PAPER

# Systemic Coagulation and Fibrinolysis After Laparoscopic and Open Gastric Bypass

*Ninh T. Nguyen, MD; John T. Owings, MD; Robert Gosselin, MT; William C. Pevec, MD; Steven J. Lee, MS; Charles Goldman, MD; Bruce M. Wolfe, MD*

**Hypothesis:** Laparoscopic gastric bypass (GBP) induces a postoperative hypercoagulable state that is similar or reduced compared with open GBP.

**Setting:** University hospital.

**Patients:** Between May 1999 and June 2000, 70 patients were randomly assigned to laparoscopic (n=36) or open (n=34) GBP. Deep venous thrombosis (DVT) prophylaxis consisted of antiembolism stockings and sequential pneumatic compression devices.

**Main Outcome Measures:** Plasminogen, thrombin-antithrombin complex (TAT), prothrombin fragment 1.2 (F1.2), fibrinogen, D-dimer, antithrombin III (AT), and protein C levels were measured at baseline and at 1, 24, 48, and 72 hours postoperatively. A venous duplex examination of both lower extremities was performed preoperatively and between the third and fifth day postoperatively.

**Results:** The 2 groups were similar in age, weight, and body mass index. Plasminogen levels decreased, and TAT, F1.2, and fibrinogen levels increased after laparoscopic and open GBP. There was no significant difference in these levels between groups. D-dimer levels increased in both groups, but the levels were significantly higher after open GBP than after laparoscopic GBP ($P<.01$). Antithrombin III and protein C levels decreased in both groups. The reduction of AT (at 1 hour) and protein C (at 72 hours) was significantly less after laparoscopic GBP than after open GBP ($P<.05$). Postoperative venous duplex examination revealed DVT in 1 (2.9%) of 34 patients after open GBP but in none of 36 patients after laparoscopic GBP. One patient developed pulmonary embolism after open GBP.

**Conclusions:** Laparoscopic GBP induces a hypercoagulable state similar to that of open GBP. Our findings suggest that DVT prophylaxis should be used during laparoscopic GBP as in open GBP.

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POSTOPERATIVE venous thromboembolism (ie, deep venous thrombosis [DVT] and pulmonary embolism [PE]) represents an important concern after major abdominal operations such as Roux-en-Y gastric bypass (GBP). The reported incidence of PE for patients undergoing open GBP with prophylaxis has ranged from 0.36% to 3.0%.[1-5]

Laparoscopic GBP is now an accepted alternative to open GBP, but there remains concern regarding the risk of venous thromboembolism after laparoscopic GBP. Schauer et al[6] reported a 0.73% postoperative incidence of venous thromboembolism in a prospective series of 275 patients who underwent laparoscopic GBP. Wittgrove and Clark[7] reported no thromboembolic complications in a series of 500 patients undergoing laparoscopic GBP. Higa et al[8] reported a 0.2% incidence of DVT and a 0.3% incidence of PE in 1040 patients undergoing laparoscopic GBP. To date, the evidence is inconclusive as to the relative risk of postoperative thromboembolism after laparoscopic GBP when compared with open GBP.

All elements of the Virchow triad (venous stasis, hypercoagulability, and endothelial injury) occur during laparoscopic GBP and may influence the risk of postoperative DVT. Pneumoperitoneum and reverse Trendelenburg position during laparoscopic surgery are 2 conditions that may increase venous stasis and thus increase the risk of DVT.[9,10] Conversely, the degree of activation of the coagulation cascade (hypercoagulable state) has been demonstrated to be lower after laparoscopic surgery than after open operation.[11,12] In this prospective, randomized trial, we aimed to compare (1) the degree of postoperative hypercoagulability and (2) the rate of postoperative DVT after laparoscopic and open GBP.

*From the Department of Surgery, University of California–Davis Medical Center, Sacramento.*

## PATIENTS AND METHODS

### STUDY DESIGN

The study protocol was approved by the Institutional Review Board of the University of California–Davis Medical Center, Sacramento. All patients being evaluated for surgical treatment of morbid obesity were considered for entry into the trial. Patients were considered eligible if they had a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) of 40 to 60, were younger than 60 years, and had failed previous nonsurgical attempts at weight loss. Patients with previous obesity surgery, previous gastric surgery, a large abdominal ventral hernia, or a history of DVT or PE were excluded. Written informed consent was obtained from all patients, after which patients were randomly assigned to undergo either laparoscopic or open GBP. Patients were informed of their treatment group during their preoperative clinic visit. Randomization was performed by using sealed envelopes that were stratified according to a BMI of 40 to 50 or 51 to 60.

Demographic data, BMI, operative time, length of hospital stay, and incidence of postoperative DVT or clinical evidence of PE were contemporaneously recorded. Patients in both groups were hospitalized postoperatively for at least 3 days. After discharge, all patients were evaluated in the outpatient clinic on postoperative day 7 and at 1, 3, 6, and 12 months, and yearly thereafter.

### DVT PROPHYLAXIS

Thigh-length pneumatic sequential compression sleeves (SCD) (Kendall Healthcare Products Co, Mansfield, Mass) and thigh-length antiembolic stockings (TED) (Kendall Healthcare Products Co) were placed on both lower extremities for DVT prophylaxis in both groups before the induction of anesthesia. The SCD cycled continuously with 11 seconds of gradient compression at 45 mm Hg, followed by 60 seconds of decompression.

### OPERATIVE TECHNIQUE

Anesthetic management was similar for both groups. All patients were given a single dose of antibiotic preoperatively and postoperatively. A 15- to 20-mL transected gastric pouch was created in both groups; a 75-cm Roux limb was constructed for patients with a BMI of 40 to 50 and a 150-cm Roux limb was constructed for patients with a BMI of 51 to 60. A stapled gastrojejunostomy anastomosis was performed in both groups. Laparoscopic GBP was performed through 5 abdominal trocars and open GBP was performed through an upper midline incision. Our technique of laparoscopic GBP has been previously described.[13]

### POSTOPERATIVE CARE

All patients were extubated and transferred to the surgical ward postoperatively unless they required ventilatory support or close observation in the intensive care unit. A nasogastric tube was not used routinely in the postoperative period. Patient-controlled analgesia using morphine was started in the recovery room once the patient became alert. Patients were encouraged to ambulate on the first postoperative day. The SCD and TED were continued postoperatively on the ward until patients were discharged.

### END POINTS

The primary end point of our study was the change in molecular coagulation activity after laparoscopic and open GBP. Secondary end points were clinical evidence of

## RESULTS

### PATIENT DEMOGRAPHIC AND OPERATIVE DATA

Seventy patients were randomly assigned to undergo either laparoscopic (n=36) or open (n=34) GBP from May 1999 to June 2000. During this time, 12 eligible patients were not enrolled: 11 patients specifically requested laparoscopic GBP, and 1 patient requested open GBP. Two patients randomized to open GBP were excluded from the study after randomization: one patient withdrew informed consent and elected for laparoscopic GBP, and the other patient had hemorrhage during exploration that ultimately required splenectomy. Gastric bypass was not performed in this latter patient.

There was no significant difference in age, sex, and preoperative BMI between groups, although the mean operative time was longer in the laparoscopic GBP group than in the open GBP group (**Table**). Two patients in the laparoscopic group underwent conversion to laparotomy: one for revision of the gastrojejunostomy anastomosis, and the other for inability to insufflate the abdomen. The median length of hospital stay was 3 days after laparoscopic GBP and 5 days after open GBP.

### LABORATORY AND ULTRASOUND FINDINGS

#### Thrombin-Antithrombin Complex

The TAT levels after laparoscopic and open GBP are summarized in **Figure 1**. The TAT levels increased significantly from baseline values after laparoscopic and open GBP ($P<.05$) without a significant difference between groups at any time.

#### Prothrombin Fragment 1.2

The F1.2 levels after laparoscopic and open GBP are summarized in **Figure 2**. The F1.2 levels increased and peaked at 1 hour after both laparoscopic and open GBP ($P<.05$) and then decreased at 24 hours without a significant difference between groups.

#### D-Dimer

D-dimer levels after laparoscopic and open GBP are summarized in **Figure 3**. D-dimer levels increased significantly from baseline values after laparoscopic and open GBP ($P<.05$). D-dimer levels were significantly higher after open GBP than after laparoscopic GBP at 1 hour (306±240 ng/mL

postoperative DVT and PE and duplex ultrasound examination of the lower extremities for DVT.

### COAGULATION AND FIBRINOLYSIS

Plasma samples from all patients were drawn at anesthetic induction and then at 1, 24, 48, and 72 hours postoperatively. Samples were drawn in tubes buffered with 3.2% sodium citrate and then spun at 3500 rpm for 10 minutes to yield platelet-poor plasma (<10 000/mm$^3$). Aliquots of plasma were frozen and stored at −70°C until analysis. Before analysis, the samples were quick-thawed in a 37°C water bath for 5 minutes. Two down-regulators of coagulation were sampled: antithrombin III (AT) and protein C. The AT was measured with a kinetic, functional chromogenic anti-Xa method (Chromogenix AB, Molndal, Sweden), and levels were expressed as the percent of normal human plasma (NHP) (reference range, 80%-120%). Protein C was measured via a functional clotting method (Dade Behring International, Deerfield, Ill), and levels were expressed as the percent of NHP (reference range, 80%-120%). Two markers of subclinical thrombosis, thrombin-antithrombin complex (TAT), and prothrombin fragment 1.2 (F1.2) were tested. The TAT was measured using an enzyme immunosorbent assay (ELISA) method (Dade Behring International) and expressed in nanograms per milliliter. The F1.2 was measured using an ELISA method (Dade Behring International) and expressed in nanomoles per liter. The marker of fibrinolysis D-dimer was studied via an enzyme immunoassay method (American Diagnostica, Greenwich, Conn) with results expressed as nanograms per milliliter. Plasminogen was measured using the chromogenic functional methods (Dade Behring International) with results expressed as milligrams per deciliter. Fibrinogen was measured using the Clauss method (Dade Behring International) with results expressed as milligrams per deciliter. All blood plasma samples were analyzed in batches by a single investigator (R.G.) blinded to the type of surgery performed and to all clinical endpoints.

### LOWER EXTREMITY ULTRASOUND

A duplex ultrasound examination of the lower extremities was performed preoperatively and again postoperatively between day 3 and day 5. Duplex ultrasound examinations were conducted with a color flow method (Ultra Mark 9 Ultrasound; Advanced Technology Laboratory, Bothell, Wash). All ultrasound examinations were performed by a registered vascular technologist and reviewed by a single vascular surgeon (W.C.P.) blinded to the procedure performed and the clinical outcome.

### STATISTICAL ANALYSIS

Continuous variables are presented as mean±SD. Demographic data were compared using 2-tailed *t* tests or Fisher exact tests. Repeated-measures analysis of variance (ANOVA) was used to analyze all normally distributed data. After the initial ANOVA, a series of stratified models were run to look for significant differences between groups at each time point using unpaired *t* tests or significant differences from baseline within each group using paired *t* tests. For variables not normally distributed, Freidman tests were used to analyze the significance of temporal effects within each surgical group. Wilcoxon signed rank tests were used to evaluate significant differences from baseline values within each group, and Mann-Whitney U-tests were used to assess the significance between groups at each time point. Statistical evaluations were performed using standardized software (Statview; SAS Institute Inc, Cary, NC). A *P* value of less than .05 was considered significant. All data were analyzed on an "intention-to-treat" basis. Laparoscopic GBP operations that were converted to open GBP were analyzed as laparoscopic operations.

**Characteristics of Patients Undergoing Laparoscopic and Open Gastric Bypass***

| Characteristic | Laparoscopic GBP (n = 36) | Open GBP (n = 34) | *P* Value |
|---|---|---|---|
| Sex ratio, female-male | 34:2 | 28:6 | NS† |
| Age, y | 41 ± 8 | 43 ± 8 | NS‡ |
| Preoperative BMI, kg/m$^2$ | 48 ± 5 | 50 ± 5 | NS‡ |
| ASA classification, 1-5 | 2.9 ± 0.3 | 2.8 ± 0.5 | NS‡ |
| Operative time, min | 230 ± 46 | 202 ± 40 | .01§ |

*GBP indicates gastric bypass; NS, not significant; BMI, body mass index; and ASA, American Society of Anesthesiology.
†Fisher exact test.
‡2-tailed *t* test.
§Mann-Whitney U-test.

vs 181±144 ng/mL, respectively; *P*=.01) and at 24 hours (596±327 ng/mL vs 494±408 ng/mL, respectively; *P*=.03).

### Antithrombin III

The AT levels after laparoscopic and open GBP are summarized in **Figure 4**. They decreased significantly at 1 hour postoperatively after laparoscopic and open GBP (*P*<.05).

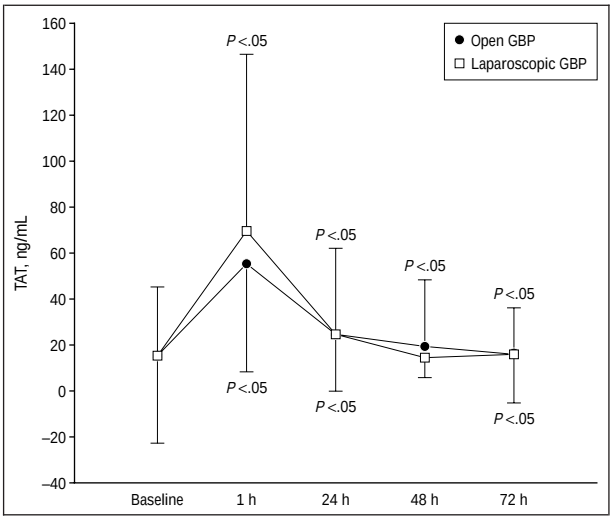


**Figure 1.** Thrombin-antithrombin complex (TAT) levels after laparoscopic and open gastric bypass (GBP). *P* values compared with baseline value (Wilcoxon signed rank tests).

The AT levels at 1 hour postoperatively were significantly lower after open GBP than after laparoscopic GBP (86.2%±11.6% vs 95.7%±9.6%, respectively; *P*<.001). At

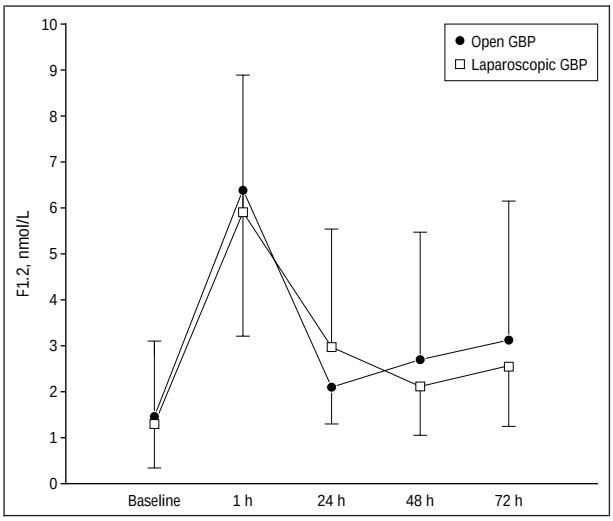


**Figure 2.** Prothrombin fragment 1.2 (F1.2) levels after laparoscopic and open gastric bypass (GBP). $P<.05$ for all values compared with baseline (Wilcoxon signed rank tests).

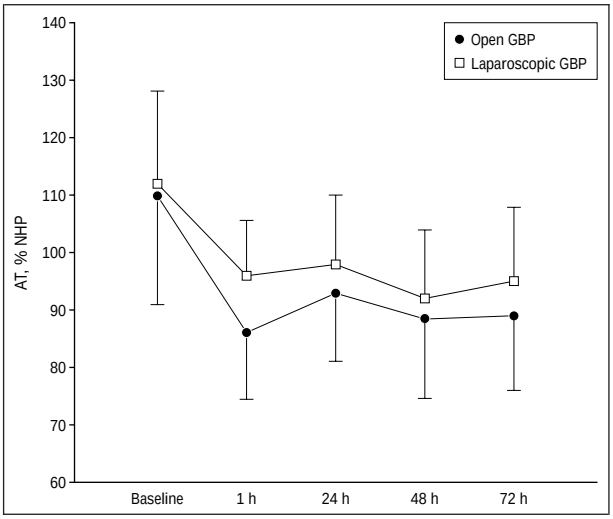


**Figure 4.** Antithrombin III (AT) levels expressed as the percentage of normal human plasma (NHP) after laparoscopic and open gastric bypass (GBP). $P<.05$ for all values compared with baseline (paired *t* tests). For the laparoscopic GBP group at 1 hour, $P<.05$ compared with open GBP (unpaired *t* tests).

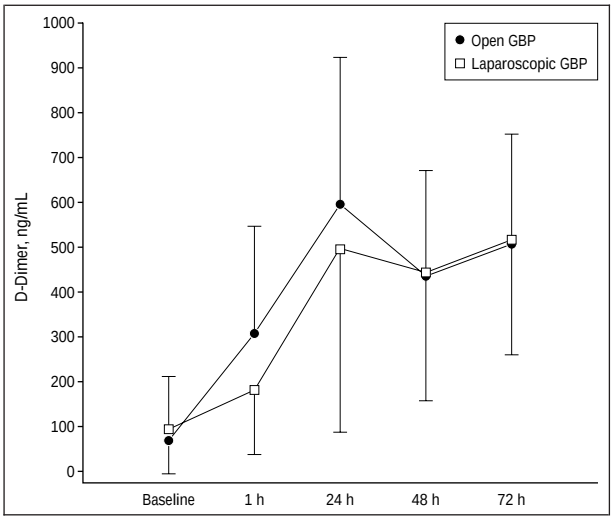


**Figure 3.** D-dimer levels after laparoscopic and open gastric bypass (GBP). $P<.05$ for all values compared with baseline (Wilcoxon signed rank tests). For the laparoscopic GBP group at 1 and 24 hours, $P<.05$ compared with open GBP (Mann-Whitney *U* tests).

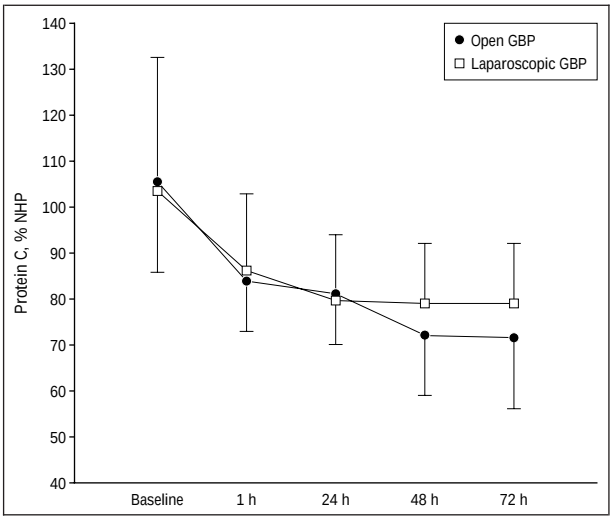


**Figure 5.** Protein C levels expressed as the percentage of normal human plasma (NHP) after laparoscopic and open gastric bypass (GBP). $P<.05$ for all values compared with baseline (paired *t* tests). For the laparoscopic group at 72 hours, $P<.05$ compared with open GBP (unpaired *t* tests).

24, 48, and 72 hours, AT levels continued to remain lower than the levels at baseline in both groups without a significant difference between groups.

### Protein C

Protein C levels after laparoscopic and open GBP are summarized in **Figure 5**. Protein C levels decreased significantly after both laparoscopic and open GBP, but protein C levels were significantly lower after open GBP than after laparoscopic GBP at 72 hours (71.5%±10.4% vs 79.8%±18.4%, respectively; $P=.04$).

### Plasminogen

Plasminogen levels after laparoscopic and open GBP are summarized in **Figure 6**. Plasminogen levels decreased significantly after laparoscopic and open GBP ($P<.05$) without a significant difference between groups.

### Fibrinogen

Fibrinogen levels after laparoscopic and open GBP are summarized in **Figure 7**. Fibrinogen levels decreased from baseline values at 1 hour postoperatively. By 24 hours, fibrinogen levels increased significantly from baseline ($P<.05$) to reach maximum levels at 72 hours without a significant difference between groups.

### Lower Extremity Ultrasound and Thromboembolism

All patients in both groups had negative findings on venous duplex ultrasound examination preoperatively. One (2.9%) of 34 patients in the open GBP group developed

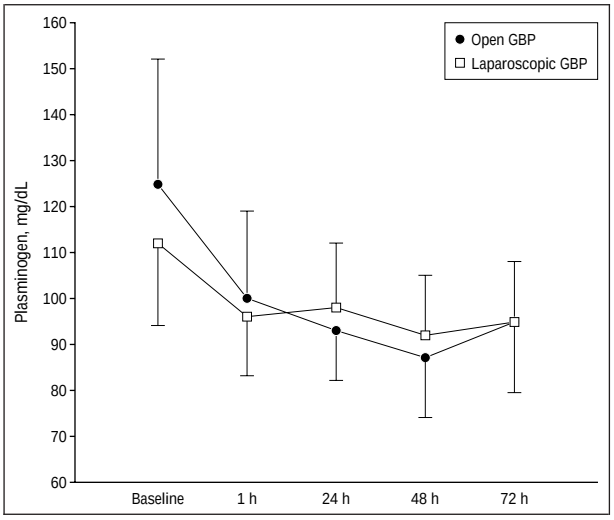


**Figure 6.** Plasminogen levels after laparoscopic and open gastric bypass (GBP). $P<.05$ for all values compared with baseline (paired *t* tests).

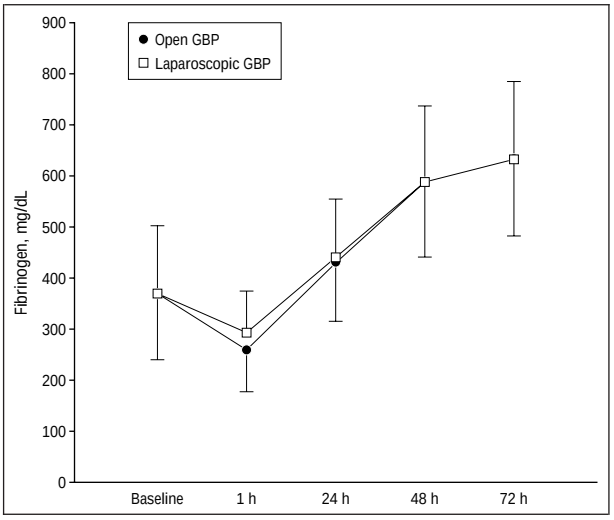


**Figure 7.** Fibrinogen levels after laparoscopic and open gastric bypass (GBP). $P<.05$ for all values compared with baseline (paired *t* tests).

an asymptomatic thrombus in the posterior tibial vein identified on the postoperative duplex examination. None of the patients in the laparoscopic GBP group had DVT identified on postoperative venous duplex examination. Though not the primary clinical end point of our study, we observed one PE in one patient in the open GBP group after discharge on postoperative day 14. This patient had negative findings on lower extremity venous duplex scan before discharge. There were no postoperative PE complications in the laparoscopic GBP group.

## COMMENT

Venous thromboembolism after open GBP is a major concern. The postoperative risk of venous thromboembolism is related to the extent of surgical trauma, site of surgery, length of surgery, and length of postoperative immobilization. A transient postoperative hypercoagulable state is 1 of 3 important factors that may contribute to the development of DVT and occurs after abdominal operations such as GBP. The mechanism for postoperative hypercoagulability is in part owing to an imbalance between the up-regulators and the down-regulators of coagulation.[14] Postoperative hypercoagulability can occur as a result of a hyperactive clotting system (enhanced thrombin generation with a concomitant reduction of naturally occurring anticoagulants) or a reduction in activity of the fibrinolytic system.[15] In this study, we evaluated the balance between the up-regulators and down-regulators of coagulation and markers of fibrinolysis. All were assessed after laparoscopic or open GBP to determine if laparoscopic GBP predisposes patients to a higher risk of postoperative hypercoagulability and thereby an increased risk of venous thromboembolism.

Postoperative hypercoagulability has been examined after laparoscopic cholecystectomy. Caprini et al[16] reported a marked hypercoagulable state after laparoscopic cholecystectomy, as seen by an increase in the thromboelastographic index, on the first postoperative day compared with preoperative values. Other reports have documented a reduction in postoperative hypercoagulability after laparoscopic cholecystectomy compared with after open cholecystectomy.[11,12] Prisco et al[12] reported a significant increase in F1.2 levels after laparoscopic cholecystectomy, but these levels were significantly lower than after open cholecystectomy. Conversely, other investigators have demonstrated no difference in postoperative hemostasis between laparoscopic and open surgery.[17,18] Dexter et al[17] reported similar F1.2, AT, and D-dimer levels after laparoscopic and open cholecystectomy. Vander Velpen et al[18] also reported no significant difference in levels of tissue-type plasminogen activator antigen response and plasma plasminogen activator inhibitor-1 response after laparoscopic and open cholecystectomy. None of these trials, however, were prospective, randomized trials, so we sought to clarify the disagreement with our trial.

Prothrombin fragment 1.2 forms when factor Xa cleaves prothrombin to form thrombin and TAT forms when AT binds with thrombin. Each is thus a measure of thrombin formation and index of clot formation. In our study, we found that F1.2 and TAT levels significantly increased over baseline levels in both groups after initiation of the operation. The increase of F1.2 and TAT levels 24 hours postoperatively suggests a marked increase in the generation of thrombin. That is, laparoscopic GBP induced a degree of increased activation of the coagulation response (hypercoagulability) similar to that of open GBP.

D-dimer levels have been used as a marker of intravascular clot formation.[19] D-dimer is a cross-linked fibrin degradation product, which forms as a result of a breakdown of fibrin. D-dimer levels are frequently increased after surgery or trauma and indicate the presence of intravascular clot that has undergone lysis. D-dimer levels were elevated in both groups postoperatively but significantly less so after laparoscopic than after open GBP at 1 and 24 hours. This, when combined with the F1.2 and TAT data, may be evidence that at the subclinical level there is less intravascular clot formation with a laparoscopic than with a traditional surgical insult.

In the present study, fibrinogen levels increased and reached maximum levels at 72 hours, and plasminogen levels decreased postoperatively in both groups. Fibrinogen is produced by the liver and is the precursor of fibrin. Fibrinogen is known to behave as an acute-phase reactant, with stores released at times of physiologic stress. Plasminogen is the precursor to plasmin, which, in turn, is the primary molecule responsible for fibrin degradation. The increase in fibrinogen with a concomitant decrease in plasminogen may also favor increased fibrin formation.

The primary down-regulators of the coagulation cascade are AT and protein C. Antithrombin has its down-regulatory effect through the inactivation of several activated factors, including factors X, IX, XII, and thrombin. By inactivating the numbered factors, thrombin production is reduced. Antithrombin also binds with thrombin and thereby blocks thrombin's interaction with fibrinogen. Protein C reduces thrombin generation by inactivation of activated factor V and VIII. We found a significant difference between the open and laparoscopic groups in both AT and protein C levels. The antithrombin levels at 1 hour and protein C levels at 72 hours postoperatively were significantly higher after laparoscopic GBP than after open GBP. These higher levels of postoperative antithrombotics after laparoscopic GBP may represent a physiologic advantage of laparoscopic GBP. Of note, we found AT activity in our patient population (morbidly obese) at baseline to be in the high range of the normal values (109% ± 15% of NHP). This may suggest that, at baseline, morbidly obese patients require higher levels of AT to avoid hypercoagulability.

Patients with AT levels less than 70% NHP have been reported to have an increased risk of spontaneous DVT.[20] Three patients in the open GBP group had AT levels less than 70% NHP in the postoperative period, but none of the patients in the laparoscopic GBP group did. One of 34 patients in the open GBP group developed postoperative PE. The AT activity in that patient decreased from a baseline value of 100% to 70% NHP at 48 hours and 68% NHP at 72 hours.

We used SCD and TED for DVT prophylaxis using the DVT risk factor assessment as described by Caprini et al.[21] The combination of SCD and TED reduces the risk of DVT by increasing lower extremity venous blood flow and arguably by increasing serum fibrinolytic activity.[9,10,22] In this study, the rate of DVT after laparoscopic GBP was 0% and after open GBP, 2.9%.

The optimal method for DVT prophylaxis in patients undergoing GBP is still unknown. Wu and Barba[23] surveyed members of the American Society for Bariatric Surgery regarding their practice of DVT prophylaxis. They reported that 95% of the members used at least 1 form of DVT prophylaxis, and 38% of members used 2 or more prophylactic methods simultaneously. The preferred methods were low-dose heparin (50% of members) and SCD (33% of members). It was clear from the study by Wu and Barba that there was no consensus among bariatric surgeons as to the best method to prevent DVT, but DVT prophylaxis was considered an important aspect in the management of GBP patients.

In conclusion, our study demonstrates that the changes that occur in postoperative coagulation and fibrinolysis after laparoscopic GBP are similar to those after open GBP. Thrombin generation was increased postoperatively in both groups. Plasma activity of AT and protein C was reduced in both groups. The combination of increased thrombin production and reduced antithrombotic activity seen after laparoscopic GBP confirms the hypercoagulable state and hence the risk for postoperative DVT. Although the reduction of antithrombotic parameters (AT and protein C) and the increase in D-dimer levels were less at specific time points after laparoscopic than after open GBP, any clinical benefit of these findings is uncertain. A much larger clinical trial would be required to show a difference in DVT incidence between laparoscopic and open GBP. From our data, we conclude that laparoscopic GBP does not increase the degree of postoperative hypercoagulability compared with open GBP, and that DVT prophylaxis should be used with both the open and laparoscopic methods of GBP.

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*Corresponding author and reprints: Ninh T. Nguyen, MD, Department of Surgery, University of California, Davis, Medical Center, 2221 Stockton Blvd, 3rd Floor, Sacramento, CA 95817-1418 (e-mail: ninh.nguyen@ucdmc.ucdavis.edu).*

## REFERENCES

1. Balsiger BM, Kennedy FP, Abu-Lebdeh HS, et al. Prospective evaluation of Roux-en-Y gastric bypass as primary operation for medically complicated obesity. *Mayo Clin Proc.* 2000;75:673-680.
2. Fobi MA, Lee H, Holness R, Cabinda D. Gastric bypass operation for obesity. *World J Surg.* 1998;22:925-935.
3. Hall JC, Watts JM, O'Brien PE, et al. Gastric surgery for morbid obesity: the Adelaide Study. *Ann Surg.* 1990;211:419-427.
4. Brolin RE, Kenler HA, Gorman JH, Cody RP. Long-limb gastric bypass in the superobese: a prospective randomized study. *Ann Surg.* 1992;215:387-395.
5. MacLean LD, Rhode BM, Nohr CW. Late outcome of isolated gastric bypass. *Ann Surg.* 2000;231:524-528.
6. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Ann Surg.* 2000;232:515-529.
7. Wittgrove AC, Clark GW. Laparoscopic gastric bypass, Roux-en-Y, 500 patients: technique and results, with 3-60 month follow-up. *Obes Surg.* 2000;10:233-239.
8. Higa KD, Boone KB, Ho T. Complications of the laparoscopic Roux-en-Y gastric bypass: 1040 patients: what have we learned? *Obes Surg.* 2000;10:509-513.
9. Schwenk W, Bohm B, Fugener A, Muller JM. Intermittent pneumatic sequential compression (ISC) of the lower extremities prevents venous stasis during laparoscopic cholecystectomy. A prospective randomized study. *Surg Endosc.* 1998;12:7-11.
10. Ido K, Suzuki T, Kimura K, et al. Lower-extremity venous stasis during laparoscopic cholecystectomy as assessed using color Doppler ultrasound. *Surg Endosc.* 1995;9:310-313.
11. Nguyen NT, Luketich JD, Shurin MR, et al. Coagulation modifications after laparoscopic and open cholecystectomy in a swine model. *Surg Endosc.* 1998;12:973-978.
12. Prisco D, De Gaudio AR, Carla R, et al. Videolaparoscopic cholecystectomy induces a hemostasis activation of lower grade than does open surgery. *Surg Endosc.* 2000;14:170-174.
13. Nguyen NT, Ho HS, Palmer LS, Wolfe BM. A comparison study of laparoscopic versus open gastric bypass for morbid obesity. *J Am Coll Surg.* 2000;191:149-155.
14. Owings JT, Bagley M, Gosselin R, Romac D, Disbrow E. Effect of critical injury on plasma antithrombin activity: low antithrombin levels are associated with thromboembolic complications. *J Trauma.* 1966;41:396-405.

15. Mammen EF. Pathogenesis of venous thrombosis. *Chest*. 1992;102:640S-644S.
16. Caprini JA, Arcelus JI, Laubach M, et al. Postoperative hypercoagulability and deep-vein thrombosis after laparoscopic cholecystectomy. *Surg Endosc*. 1995; 9:304-309.
17. Dexter SP, Griffith JP, Grant PJ, McMahon MJ. Activation of coagulation and fibrinolysis in open and laparoscopic cholecystectomy. *Surg Endosc*. 1996;10: 1069-1074.
18. Vander Velpen G, Penninckx F, Kerremans R, Van Damme J, Arnout J. Interleukin-6 and coagulation-fibrinolysis fluctuations after laparoscopic and conventional cholecystectomy. *Surg Endosc*. 1994;8:1216-1220.
19. Owings JT, Gosselin RC, Battistella FD, Anderson JT, Petrich M, Larkin EC. Whole blood D-dimer assay: an effective noninvasive method to rule out pulmonary embolism. *J Trauma*. 2000;48:795-799.
20. Bauer KA, Goodman TL, Kass BL, Rosenberg RD. Elevated factor Xa activity in the blood of asymptomatic patients with congenital antithrombin deficiency. *J Clin Invest*. 1985;76:826-836.
21. Caprini JA, Arcelus JI, Hasty JH, Tamhane AC, Fabrega F. Clinical assessment of venous thromboembolic risk in surgical patients. *Semin Thromb Hemost*. 1991; 17:304-312.
22. Comerota AJ, Chouhan V, Harada RN, et al. The fibrinolytic effects of intermittent pneumatic compression: mechanism of enhanced fibrinolysis. *Ann Surg*. 1997;226:306-313.
23. Wu EC, Barba CA. Current practices in the prophylaxis of venous thromboembolism in bariatric surgery. *Obes Surg*. 2000;10:7-13.

## DISCUSSION

**George Velmahos, MD, Los Angeles, Calif:** A prospective randomized trial becomes always a major attraction due to its superior methodological design and scientific rigor. This study is no exception. It is well prepared, well written, and well presented. The combination of the expertise of Drs Wolfe and Nguyen in bariatric surgery and Dr Owings in venous thromboembolism ensures good results.

This is why I have almost no comments on the methodology and would like to focus on the concept. Even more importantly, I want to examine closely the message that is given on the basis of the study's results. The authors randomized their patients to those receiving open and those receiving laparoscopic bypass for morbid obesity. Their outcome parameters were 2: coagulation abnormalities and clinical evidence of venous thromboembolism. They found that both open and laparoscopic gastric bypass are potentially thrombogenic procedures as shown by the significantly different concentrations of various coagulation parameters detected postoperatively compared to preoperatively. By some measurements, the laparoscopic technique showed superiority over the open method because it had less thrombogenic potential. However, the differences in blood test results did not translate into any statistically significant or even clinically important difference in the rate of venous thromboembolism between the 2 groups.

Hence, my first question. Is venous thromboembolism of real clinical significance in the population that you examined? If it is, why did you fail to find any clinical events? Maybe because your method of detection, ie, the duplex scan, is not sensitive and is operator-dependent, or because your methods of thromboprophylaxis are very efficient, or because the incidence of the disease is not as high as thought. There is a common belief that obesity is a risk factor for venous thromboembolism. According to your results and literature search, which revealed postoperative venous thromboembolism rates of approximately 0.3% in this population (that was in your manuscript), one realizes that the significance of venous thromboembolism in this group of patients may have been overrated.

My second question is also relevant to the previous issue. With such a low incidence of clinically significant disease, how many thousands of patients should be accrued to show us a statistically significant difference between the 2 methods if one exists? It is almost unrealistic to try to find the effect of open or laparoscopic bariatric surgery in the development of venous thromboembolism if the incidence of venous thromboembolism is around 1%.

My third question relates to the use of pneumatic compression devices as the only method of thromboprophylaxis. Why are you avoiding subcutaneous heparin when it is given in almost all other elective abdominal procedures? Previous studies from our and other institutions have shown that pneumatic compression devices are associated with low compliance, unreliable function, immediate cessation of the thromboprophylactic effect upon even short-term discontinuation, and therefore should not be used alone in patients with contraindications to heparin.

On closing, I would like to summarize my comments and reemphasize that this is a carefully done study which deserves our attention. Venous thromboembolism is still an unknown entity, and practices are driven predominantly by anecdotal experience rather than scientific evidence. The real conclusion of this study should be that in an inadequately powered sample of morbidly obese patients, there is no evidence that the type of bariatric operation influences a disease with very low incidence, venous thromboembolism. While making an important contribution by this conclusion, the study serves to remind us that the risk of deep venous thrombosis and pulmonary embolism may not be as high as we think. One clinically insignificant in-hospital event, a posterior tibial venous thrombosis, does not justify too much worry. This study, like every good study, stimulates more questions than it answers and prompts us to think that we do not know what we think we know.

**Donald B. McConnell, MD, Portland, Ore:** This is a very interesting paper and very provocative. It's an important study with implications to other fields in surgery since the incidence of obesity is so high in our population. I have had one postoperative pulmonary embolism in over 300 patients primarily with open bariatric surgery. I have had one pulmonary embolism death 5 months after surgery. So I would argue that the incidence of pulmonary embolism and fatal pulmonary embolism is relatively low. However, this has been in the setting of using routine sequential compression devices and prophylactic heparin and/or low molecular weight heparin postoperatively and 1 week postdischarge home.

I have a couple of questions. Was there any screening done preoperatively with regard to the hypercoagulable state? There is a significant incidence of factor V Leiden in the population, and this might have influenced the DVT rate. Do you think that super-obese patients are at greater risk since they tend to be a little bit more difficult to get out of bed postoperatively and they are less mobile than their lighter morbidly obese patients?

**Ronald G. Latimer, MD, Santa Barbara, Calif:** Did the anesthesia management of these patients differ in any way? Could the use of muscle relaxants or other anesthetic agents or solutions produce the results that they found, and were the open patients done in the supine position and the laparoscopic patients done in the lithotomy position, and do the authors think that had any bearing on the results?

**Jan K. Horn, MD, San Francisco, Calif:** I also was intrigued by this study and congratulate the authors. I was wondering whether there was a difference in the postoperative recovery periods and whether those with laparoscopic procedures were more rapidly mobilized. Were they out of the hospital more quickly by virtue of their different approach, or was there no difference in the postoperative time of recovery?

**Dr Owings:** Dr Velmahos, thank you very much for your insightful comments and your questions. Regarding the first, is thromboembolism really important in this population? I would answer yes. It's the second most common cause of death in the

obese patient undergoing a bariatric procedure. Certainly death is important, however infrequently it occurs, especially if it is due to a recurring theme. In our study we saw an approximately 3% incidence of pulmonary embolism in the open group. Although our total population was small, I would still argue that that is a significant finding.

Why didn't we see thromboembolism more frequently? I think that the answer to that may be 2-fold: (1) It may be as you suggest somewhat less common than as otherwise thought, and (2) it may possibly be that duplex screening, this was routine screening as opposed to based on clinical diagnosis, in the morbidly obese patient may be very insensitive due to their body habitus and the constraints of the device. So it may be a combination of the two issues.

Your next question was with regard to the power required in order to show a clinical difference in this study, and our power analysis suggested that we would need approximately 300 patients per arm to demonstrate a significant difference in DVT on the basis of our preliminary findings. That was why our true and prospective primary end points were in fact biochemical markers rather than clinical outcomes, just due to the reality of the population size required to show a clinical difference.

Your third question was with regard to using SCDs and the TED hose as opposed to heparin, specifically subcutaneously administered heparin as a prophylactic method. You answered your own question later in your comments, which is to say that it is really only based on scientifically performed studies that are prospective and randomized that we know the right method to deal with issues. There are no prospective randomized trials demonstrating efficacy in this patient population of one method of thromboembolism prophylaxis over the other. We chose to use the sequential compression device stockings for several reasons, in part because there is no demonstrated benefit of one method, that is, those over heparin or vice versa, and also heparin has an effect on the biochemical markers. Further, since heparin has its effect through antithrombin, our suspicion being that antithrombin might be depleted, we really wouldn't have a good idea of how much heparin to give without first laying out the basis for knowing what happened to the antithrombin, so we are still working on that question and trying to derive a scientific answer.

Dr McConnell, thank you for your question. Was screening done preoperatively? The answer is yes, it was. It was done both as far as clinical screening so all patients underwent duplex examination prior to operation, and all patients underwent all of the biochemical markers prior to operation to get a baseline measure. We also looked for the factor V Leiden mutation, but in our population that's vanishingly rare at about 1%, so that was not a significant factor.

Dr Latimer, thank you. Were there differences in the anesthesia? The answer is no. The anesthesia technique was the same for both groups. With regard to the position, the position was in both cases supine.

Dr Horn, thank you for your question. Was there a difference in postoperative mobilization? No, all patients were mobilized at postoperative day 1, and the one interesting finding was that the patients with the laparoscopic approach were discharged at day 3 rather than day 5 so they may have been slightly more mobile in that regard.

Again, in summing up our conclusions on this paper, we expected honestly to see that there might be a difference between the biochemical markers in laparoscopic being potentially more favorable than those in the open. We were surprised to find that the differences were very small and the salient point that we bring from that is that it is important to remember that both of these patient groups are at risk for thromboembolism. If it is a fatal pulmonary embolism, that is certainly significant, however rare, and efforts should be taken to prevent it.