT postoperatively ($p<0.01$). Postoperative fibrinogen and D-dimer levels were significantly higher than the preoperative levels ($p<0.01$). No symptomatic thromboembolic event was observed in any patient in the early postoperative period. **Conclusion:** In morbidly obese patients undergoing LSG, coagulation parameters are affected in line with the increased risk of thrombosis. Close monitoring of these patients for postoperative thromboembolic complications is important.

Keywords: Bariatric surgery; obesity, morbid; thrombosis; fibrinogen; venous thromboembolism

ÖZET Amaç: Obez hastaların tromboza yatkınlığı yüksektir ve bariatrik cerrahilerle ilişkili trombotik komplikasyonlar açısından yüksek risk altındadır. Bu çalışma, morbid obez hastalarda laparoskopik sleeve gastrektominin (LSG) koagülasyon parametreleri üzerine etkisini değerlendirmeyi amaçladı. **Gereç ve Yöntemler:** Bu prospektif çalışma, beden kitle indeksi ≥40 kg/m² olan ve LSG geçiren Amerikan Anestezistler Derneği II-III 40 morbid obez hasta ile yapılmıştır. Hastalarda anestezi indüksiyonu sonrası sevofluran ile anestezi idamesi sağlandı. Operasyon öncesi, operasyon sonrası 1, 24 ve 48. saatlerde alınan kan örneklerinde hemoglobin, hematokrit, platelet, protrombin zamanı [prothrombin time (PT)], aktive parsiyel thromboplastin zamanı [activated partial thromboplastin time (aPTT)], "international normalised ratio (INR)," D-dimer ve fibrinojen düzeyleri bakılarak karşılaştırıldı. Ayrıca hastalarda ameliyat süresi, hastane yatış süresi ve operasyon sonrası 7 gün içinde semptomatik tromboembolik komplikasyon varlığı incelendi. **Bulgular:** PT ve INR postoperatif tüm dönemlerde anlamlı artış gözlenmiştir ($p<0,001$). Postoperatif 1. saatde aPTT'de anlamlı düşme gözlenirken, 24 ve 48. saaatlerde anlamlı artış gözlenmiştir ($p<0,01$). Ameliyat sonrası fibrinojen ve D-dimer seviyeleri ameliyat öncesi seviyelere göre anlamlı derecede yüksekti ($p<0,01$). Postoperatif erken dönemde hiçbir hastada semptomatik tromboembolik hadise görülmemiştir. **Sonuç:** LSG geçiren morbid obez hastalarda, koagülasyon parametreleri artmış tromboz riskiyle uyumlu olarak etkilenmektedir. Operasyon sonrası tromboembolik komplikasyonlar açısından bu hastaların yakından takibi önemlidir.

Anahtar Kelimeler: Bariatrik cerrahi; obezite, morbid; tromboz; fibrinojen; venöz tromboembolizm

Obesity is a serious health problem that can cause respiratory, haemodynamic and certain systemic disorders, and its worldwide incidence is increasing day by day. A body mass index (BMI) ≥30 kg/m² is defined as obesity, and over 40 kg/m² is defined as morbid obesity.[1,2] Bariatric surgery is currently accepted as the most effective treatment option in morbidly obese patients because of its good results

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in terms of weight loss and improvement in obesity-related comorbidities.[3] Laparoscopic sleeve gastrectomy (LSG) is one of the most commonly performed bariatric surgeries.[3,4] Although bariatric surgery is an effective method in the treatment of morbid obesity, it poses a risk in terms of thrombotic complications, such as venous thromboembolism (VTE) and pulmonary embolism (PE), in the postoperative period.[5]

Predisposition to thrombosis is increased in obesity as a result of prothrombotic changes and increased platelet activation. Thrombotic complications, such as atherothrombotic cardiovascular diseases and VTE, are common in these patients.[2] Apart from obesity, abdominal surgical procedures are another known risk factor for thrombotic complications.[5] Studies report that VTE occurs 2-3 times more commonly in obese patients, half of the patients who die from postoperative PE are morbidly obese and the risk of fatal PE increases twelvefold in morbidly obese patients.[6,7] In addition to patient-related factors, such as age, gender and BMI, many other factors, such as the type and duration of the surgical procedure and whether the procedure is open or laparoscopic, play a role in determining the risk of thrombosis.[7]

This prospective study aimed to evaluate the effect of LSG on postoperative coagulation parameters in and compare them with preoperative levels in morbidly obese patients.

MATERIAL AND METHODS

The study was conducted prospectively on 40 morbidly obese patients with a BMI ≥40 kg/m², class II-III according to the American Society of Anesthesiologists (ASA) physical status classification and who underwent LSG at Fatih Sultan Mehmet Training and Research Hospital. The study was approved by the Clinical Research Ethics Committee of Yeditepe University (Decision date: 14.08.2012, Decision no: 226) and was conducted in accordance with the Declaration of Helsinki. Patients under the age of 18, over the age of 65, with hematologic, malignancy, rheumatologic, vascular, renal or liver disease, with a history of thromboembolism in the last year, using anticoagulant or drugs that may affect the immune system, and taking estrogen or steroid therapy were excluded from the study. Patients were included in the study by being randomly selected by the closed envelope method before the operation. The study protocol was explained to the patients included in the study and their consent was obtained.

The patients were taken to the operating room before surgery, and electrocardiography, non-invasive blood pressure assessment and pulse oximetry for measuring peripheral oxygen saturation (SpO_2) were used for standard monitoring, and the bispectral index (BIS) (Covidien®-Singapore) was used to monitor the depth of the anaesthesia. Midazolam was used for sedation in the operating room.

Anaesthesia was induced with propofol, fentanyl and rocuronium dosages of 2-2.5 mg/kg, 1-2 µg/kg and 0.6 mg/kg, respectively, according to corrected body weight (BW).[8] Orotracheal intubation was performed after patients achieved adequate muscle relaxation. Patients were administered volume-controlled ventilation with a tidal volume of 8 mL/kg, positive end-expiratory pressure of 6 cm H_2O, peak airway pressure of ≤35 cm H_2O and a respiratory frequency of 12-14 breaths/minute such that the end tidal carbon dioxide was 35±5 mmHg. Anaesthesia was maintained with a sevoflurane concentration of 2-2.5%+50%O_2-air mixture. Additionally, 0.05-0.5 µg/kg/min infusion of remifentanil was administered to all patients. Anaesthetic agents were titrated with a BIS value of 40-60 and mean arterial pressure (MAP) with a baseline value of ±20%. For intraoperative fluid replacement, standard fluid therapy was applied at an hourly rate of 4-6 mL/kg, with balanced crystalloid solutions, adding fluid according to the fasting period. Fluid replacement was applied according to ideal BW.[9] At the end of the operation, 0.03-0.05 mg/kg of neostigmine and 0.01-0.02 mg/kg of atropine were administered to reverse the effects of the muscle relaxants. The patients were extubated and taken to the post-anaesthesia recovery room when they met all the extubation criteria. The patients who were adequately alert (Modified Aldrete Score=9) after being monitored in the recovery room were transferred to the ward. The same surgical team performed LSG in all the patients by maintaining a pneumoperitoneum pressure of 13 mmHg. Anticoagulant drug treatment was not administered in the preoper-

ative period, as the standard practice of the surgical team. During this period, mechanical venous thromboprophylaxis with elastic compression stockings was applied to the patients. Prophylactic anticoagulant drug treatment was started in the patients at the 8th postoperative hour (with 60 mg low molecular weight heparin daily). The patients were mobilized on the evening of the operation day.

The age, gender, BW (kg), height (cm) and BMI (kg/m^2) of the patients were recorded. Heart rate (HR), MAP and SpO_2 values were recorded before anaesthesia induction, during the operation and during recovery after anaesthesia. The duration of anaesthesia, pneumoperitoneum period and duration of operation were recorded. Haemoglobin (Hb), haematocrit (Hct), platelet, D-dimer and fibrinogen levels as well as prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalised ratio (INR) were measured and recorded before the operation and at the 1st (immediately after the transfer of the patients to the ward), 24th and 48th hours after the operation. Postoperative length of hospital stay was recorded. Patients were evaluated for symptoms suggestive of VTE or PE during hospitalization and postoperative 7th day routine surgical outpatient controls. For the diagnosis of VTE, sudden onset of pain, tenderness, warmth, swelling in the leg, and the presence of Homans sign (pain in the calf with on active or passive dorsiflexion of the foot) were examined. Sudden onset of dyspnea, cough, chest pain, hypotension or syncope were questioned for suspected PE. It was planned to request additional imaging method in patients with symptomatic complaints suggesting thromboembolic complications. Screening imaging examination was not applied. Preoperative and postoperative values were compared statistically.

STATISTICAL ANALYSIS

Power analysis was performed using the G-power 3.1.9.7 software. The sample size was calculated based on a study by Milic et al. by ensuring an effect size of 0.50 at 90% power and 95% confidence interval according to the D-dimer parameter, and it was determined that at least 38 patients should be included in the study.[10]

The study data were analysed using IBM SPSS Version 26.0 statistical Package Software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Descriptive statistics were presented as mean±standard deviation for quantitative data and as frequency and percentage for qualitative data. Continuous variables were presented as mean±standard deviation. The change in the parameters over time was evaluated using the Friedman test, and the Bonferroni adjusted Wilcoxon signed-ranks test was used to determine the time period that led to the difference. Statistical significance was set as $p<0.05$.

RESULTS

A total of 40 patients aged 21-54 years belonging to the ASA II-III class were included in the study (Table 1).

The values of HR, MAP, and SpO_2 were within normal limits, and remained stable in all patients.

When the preoperative and postoperative Hb, Hct and platelet values of the patients were compared, a statistically significant difference was found between the levels at the 1st, 24th and 48th hour compared with those in the preoperative period for all parameters ($p<0.05$). A significant decrease was observed in Hb, Hct and platelet levels in all the postoperative periods compared with the preoperative period ($p<0.01$).

Significant changes were found in PT, aPTT and INR values in all the postoperative periods when

TABLE 1: Demographic characteristics.

	Mean±SD (n=40)
Gender n (%)	
Female/male	24/16 (60/40)
ASA n (%)	
II/III	31/9 (77.5/22.5)
Age	35.1±8.9
Body mass index (kg/m^2)	45.88±4.43
Duration of anaesthesia (minutes)	98.38±19.94
Duration of operation (minutes)	80.18±18.95
Pneumoperitoneum period (minutes)	65.45±19.32
Postoperative length of hospital stay (days)	3.03±0.56

SD: Standard deviation; ASA: American Society of Anesthesiologists.

TABLE 2: Preoperative and postoperative Hb, Hct, Platelet, PT, aPTT and INR values.

	Preoperative	Postoperative 1st hour	Postoperative 24th hour	Postoperative 48th hour	p*
	Mean±SD				
Hb (g/dL)	13.1±1.1	12.4±1.1	11.9±1.1	11.4±1.0	<0.0001
Hct (%)	38.8±2.9	37.4±3.1	35.6±3.0	34.5±2.8	<0.0001
Platelet (103/mL)	285.3±56.9	256.8±60.5	253.3 ±51.6	241.8±46.2	<0.0001
PT (seconds)	11.5±1.5	12.6±1.7	12.6±1.7	12.3±1.3	<0.0001
aPTT (seconds)	26.9±2.8	25.4±4.9	28.5±3.4	30.0±4.8	<0.0001
INR	0.96±0.9	1.05±0.29	1.06±0.11	1.06±0.09	<0.0001

*Friedman test. Hb: Haemoglobin; Hct: Haematocrit; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; INR: International normalised ratio.

compared with the preoperative period. A significant increase was observed in PT and INR values in all the postoperative periods compared with the preoperative period ($p<0.001$). The increase in PT and INR values at the postoperative 24th hour compared with the 1st hour was significant ($p<0.01$), whereas no significant change was observed between the values measured at the 24th and 48th hours ($p>0.05$).

Compared with the aPTT levels obtained during the preoperative period, a significant decrease was observed in the level at the postoperative 1st hour ($p<0.05$), whereas a significant increase was observed at the postoperative 24th and 48th hours ($p<0.01$). The change in the aPTT level at the 24th and 48th hours was significant compared with the value at the 1st hour postoperatively ($p<0.01$), but no significant change was observed between the levels obtained at the 24th and 48th hours ($p>0.01$) (Table 2).

When compared with the values obtained in the preoperative period, significant changes were found in fibrinogen and D-dimer values in all the postoperative periods. The fibrinogen levels at the 1st, 24th and 48th hours was found to be significantly higher than the preoperative value ($p<0.01$); the difference was significant at the postoperative 24th hour compared with the 1st hour, but no significant difference was observed in the se levels measured at the 24th and 48th hours ($p>0.01$). On the other hand, the D-dimer level at the postoperative 1st hour was found to be significantly higher than the preoperative value ($p<0.01$), whereas no significant change was observed among the values in the postoperative period ($p>0.01$) (Figure 1, Figure 2).

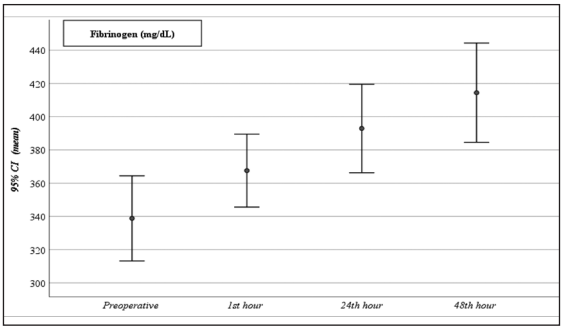

FIGURE 1: Change in preoperative and postoperative fibrinogen levels.

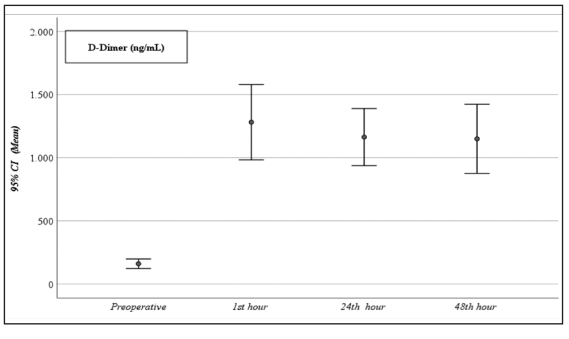

FIGURE 2: Change in preoperative and postoperative D-dimer levels.

None of the patients developed surgical bleeding requiring blood products and massive fluid replacement during the operation, and all of the patients were mobilised in the evening of the day of the operation. During the operation and in the first 7 days after the operation, no symptoms such as sudden onset of pain, warmth, tenderness, swelling in the leg, Homans sign, sudden onset of dyspnea, cough, chest pain, sudden hypotension or syncope were observed in any of the patients suggesting the development of VTE and/or PE.

DISCUSSION

This study aimed to evaluate the effects of LSG on postoperative PT, INR, aPTT, fibrinogen and D-dimer levels in comparison with those in the preoperative period in morbidly obese patients. PT, aPTT, INR, D-dimer and fibrinogen values were within normal limits in the blood samples obtained from the patients before the operation. A significant increase in these parameters was observed in the postoperative period, which continued until the postoperative 48th hour. Fibrinogen and D-dimer levels were observed to be above normal levels till the postoperative 48th hour. In our patients, there was a concurrent decrease in platelet count with Hb and Hct values in the postoperative period, and their levels were within normal limits.

Obesity causes a chronic metabolic inflammation through immune regulatory molecules and immune cells.[11] Von Willebrand factor, tissue factor, factor VIIa, factor VIII, thrombin f1+2 and fibrinogen levels in the blood increase in obese patients leading to a mild to moderate increase in coagulation, whereas increased secretion of plasminogen activator inhibitor can cause fibrinolytic system impairment.[12] Abnormally increased levels of fibrinogen and D-dimer in the postoperative period indicate an increased coagulation-fibrinolysis function and risk of thrombosis.[13] An increase in plasma D-dimer level is an important indicator for the diagnosis of deep vein thrombosis (DVT).[14] In this study, our patient group consisted of morbidly obese patients, and the coagulation parameters and D-dimer levels were within normal limits in the preoperative period. However, the preoperative baseline mean fibrinogen levels of the patients were close to the upper limit of the normal range.

Laparoscopic surgical interventions may stimulate the coagulation system and cause hypercoagulation. Amin et al. showed a decrease in aPTT and a significant increase in D-dimer and fibrinogen values at the postoperative 0th and 8th hours in laparoscopic cholecyctectomies. They reported that the increase in D-dimer occurred earlier and was associated with the coagulation-enhancing effect of pneumoperitoneum.[15] A study by Dönmez et al. showed an increase in coagulation parameters, fibrinogen and D-dimer levels after laparoscopic cholecystectomy.[16] Garg et al. showed that a decrease in aPTT and an increase in D-dimer on the first postoperative day in laparoscopic cholecystectomy.[17] Lauro et al. reported in their study that there was an increase in D-dimer and fibrinogen on the first postoperative day and that the coagulation and fibrinolytic system was stimulated in laparoscopic cholecystectomy.[18] In our study, we observed that fibrinogen levels started to increase at the first postoperative hour and continued to increase until the 48th hour, whereas the increase in D-dimer reached a peak at the first postoperative hour and remained at similarly high levels until the 48th hour. This increase in fibrinogen and D-dimer levels in the early postoperative period was related to the activation of the coagulation-fibrinolytic system. Martinez-Ramos et al. also showed that D-dimer increased in the early postoperative period and returned to baseline on the seventh day. They stated that there is a greater increase in fibrinolytic activity after laparoscopic cholecystectomy compared to open operations of similar duration, and unlike other studies, this may mean hypocoagulation in the postoperative period and less thrombotic risk for patients.[19]

Laparoscopic surgery can increase the risk of thrombosis in obese patients, although not as much as open surgery can.[20,21] A study by Liu et al. reported that they observed an increase in PT and D-dimer levels and a decrease in aPTT value without any significant change in fibrinogen values in the postoperative period in cases that underwent LSG. They reported that these changes in PT, aPTT and D-dimer levels are indicative of activation of the coagulation system because of tissue trauma and pneumoperitoneum.[22] Rottenstreich et al. in their study, showed an increase in fibrinogen, von Willebrand factor activity and factor VIII levels on the 3rd and 10th days postoperatively in cases that underwent LSG, and reported that the increase in hypercoagulability in these surgeries continued until the late surgical period.[23] Nguyen et al. reported that in morbidly obese patients who underwent open and laparoscopic gastric bypass operations, there was an increase in fibrinogen and D-dimer levels in the first 24 hours postoperatively in both groups, and the increase in fibrinogen levels continued until the third postoperative day. They

noted that laparoscopic gastric bypass activates hypercoagulation similar to the open group.[24] In our study, we observed that fibrinogen levels started to increase immediately after the operation, as did PT and D-dimer values, and this increase continued until the 48th hour after the operation. A decrease in the aPTT was observed at the postoperative 1st hour, similar to the results of Liu et al.; however, the aPTT value increased after the postoperative 24th hour, as did PT and INR, which was in contrast to their study results. However, these values were within normal limits and did not causing an increased risk of bleeding.

Different incidences of DVT and PE are mentioned in studies in morbidly obese patients. The rate of postoperative VTE has been reported to be 0.13-0.34% in obese patients who undergo laparoscopic surgeries and 0.63% in those who undergo sleeve gastrectomy.[20,21] Becattini et al. reported in their study that the incidence of PE after laparoscopic bariatric surgery was <1%, and the incidence of asymptomatic DVT according to screening tests was approximately 2%.[5] Higa et al. reported in their study that the risk of VTE was 0.2% and the risk of PE was 0.3% in laparoscopic gastric bypass cases.[25]

DVT may occur immediately after the operation or it may occur after discharge.[21,26] In the study of Winegar et al. in patients undergoing bariatric surgery, the risk of VTE was reported to be 0.42% within 90 postoperative days, and VTE developed in 27% of these patients while in hospital and 73% after discharge.[21] Froehling et al. reported that in cases that developed VTE after laparoscopic bariatric surgery, DVT occurred in 56% of the cases within 30 days after discharge.[26] Wittgrove et al. reported that they did not encounter any thromboembolic complications after laparoscopic bariatric surgery.[27] Nguyen et al. in their study, showed that laparoscopic bariatric surgery causes hypercoagulation, such as open surgeries. However, thromboembolic complications did not develop in any patient who underwent laparoscopic surgery, while they reported VTE in one patient who underwent open surgery and PE in one patient (on the 14th postoperative day). They used mechanical thromboprophylaxis in their patients, starting in the preanaesthetic period.[24] Liu et al. showed that coagulation was activated by surgery in LSG patients, but they reported that they did not encounter any postoperative thromboembolic events. They did not use anticoagulant treatment in the preoperative and postoperative period, and they applied mechanical thromboprophylaxis in the postoperative period in their patients.[22] Although postoperative fibrinogen and D-dimer levels were high, thrombotic complications, such as symptomatic DVT and PE, did not occur in the early postoperative period in our patients. In our patients, mechanical thromboprophylaxis was preferred by the surgical team in the preoperative period due to the risk of intraoperative bleeding, and the use of anticoagulant agents was started in the postoperative period.

There are different opinions and applications on the optimal venous thromboprophylaxis strategy to be applied in the prevention of VTE. Various methods such as anticoagulant agents (unfractionated heparin or low-molecular-weight heparin), mechanical antithrombotic prophylaxis (thromboembolic deterrent stockings, foot pump, and intermittent venous compression device) and inferior vena cava filter, early mobilization can be used in the prophylaxis of VTE.[21] Wu et al. reported that routine prophylaxis is applied with a frequency of 95% in bariatric surgeries, low-dose heparin is preferred 50%, intermittent pneumatic compression stockings are preferred 33%, low molecular weight heparins are preferred 13% and other methods are preferred 4%.[28] Although mechanical thromboprophylaxis alone was applied in the preoperative period, symptomatic VTE or PE was not encountered in our patients; we think that factors such as the fact that our patients are mostly young and female patients, shorter operation times, early mobilization, shorter hospital stay, and anticoagulant treatment initiated in the postoperative period contribute positively.

There are some limitations of our study. One of our limitations is the lack of screening with imaging methods to determine the current VTE risk in our patients in the preoperative period and to detect asymptomatic VTE in the postoperative period. But this procedure, which is not routinely performed, could not be implemented, as it would cause additional cost in the study. A second limitation is that we did not have a control group in our study. A comparison

group could not be formed because the preferred practice in bariatric surgery in our hospital is LSG and surgical teams often use the same thromboprophylaxis methods. A third limitation is that we did not reflect the late period data of our patients after discharge in our study. Another limitation of our study is that we could not obtain a higher number of cases, since our study required repeated laboratory examinations.

CONCLUSION

We observed that coagulation parameters were affected in favor of hypercoagulation in the postoperative period in morbidly obese patients undergoing LSG. This may lead to an increased risk of thrombosis. As the hospitalisation durations in these patients are short and as these patients receive early mobilisation after operation for ensuring that they return to their daily activities within a short period, it is important to monitor these patients closely for thromboembolic complications after discharge.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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