

ORIGINAL RESEARCH ARTICLE

Efficacy and safety of short-term (3 days) enoxaparin in preventing venous thromboembolism after gastric cancer surgery: A single-center, prospective cohort study

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Running title: Three days of enoxaparin for VTE prevention

Abstract

Background: Pharmacologic prophylaxis such as enoxaparin for venous thromboembolism (VTE) is rarely used in Japan, even following abdominal cancer surgery, for which it is recommended in relevant guidelines (at least 7 days of use) along with mechanical prophylaxis with intermittent pneumatic compression. Reasons for enoxaparin's unpopularity include concerns over postoperative bleeding and its inconvenience in clinical practice. Here, we conducted a prospective clinical study of short-term (3 days) use of enoxaparin, which is considered to minimally impact postoperative management without increasing bleeding risk.

Methods: Gastric cancer patients who underwent gastrectomy received enoxaparin for 3 days from postoperative day (POD) 1 to 4. The primary endpoint was the incidence of deep vein thrombosis (DVT), which was examined primarily via Doppler ultrasonography of the lower limbs between POD 8 and 14. The planned sample size was 70, which was calculated based on an estimated incidence rate of 9% and an upper limit of incidence rate of 20%, with alpha of 0.05 and beta of 0.2.

Results: A total of 70 gastric cancer patients were enrolled, and ultimately, 68 patients received the protocol intervention and DVT evaluation. Sixty-seven patients completed 6 enoxaparin injections, but 1 patient did not complete the course due to abdominal bleeding after initiation. The incidence of DVT was 4.4% (3/68), and the 95% upper confidence interval was 12.2%, lower than the 20% threshold we set as the upper limit of DVT incidence. DVT was detected only in the peripheral veins of the lower extremities in all 3 affected patients. The incidence of bleeding-related complications, which were not severe, was 1.5% (1/68).

Conclusions: Short-term (3 days) use of enoxaparin was shown to be effective and safe

for VTE prophylaxis, comparable to regular use (at least 7 days), in postoperative management of gastric cancer surgery.

Keywords

Venous thromboembolism; Prevention; Enoxaparin; Short-term use; Gastric cancer surgery

Introduction

Venous thromboembolism (VTE), consisting of pulmonary thromboembolism (PE) and deep vein thrombosis (DVT), is a major postoperative complication. PE is a particularly critical complication in which patients can die suddenly; and therefore, measures to prevent VTE are indispensable in the perioperative period. Based on this background, guidelines for VTE prevention first established in Japan in 2004 and later revised in 2017 classify the risk of VTE into 4 categories, with recommended prevention strategies proposed for each category [1]. Most abdominal surgeries for cancer patients are included in the high-risk group, for which the guidelines recommend either mechanical prophylaxis with intermittent pneumatic compression (IPC) or pharmacologic prophylaxis. Although prophylaxis with IPC has steadily spread across the country and reduced the incidence of perioperative VTE to some degree, approximately 20% (17.6-23.7%) of patients who underwent abdominal surgery in prospective clinical studies were still diagnosed with DVT (which could cause PE) even after mechanical prophylaxis with IPC [2, 3, 4]. In addition, the mortality rate associated with perioperative PE has not decreased significantly since the first guideline was published [5], and therefore, pharmacologic prophylaxis is increasingly considered necessary for patients who undergo major abdominal surgery, unless they have active bleeding or high bleeding risk.

Detailed information about pharmacologic prophylaxis for VTE in cancer patients is described in the guidelines from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO), in which pharmacologic prophylaxis with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) products such as enoxaparin for at least 7-10 days is recommended [6,

7]. In the new Japanese guideline revised in 2017, prophylactic use of enoxaparin (LMWH) and fondaparinux (a selective factor Xa inhibitor) is recommended for patients classified in the high- or very-high-risk groups, although the recommended duration of administration is not mentioned. In the ENOXACAN study, which was the first randomized clinical trial comparing the prophylactic use of enoxaparin with UFH in cancer patients who underwent abdominal or pelvic surgery, the frequency of VTE was lower in the enoxaparin group (14.7%) than the UFH group (18.2%), but there were no differences in bleeding events or other complications [8]. In a meta-analysis comparing LMWH and UFH, LMWH seemed to be as effective and safe as UHF [9]. Amid the growing need for pharmacologic prophylaxis for VTE in Japan, a multicenter randomized clinical trial was conducted in patients undergoing curative abdominal or pelvic surgery, in which use of enoxaparin for 14 days reduced the incidence of VTE to only 1.2%, compared to 19.4% VTE incidence with IPC [4].

Despite these impressive results, prophylactic use of LMWH remains unpopular in abdominal surgery in Japan due to concerns over postoperative bleeding. In addition, if enoxaparin is used for at least 7-10 days after surgery, as recommended in the ASCO and ESMO guidelines, any abdominal drain or an epidural catheter present for pain control must be removed during enoxaparin use, which could increase the risk for bleeding-related complications caused by removal of the drain or epidural catheter. If short-term (3 days) use of enoxaparin is as effective and safe as regular use, the abdominal drain or epidural catheter could be removed after completion of enoxaparin use, thus reducing the risk of bleeding-related complications and making postoperative management easier compared with regular use of enoxaparin. In the present study, we conducted a prospective clinical trial to evaluate the efficacy and safety of short-term (3

days) use of enoxaparin for VTE prophylaxis in patients undergoing gastric cancer surgery.

Materials and Methods

Study design and participants

This study was designed as a single-arm, non-comparative, open label, single-center, prospective clinical trial. The design of the trial was previously reported [10].

The inclusion criteria were as follows: age ≥ 40 years and histologically diagnosed with gastric cancer.

The exclusion criteria were as follows: history of VTE, history of allergic reaction to heparin or heparinoid (including LMWH), active bleeding (except for bleeding from gastric cancer planned to be resected), acute bacterial endocarditis, serious renal disorder (creatinine clearance [Ccr] < 30 mL/min), history of heparin-induced thrombocytopenia, or otherwise judged by the investigator as unsuitable for enrollment.

All patients who met the inclusion/exclusion criteria were invited for screening, and written informed consent was obtained from the patient by an investigator before the intervention.

Intervention

Prophylaxis for VTE was performed using two IPC and enoxaparin regimens. IPC use was started during the operation and continued until patients were able to walk adequately after surgery. Enoxaparin (20 mg, 2000 units) was subcutaneously injected twice a day for 3 days, beginning 36 hours after surgery (in the evening on

postoperative day [POD] 1), and continued until the morning of POD 4. Delay of initiation of enoxaparin due to concern over bleeding-related complications was permitted at the physician's discretion; however, enoxaparin was injected 6 times in total in principle. Enoxaparin was used once a day for 3 days for patients with Ccr of 30-50 mL/min. Any abdominal drain or epidural catheter was removed at least 10-12 h after the final injection of enoxaparin.

Endpoints

The primary endpoint was the incidence of DVT, which was evaluated via Doppler ultrasonography (US) of the lower limbs or a contrast-enhanced computed tomography (CT) between POD 8 and 14.

The secondary endpoint was the incidence of bleeding-related adverse events, which were classified into two groups: major and minor bleeding events. Bleeding was classified as major if the event met at least one of the following criteria: resulted in death; was clinically overt (required transfusion of ≥ 2 units [400 mL] of packed red blood cells or whole blood, or decreased hemoglobin levels by at least 2 g/dL); was retroperitoneal, intracranial, or intraocular; or resulted in serious or life-threatening clinical events (e.g., myocardial infarction, cerebrovascular accident) or required surgical or medical intervention to control the event. Bleeding was classified as minor if the event did not meet any of the major bleeding criteria but resulted in one of the following: epistaxis lasting ≥ 5 min or epistaxis that required treatment; ecchymosis or hematoma ≥ 5 cm in diameter; hematuria not associated with intubation of a urinary catheter; gastrointestinal hemorrhage not related to intubation or nasogastric tube placement; and subconjunctival hemorrhage requiring treatment discontinuation. The

safety of the protocol was also evaluated based on the incidence of adverse events not related to bleeding.

All patients were followed-up until a regular check-up at approximately 1 month after surgery. All adverse events were recorded according to the Clavien-Dindo (CD) classification (ver. 2.0) [11]. Information regarding each patient's background, surgery, pathology, and pre- and postoperative laboratory data was also obtained from the medical record.

Statistical methods

The estimated incidence rate of VTE with mechanical prophylaxis with IPC is approximately 18% based on the incidence rate in 2 phase III clinical studies conducted in Japanese cancer patients undergoing abdominal surgery [3, 4]. Given that a 50% reduction in VTE risk results from use of enoxaparin for at least 7 days according to a clinical study of Japanese patients who underwent total hip or knee replacement [12], the estimated risk of a VTE event would be 9% with at least 7 days of enoxaparin use. If it is assumed that 3 days of enoxaparin use would have a similar prophylactic effect as use for at least 7 days, the estimated event risk would also be 9% with 3 days of enoxaparin use.

Sample size was calculated based on an estimated incidence rate of 9% and an upper incidence rate limit of 20%, with alpha of 0.05 and beta of 0.2, according to Simon's two-stage design [13]. The study design therefore called for 62 evaluable patients to be entered into the first stage of the study. If ≤ 8 incidents were observed among these initial patients, an additional 4 patients were planned to be enrolled. At the time of the final analyses, ≤ 8 incidents among 66 patients indicated that 3 days of

enoxaparin use merited further investigation. It was planned to recruit a total of 70 patients for this study in consideration that some patients would be unevaluable. An interim analysis was planned after the first 31 patients, half of the patients in the first stage, in order to re-evaluate the sample size.

Statistical analyses were conducted using JMP software (SAS Institute, Cary, NC, USA). The Wilcoxon signed-rank test was used for non-parametric analysis of D-dimer formation. A *p* value <0.05 was considered significant.

The work has been reported in line with the STROCSS criteria [14].

Results

Patient characteristics

From April 2016 to April 2017, a total of 70 patients were registered in the study based on the inclusion/exclusion criteria. Sixty-eight patients received the protocol intervention and DVT evaluation, except for 2 patients who investigators determined should not receive enoxaparin after surgery due to concerns over bleeding (Fig. 1).

Table 1 shows details of the characteristics of all 68 patients. The average age was 68.5 years, and the male-to-female ratio was approximately 7:3. The average body mass index was 22.9 kg/m². Fifteen patients (22%) who received neoadjuvant chemotherapy were included. Regarding surgery, a laparoscopic approach was selected in 61 patients (90%). Distal gastrectomy was the most frequent procedure, performed in 51 patients (75%), and total gastrectomy was performed in 14 patients (21%). D1+ and D2 lymph node dissection were performed in 34 patients (50%) and 30 patients (44%), respectively. Billroth-I reconstruction was the most common reconstruction procedure, performed in 38 patients (56%), followed by Roux-en-Y reconstruction in 25 patients

(37%). The median operation time was 314 min, and the median blood loss was 80 mL. Curative resection was achieved in 66 patients (97%). Tumors were classified based on the Japanese Classification of Gastric Carcinoma, 3rd English edition [15], with differentiated type and undifferentiated type accounting for 53% and 46%, respectively. A total of 45 patients (66%) were classified as pathological T1 (pT1) and 47 patients (69%) as pathological N0 (pN0); in total, 47 patients (69%) were diagnosed with pathological stage IA (pStage IA).

Postoperative course

Table 2 summarizes the postoperative course. Sixty-seven patients (99%) completed 6 enoxaparin injections, but 1 patient had abdominal bleeding after initiation of enoxaparin. The median duration of IPC use was 1 day after surgery, and the median time to achievement of adequate walking was also 1 day after surgery. The median period until removal of any epidural catheter was 5 days. Whereas 63 patients (94%) had a scheduled removal of an epidural catheter, the remaining 5 patients experienced accidental removal; however, no bleeding events occurred. The number of abdominal drains was one in 59 patients (87%) and two in 9 patients (13%). The median period until removal of the final abdominal drain was 5 days, and all abdominal drains were removed on schedule.

After a significant increase on POD 1, D-dimer decreased significantly by POD 3 (or 4) ($p=0.0003$) in response to enoxaparin use and then increased again on POD 7 after termination of enoxaparin (Fig. 2). When the natural course of D-dimer after gastrectomy was monitored in a different cohort, the level changed similarly, although there was no significant difference between POD 1 and 3 (or 4) ($p=0.4258$).

(Supplementary Fig. S1).

Incidence of DVT

DVT was detected in 3 patients (4.4%) by Doppler US of the lower limbs performed between POD 8 and 14 (Fig. 3). The 95% upper confidence interval (CI) was 12.2%, which was lower than the 20% threshold we set as the upper limit of DVT incidence rate, meaning that short-term (3 days) use of enoxaparin was statistically comparable to regular use (at least 7 days) in terms of prophylactic effect on DVT. Table 3 shows detailed information regarding patients who had DVT. DVT was detected only in the calf region, such as the peroneal vein or soleal vein, in all 3 affected patients and not in the femoral or iliac regions. Two patients (Cases 2 and 3) were females who had neoadjuvant chemotherapy. The patient in Case 2 had some additional risk of advanced-stage DVT (pStage III) due to gastric cancer and suffered from postoperative complications, although her D-dimer level was not high until POD 7. The patient in Case 3 underwent paraaortic lymph node dissection, which is considered to increase the risk of DVT. No specific DVT risk factors were found in the patient in Case 1.

Incidence of bleeding-related and other adverse events

Bleeding-related complications classified as minor bleeding were observed in 1 patient (1.5%) (Fig. 4). This case involved intraabdominal bleeding (CD grade I) that began just after initiation of enoxaparin injections, resulting in hemostasis following interruption of enoxaparin. Other postoperative complications included four abdominal abscesses, three anastomotic leakages, and two pancreatic fistulas (Supplementary Table 1).

Discussion

The association between cancer and thrombosis, first reported by Trousseau in 1865, is currently known as Trousseau syndrome. Cancer-associated thrombosis is now widely recognized as a major complication in cancer patients, with a cancer-associated VTE incidence as high as 27% in the general population [16]. The 90-day cumulative incidence of postoperative PE is surprisingly high, at 18.6% (217/1,168), including incidental findings in postoperative routine diagnostic imaging, regardless of symptoms [17]. The risk of VTE in cancer patients undergoing surgery is reportedly 3.7 times higher than that in non-cancer patients [18], which suggests that proper prophylaxis for VTE in the perioperative period is important, especially for cancer surgical patients.

We decided to primarily use lower-limb US in this study to evaluate thromboembolism because it is less invasive for patients, in contrast to many other clinical studies in which venography or pulmonary scintigraphy were used [4, 8]. Although evaluation only by lower-limb US increased the possibility of missing asymptomatic thromboembolisms occurring in other areas of the body, we thought that it would be acceptable because PE and DVT are thought to be caused by the same pathologic condition and the incidence of PE concurrent with DVT is reportedly over 80% [19]. In the present study, we had no patients suspected of having symptomatic PE but 3 patients with DVT, all identified in peripheral veins of the lower extremities. The question arises as to whether these DVTs were new-onset or pre-existing, but this remains unknown because we did not perform additional examinations for VTE before surgery so that the study would remain as close as to clinical practice as possible, although we did exclude patients who had a history of VTE.

Assessments of D-dimer level for VTE screening are generally characterized by high sensitivity and low specificity, and the significance of D-dimer testing for VTE

screening in the perioperative period is considered low because D-dimer levels also increase due to aging, cancer, and surgery itself [20]. In terms of aging, the age-adjusted D-dimer cutoff, defined as $\text{age} \times 10$ ($\mu\text{g/L}$), is reportedly useful to rule-out PE in patients over 50 years old [21]. In the present study, no trends in D-dimer changes were observed in the 3 patients with DVT. In terms of the natural kinetics of D-dimer after gastrectomy, the D-dimer level significantly increased on POD 1, remained at a similar level until POD 3 or 4, and increased again on POD 7, similar to a previous report [22]. In patients treated with 3 days of enoxaparin, D-dimer level on POD 3 or 4 was significantly lower than the level on POD 1, in contrast to the natural kinetics after surgery, which could be relevant for effective VTE prevention.

Although this study provided some meaningful evidence in clinical practice, it has several limitations. First, this was a single-center study with a limited number of cases, and a comparative study would be necessary to provide a higher level of evidence. Second, patients were limited to those undergoing gastrectomy for gastric cancer in order to decrease any effects on VTE incidence due to differences between surgical procedures and type of cancer. However, as the incidence of VTE is higher in surgeries for cancers in the pelvic area, such as rectal cancer, additional studies of rectal cancer surgery may be meaningful. Third, we enrolled all gastric cancer patients who planned to undergo surgery without any risk classifications. Although most abdominal surgeries for cancer are categorized as “high risk” or “very high risk” in terms of VTE incidence based on the guidelines, actual VTE risk is thought to vary widely with tumor aggressiveness and patient condition. As such, application of risk classification approaches such as the Wells score may be useful for selecting patients who need more-intensive VTE prophylaxis [23].

In the present study, we demonstrated the effectiveness and safety of short-term (3 days) use of enoxaparin for VTE prophylaxis after gastrectomy for gastric cancer. This prophylaxis is also meaningful in terms of being compatible with current enhanced recovery after surgery postoperative management protocols, as 3 days of enoxaparin use between POD 1 and 4 does not necessitate rescheduling the removal of epidural catheters or abdominal drains. As 3 days of enoxaparin use is clinically and practically useful for VTE prophylaxis, hopefully it will become popular in postoperative management after abdominal surgery to reduce the number of patients who suffer from severe PE, which could potentially lead to worst-case scenarios.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

- [1] Nakamura M. **[Guidelines for prevention of venous thromboembolism in the West and Japan]**. Nihon Rinsho, 61 (10) (2003), pp. 1811-1817
- [2] Sakon M, Maehara Y, Yoshikawa H, Akaza H. **Incidence of venous thromboembolism following major abdominal surgery: a multi-center, prospective epidemiological study in Japan**. J Thromb Haemost, 4 (3) (2006), pp. 581-586
- [3] Hata T, Yasui M, Murata K, Okuyama M, Ohue M, Ikeda M, Ueshima S, Kitani K, Hasegawa J, Tamagawa H, Fujii M, Ohkawa A, Kato T, Morita S, Fukuzaki T, Mizushima T, Sekimoto M, Nezu R, Doki Y, Mori M, Multi-Center Clinical Study Group of Osaka CCTG. **Safety of fondaparinux to prevent venous thromboembolism in Japanese patients undergoing colorectal cancer surgery: a multicenter study**. Surg Today, 44 (11) (2014), pp. 2116-2123
- [4] Sakon M, Kobayashi T, Shimazui T. **Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study**. Thromb Res, 125 (3) (2010), pp. e65-70
- [5] Seo N. **[Up-to-date medical care for perioperative venous thromboembolism in Japan--standardization of care for perioperative venous thromboembolism in Japan: preface]**. Masui, 56 (7) (2007), pp. 758-759
- [6] Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JJ, Wong SL, Balaban EP, Flowers CR, Francis CW, Gates LE, Kakkar AK, Levine MN, Liebman HA, Tempero MA, Lyman GH, Falanga A. **Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer:**

- ASCO Clinical Practice Guideline Update.** J Clin Oncol, (2019), pp. JCO1901461
- [7] Mandala M, Falanga A, Roila F, Group EGW. **Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines.** Ann Oncol, 22 Suppl 6 (2011), pp. vi85-92
- [8] **Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. ENOXACAN Study Group.** Br J Surg, 84 (8) (1997), pp. 1099-1103
- [9] Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. **Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery.** Br J Surg, 88 (7) (2001), pp. 913-930
- [10] Kuroda S, Kikuchi S, Nishizaki M, Kagawa S, Hinotsu S, Fujiwara T. **A Phase II Clinical Trial of the Efficacy and Safety of Short-term (3 days) Enoxaparin for the Prevention of Venous Thromboembolism after Gastric Cancer Surgery.** Acta Med Okayama, 70 (5) (2016), pp. 401-404
- [11] Dindo D, Demartines N, Clavien PA. **Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey.** Ann Surg, 240 (2) (2004), pp. 205-213
- [12] Fuji T, Ochi T, Niwa S, Fujita S. **Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin.** J Orthop Sci, 13 (5) (2008), pp. 442-451

- [13] Simon R. **Optimal two-stage designs for phase II clinical trials.** Control Clin Trials, 10 (1) (1989), pp. 1-10
- [14] Agha R, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C, Mathew G, Group S. **STROCCS 2019 Guideline: Strengthening the reporting of cohort studies in surgery.** Int J Surg, 72 (2019), pp. 156-165
- [15] Japanese Gastric Cancer A. **Japanese classification of gastric carcinoma: 3rd English edition.** Gastric Cancer, 14 (2) (2011), pp. 101-112
- [16] Nakamura M, Miyata T, Ozeki Y, Takayama M, Komori K, Yamada N, Origasa H, Satokawa H, Maeda H, Tanabe N, Unno N, Shibuya T, Tanemoto K, Kondo K, Kojima T. **Current venous thromboembolism management and outcomes in Japan.** Circ J, 78 (3) (2014), pp. 708-717
- [17] Matsuoka Y, Morimatsu H. **Incidence Rates of Postoperative Pulmonary Embolisms in Symptomatic and Asymptomatic Patients, Detected by Diagnostic Images- A Single-Center Retrospective Study.** Circ J, 83 (2) (2019), pp. 432-440
- [18] Kakkar AK, Haas S, Wolf H, Encke A. **Evaluation of perioperative fatal pulmonary embolism and death in cancer surgical patients: the MC-4 cancer substudy.** Thromb Haemost, 94 (4) (2005), pp. 867-871
- [19] Palareti G, Antonucci E, Dentali F, Mastroiacovo D, Mumoli N, Pengo V, Poli D, Testa S, Pujatti PL, Menditto VG, Imberti D, Fontanella A. **Patients with isolated pulmonary embolism in comparison to those with deep venous thrombosis. Differences in characteristics and clinical evolution.** Eur J Intern Med, 69 (2019), pp. 64-70
- [20] Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, Biel RK, Bharadia

- V, Kalra NK. **D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review.** Ann Intern Med, 140 (8) (2004), pp. 589-602
- [21] Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuyssen A, Rutschmann OT, Sanchez O, Jaffrelot M, Trinh-Duc A, Le Gall C, Moustafa F, Principe A, Van Houten AA, Ten Wolde M, Douma RA, Hazelaar G, Erkens PM, Van Kralingen KW, Grootenboers MJ, Durian MF, Cheung YW, Meyer G, Bounameaux H, Huisman MV, Kamphuisen PW, Le Gal G. **Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study.** JAMA, 311 (11) (2014), pp. 1117-1124
- [22] Dindo D, Breitenstein S, Hahnloser D, Seifert B, Yakarisik S, Asmis LM, Muller MK, Clavien PA. **Kinetics of D-dimer after general surgery.** Blood Coagul Fibrinolysis, 20 (5) (2009), pp. 347-352
- [23] Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, Turpie AG, Bormanis J, Weitz J, Chamberlain M, Bowie D, Barnes D, Hirsh J. **Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer.** Thromb Haemost, 83 (3) (2000), pp. 416-420

Figure Legends

Figure 1. CONSORT diagram.

Figure 2. Change in D-dimer level after gastrectomy with 3 days of enoxaparin use.

Figure 3. Incidence of DVT.

Figure 4. Incidence of bleeding-related adverse events.