Bull Yamaguchi Med Sch 62(3-4):59-65, 2015

Duration of Prophylaxis against Venous Thromboembolism with Low Molecular Weight Heparin (Enoxaparin) after Surgery for Abdominal and Esophageal Cancer: A Single Institution, Prospective, Randomized Trial in Japan

Shunsaku Katsura, Tadahiko Enoki, Naruji Kugimiya, Yoshihiro Takemoto, Kazuhito Oka, Eijiro Harada and Kimikazu Hamano

Department of Surgery and Clinical Science, Yamaguchi University Graduate School of Medicine,1-1-1, Minamikogushi, Ube, Yamaguchi 755-8505, Japan
(Received September 16, 2015, accepted November 10, 2015)
Correspondence to Shunsaku Katsura, M. D. Email: shunsaku@yamaguchi-u.ac.jp

Abstract **Background:** The optimal duration of thromboprophylaxis after surgery for cancer has not been clearly defined in Japan. The aim of this prospective study was to evaluate the efficacy and safety of 3 days of thromboprophylaxis in comparison to 10 days of thromboprophylaxis with low molecular weight heparin (enoxaparin) in patients undergoing elective surgery for abdominal and esophageal cancer.
Methods: The study population included patients who were over 40 years of age and who were planning to undergo elective surgery for abdominal and esophageal cancer. 101 patients were randomly assigned to the short thromboprophylaxis (3 days) and long thromboprophylaxis (10 days) groups. Finally, after applying the exclusion criteria, we evaluated 45 patients in each group. The primary efficiency endpoint was the incidence of venous thromboembolism between day 11 and the day of discharge.
Results: The incidence rates of distal deep vein thrombosis (DVT) after surgery were 6.7% and 8.9% in the short and long thromboprophylaxis groups, respectively. (p = 0.50). There was no significant difference.
Conclusions: We concluded that if pharmacological thromboprophylaxis with enoxaparin was combined with mechanical methods in patients undergoing elective surgery for cancer, then the adequate duration of routine thromboprophylaxis with enoxaparin was only 3 days.

Key words: low molecular weight heparin, enoxaparin, venous thromboembolism, surgery

Introduction

Patients undergoing major abdominal surgery for malignancies are at a high risk of venous thromboembolism (VTE). Patients with malignant disease have hemostatic abnormalities and abdominal surgery for cancer may lead to a hypercoagulable state in which the patient is predisposed to the development of thrombosis.[1] The incidence of VTE in Asian countries, including Japan, has been suggested to be much lower than that in Europe and North America.[2] However, recent investigations have found the incidence of VTE in Japan to be comparable with that in Western countries.[3] Because pulmonary thromboembolisms (PTEs), which are caused by VTE, develop suddenly and are associated with mortality, the importance of prevention has been recognized.[4] Physicians agree upon the need for perioperative antithrombotic prophylaxis, and several methods to reduce the incidence

of VTE have been implemented.[5,6] Low molecular weight heparin (enoxaparin) is a relatively new drug, which was approved for sale in Japan in 2009. The optimal duration of thromboprophylaxis after surgery for cancer has not been clearly defined in Japanese patients. On the other hand, extended-duration pharmacologic prophylaxis is recommended for patients undergoing surgery for cancer in Europe and North America.[7,8] The aim of this prospective study was to evaluate the efficacy and safety 3 days of thromboprophylaxis with enoxaparin in comparison to 10 days of thromboprophylaxis with enoxaparin in patients who were undergoing elective surgery for abdominal and esophageal cancer.

Methods

This study was designed as a prospective, randomized trial in the surgical department of a university hospital. The eligible patients were ≥40 years of age, and were scheduled to undergo elective and curative surgery for a malignant abdominal tumor (including esophageal cancer) under general anesthesia. The exclusion criteria were as follows: severe renal insufficiency (creatinine clearance < 30ml/min), hypersensitivity to heparin or low molecular weight heparin (LMWH), presence or a history of venous thromboembolism, hemorrhagic diathesis, cerebral and gastrointestinal hemorrhage, or having received heparin, LMWH or oral anticoagulation treatment before surgery. All patients received standard thromboprophylaxis with enoxaparin (2,000 IU subcutaneously every 12 hours) from the day after surgery and they wore graduated compression stockings (GCS) and underwent intermittent pneumatic compression (IPC) during intraoperative period. They were randomly assigned to receive thromboprophylaxis with enoxaparin for 3 days (short thromboprophylaxis group) or 10 days (long thromboprophylaxis group) after the scheduled abdominal surgery. For the allocation of the participants, a computer-generated list of random numbers was used. Venous ultrasonography of the lower limbs was routinely performed after surgery from day 11 until the day of discharge in order to detect thrombosis.

The effects of short and long thromboprophylaxis were evaluated by comparing the number of patients with thromboembolic events in the two groups. Asymptomatic DVT was detected by routine ultrasonography of the lower limbs after surgery. Cases of symptomatic DVT and PTE were assessed by the medical staff. If DVT or PTE was suspected based on clinical observations, then ultrasonography of the lower limbs and cardiopulmonary CT were immediately performed. Patients who were diagnosed with DVT or PTE received the appropriate anticoagulant treatment. The hemoglobin and platelet counts were measured before surgery and on days 1, 3, 5, 7, 10 and 14 or until discharge. We also measured activated partial thromboplastin time (APTT) for the purpose of monitoring the effects of enoxaparin treatment, and D-dimer which was a marker of coagulation and fibrinolysis. The occurrence of hemorrhage was safety end-point in this study. The administration of this trial medication was ceased and appropriate treatment was provided if a patient experienced bleeding complications after surgery; all such cases were recorded. All patients were followed up for at least 1 month after surgery. VTE and other adverse events, including bleeding episodes, were recorded.

The incidence of VTE after abdominal surgery was estimated to be 15-20%. It was hypothesized that the frequency of thromboembolism in the short thromboprophylaxis group would be 18%, and it was considered clinically important to reduce this frequency to 5% in the long thromboprophylaxis group. In order to detect a 13% decrease with a type I error of 5% and a power of 80% in a two-sided test, 50 patients were needed in each groups. The data were compared between each group with the use of either a chi-squared test or Fisher's exact test. The study was performed according to the ethical principles stated in the Declaration of Helsinki (1964). The protocol was approved by the institutional review boards of our hospital. Written informed consent was obtained from all of the participants.

Results

A total of 106 patients were recruited between August 2011 and March 2014; 101 patients entered the randomized section of this study (Fig. 1). Of these, 50 and 51 patients were randomly allocated to the short and long thromboprophylaxis groups, respectively. Eleven patients were excluded from the study: 6 patients were too ill to continue the study after surgery, and who underwent treatment with prohibited concomitant medications; 2 who did not receive ultrasonography of the lower limbs after surgery; 1 patient in the long thromboprophylaxis group who refused the medication due to the pain of injection; 2 patients who experienced bleeding events that resulted in the discontinuation of enoxaparin in the short thromboprophylaxis group (one case of bleeding at a site of surgical anastomosis, and one case of the subcutaneous bleeding). The bleeding events of both of the two patients who were excluded for bleeding occurred on day 2, thus the duration of the thromboprophylactic treatment was of no relevance and they were excluded from further analysis. The final study population included 90 patients: 45 who received short thromboprophylaxis with enoxaparin for 3 days and 45 who received long thromboprophylaxis for 10 days. The patients in the two groups were well matched for age, sex, BMI, smoking history, and medication (Table 1). The types of surgical procedures and positions in the two groups were similar. Laparoscopic surgery was the most common procedure, consequently the open leg horizontal position for laparoscopic surgery was the most common surgical position. The durations of surgery and immobility were also similar in the two groups. The incidence rates of intraoperative bleeding and surgical complications did not differ between the two groups. All of the patients received intraoperative mechanical

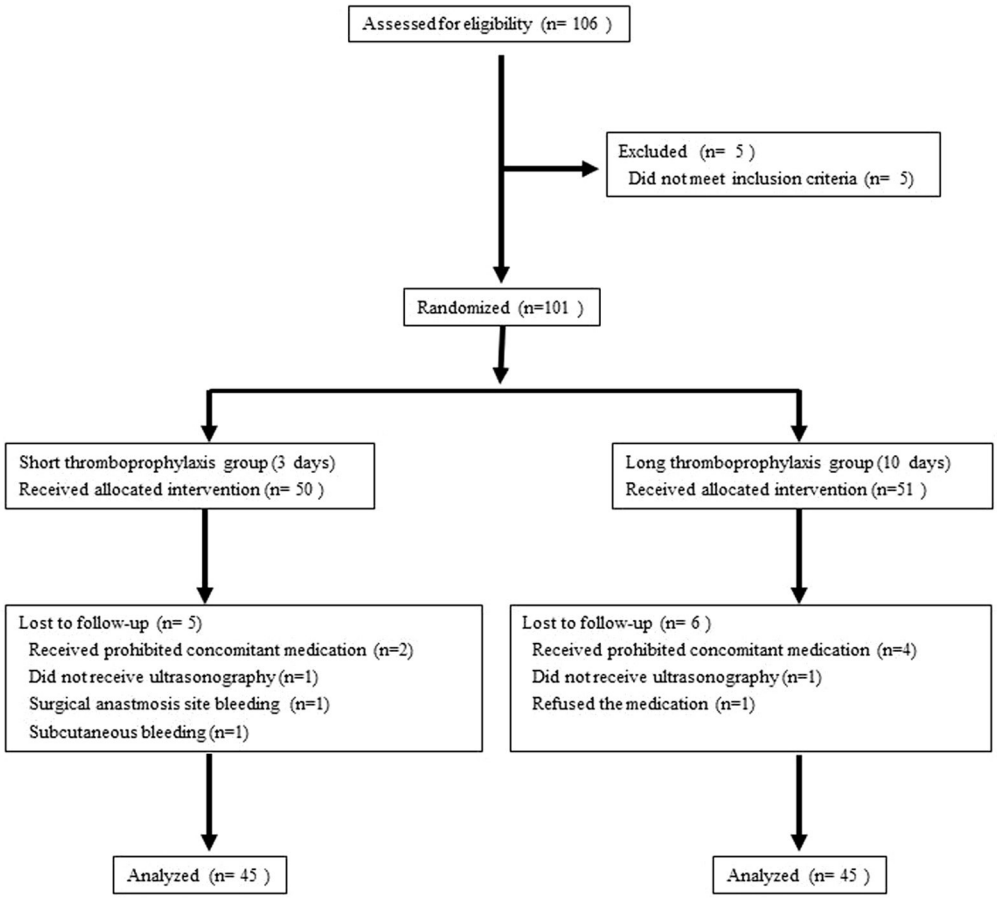

Fig. 1 A flow chart of participants in each stage of the randomized trial

Table 1 The background characteristics of the evaluable patients

	Short thromboprophylaxis group (n = 45)	Long thromboprophylaxis group (n = 45)	*P* value
Age, year	67.6 ± 10.0	68.7 ± 9.1	0.71
Male / Female	34 / 11	33 / 12	0.81
Body Mass Index, kg/m^2	22.9 ± 3.5	22.3 ± 3.7	0.43
Smoking, n (%)	27 (60.0)	29 (64.4)	0.66
Medication			
Hypertention, n (%)	25 (55.9)	21 (50.0)	0.40
Dyslipidemia, n (%)	10 (22.2)	5 (11.1)	0.16
Diabetes, n (%)	7 (15.6)	6 (13.3)	0.76
Type of surgery			
Laparotomy, n (%)	5 (11.1)	10 (22.2)	
Laparoscopic surgery, n (%)	37 (82.2)	34 (75.6)	0.24
Laparoscopic & thoracoscopic surgery, n (%)	3 (6.7)	1 (2.2)	
Position			
Supine, n (%)	7 (15.5)	12 (26.7)	
Lithotomy, n (%)	9 (20.0)	11 (24.4)	0.38
Open leg horizontal, n (%)	26 (57.8)	21 (46.7)	
Lateral & open leg horizontal, n (%)	3 (6.7)	1 (2.2)	
Duration of surgery, min	338 ± 117	324 ± 111	0.56
Intraoperative bleeding, g	308.7 ± 379.5	539.1 ± 711.1	0.06
Surgical complications, n (%)			
No complication	31 (66.7)	23 (51.1)	
Grade 1	4 (8.9)	7 (15.5)	
Grade 2	7 (15.5)	11 (24.5)	
Grade 3a	4 (8.9)	4 (8.9)	0.45
Grade 3b	0 (0.0)	0 (0.0)	
Grade 4	0 (0.0)	0 (0.0)	
Grade 5	0 (0.0)	0 (0.0)	
Duration of immobility, days	2.5 ± 1.5	2.5 ± 1.2	0.80
Mechanical thromboprophylaxis, n (%)			
intermittent pneumatic compression (IPC)	45 (100%)	45 (100%)	
graduated compression stockings (GCS)	45 (100%)	45 (100%)	
Examination date, postoperative day	15.2 ± 5.1	15.8± 3.7	0.41

thromboprophylaxis with IPC and GCS was performed by all patients in the two groups. In both groups postoperative venous ultrasonography was performed on around day 15. The perioperative clinical data of the hemoglobin, platelet, APTT, and D-dimer levels of the two groups were similar (Fig. 2). The incidence of distal DVT after surgery was 6.7% (3 of 45 patients) in the short thromboprophylaxis group and 8.9% (4 of 45 patients) in the long thromboprophylaxis groups (p = 0.50) (Table 2). No clinical symptoms were noted in any of patients with distal DVT. Proximal DVT and symptomatic PTE were not detected in the patients of either group. During the follow-up period, there were no recorded incidents of VTE or adverse events, including bleeding episodes.

Discussion

The incidence of VTE in Japan was thought to be much less than that in Europe and North America.[2] However, a Japanese

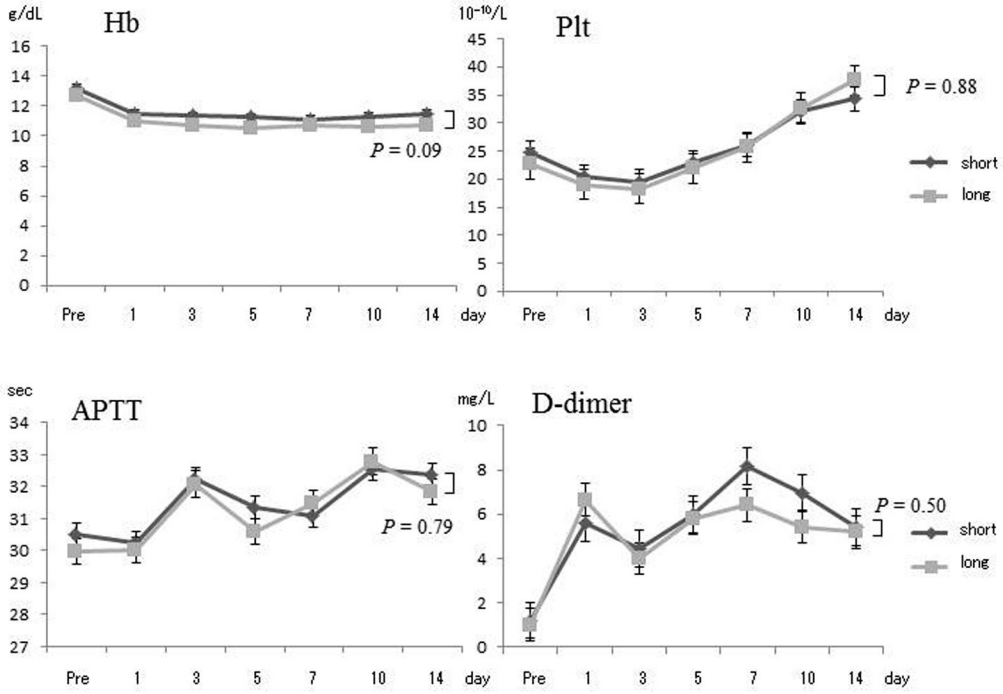

Fig. 2 The perioperative clinical data of the hemoglobin, platelet, activated partial thromboplastin time (APTT), and D-dimer levels before surgery and on days 1, 3, 5, 7, 10 and 14 after surgery

Table 2 The incidence of venous thromboembolism (VTE) in the evaluable patients

Event	Short thromboprophylaxis group (n = 45)	Long thromboprophylaxis group (n = 45)	*P* value
Distal DVT, n (%)	3 (6.7)	4 (8.9)	0.50
Proximal DVT, n (%)	0 (0.0)	0 (0.0)	
Symptomatic PTE, n (%)	0 (0.0)	0 (0.0)	

multi-center prospective study demonstrated that the incidence of VTE in Japanese patients undergoing major abdominal surgery was considerably high, and almost comparable with that in Western countries.[3] The only recommendation of the Japanese Guidelines for Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (The Japanese Circulation Society 2009) is that, at a minimum, unfractionated heparin should be administered as prophylaxis against VTE until the day that the patient achieves a fully ambulatory status.[5] The guidelines do not mention the duration of prophylaxis using LMWH. The optimal duration of thromboprophylaxis after surgery for cancer has not been clearly defined in Japan. On the other hand, the 9th edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (Grade 1B) for high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications.[9] Furthermore, the American Society of Clinical Oncology Clinical Practice Guideline states that pharmacological thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7 - 10 days.[10] We empirically led that period achieved a fully ambulatory status was 3 days. Therefore, the aim of this study was to evaluate the efficacy

3 days of thromboprophylaxis with enoxaparin in comparison to 10 days of thromboprophylaxis with enoxaparin.

Our main finding was that there was no significant difference in the incidence of VTE in the Japanese patients undergoing elective surgery for abdominal and esophageal cancer who received short and long thromboprophylaxis with enoxaparin. Because the recent review showed that combining mechanical thromboprophylaxis and pharmacological prophyraxis was more effective than a single preventative measure, methods of mechanical thromboprophylaxis (IPC and GCS) were used in addition to pharmacological thromboprophylaxis for all patients in this study.[11] The results suggest that 3 days of pharmacological thromboprophylaxis with enoxaparin is adequate when it is combined with IPC and GCS. We were of the position that this study conclusion did not rule out long-duration pharmacological prophylaxis. Rather, we suggest that the decision to continue pharmacological prophylaxis for extended periods of time should be made on a case-by-case basis, in which the needs of individual patients are considered. Patients with conditions such as restricted mobility, or with unexpected postoperative complications should continue to receive pharmacological prophylaxis for 3 days or more. We concluded that routine, long-duration pharmacological prophylaxis was not needed Japanese patients.The overall frequency of VTE in the short thromboprophylaxis group was lower than expected. One possible explanation is that all of the patients received intraoperative mechanical thromboprophylaxis with IPC and GCS. A Cochrane review summarized the results of older trials of GCS vs. no prophylaxis for various type of surgery. According to the analysis of these trials, GCS was effective in reducing the risk of DVT (including distal and asymptomatic DVT) in surgical patients.[12] Roderick et al. concluded that mechanical compression methods reduced the risk of DVT by about two-thirds when used as a monotherapy and by about half when added to a pharmacological method. The benefits of the different methods were similar (GCS, IPC or foot-pump), and were similar in each of the surgical groups that were studied.[11] Another explanation is the high rate of laparoscopic and/or thoracoscopic surgery in this study (74/90 cases, 82.2%). Several investigators have demonstrated that certain intraoperative factors during laparoscopic operations increase the intra-abdominal pressure and reverse the Trendedelenburg position, promoting the development of venous stasis.[13,14] However, these studies involved small numbers of patients. Recently, a large clinical study showed that the incidence of VTE was lower after laparoscopic operations in comparison to open operations. The authors concluded that open procedures were a significant risk factor for the development of VTE.[15] Based on the results of the above-mentioned studies, we consider it possible that the mechanical compression methods and the high rate of endoscopic surgery reduced the risk of DVT. However, the present study was limited by its small study population and there is a need for large randomized trials in this area.

In conclusion, in the present study, there was no significant difference in the incidence of VTE events in the Japanese patients undergoing elective surgery for abdominal and esophageal cancer who received short and long thromboprophylaxis with enoxaparin. We concluded that the appropriate treatment period (for patients undergoing elective surgery for abdominal and esophageal cancer) is only 3 days when pharmacological thromboprophylaxis with enoxaparin is combined with IPC and GCS.

Conflict of interest

The authors state no conflict of interest.

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