

## Low molecular-weight heparin for thromboprophylaxis in patients undergoing gastric cancer surgery: an experience from one Korean institute

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**Purpose:** This study evaluated the efficacy for preventing venous thromboembolism (VTE) and adverse effects of low-molecular-weight heparin (LMWH) in order to launch a prospective clinical trial in Korea.

**Methods:** We reviewed the medical records of 108 consecutive patients who underwent gastric cancer surgery. These patients were divided into 2 groups according to the type of thromboprophylaxis: group A, LMWH combined with intermittent pneumatic compression (IPC); group B, IPC alone. The postoperative outcomes of the two groups were compared.

**Results:** Symptomatic VTE was observed in only 1 patient (0.9%) from group B. Postoperative bleeding was more common in group A than in group B (10.9% vs. 7.5%), although the difference was not significant ( $P = 0.055$ ). Most bleeding episodes were minor and managed conservatively without intervention. Only a high body mass index was associated with a significantly increased risk of postoperative bleeding (odds ratio, 1.45; 95% confidence interval, 1.12–2.43;  $P = 0.051$ ).

**Conclusion:** A 40 mg of enoxaparin sodium is a safe and feasible dose for prevention of VTE. With the results of this study, we are planning a prospective randomized clinical trial to investigate the clinical efficacy of LMWH thromboprophylaxis in gastric cancer patients in Korea.

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**Key Words:** Feasibility, Low-molecular-weight heparin, Thromboembolism, Stomach cancer, Korea

### INTRODUCTION

Venous thromboembolism (VTE) is related to various risk factors such as cancer, peripheral vascular disease, heart disease, immobile condition, and recent history of major abdominal or orthopedic surgery [1,2]. Among these, the presence of malignant disease significantly increases the risk of developing VTE. Therefore, hospitalized cancer patients undergoing chemotherapy or surgery appear to have the greatest risk of developing VTE [3]. In particular, patients with gastric, pancreatic, hematologic, and ovarian cancers have the

greatest risks of developing VTE. Gastric cancer is associated with the fifth-highest rate of VTE [4]. A retrospective cohort study reports that the rate of VTE is 7.4% among patients with gastric cancers [5]. The American Society of Clinical Oncology VTE Guideline Panel recommends that physicians consider pharmacological thromboprophylaxis in patients undergoing major surgery for malignant disease [6]. Low-molecular-weight heparin (LMWH) has become a standard pharmacological agent for preventing VTE because it is easy to use, just once a day injection schedule.

Little study has published about the LMWH prophylaxis

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on patients with cancer surgery. Jeong et al. [7] reported that pharmacological thromboprophylaxis with LMWH is associated with a significant risk of bleeding complications.

The present study analyzed outcomes of LMWH prophylaxis during the gastric cancer surgery, and tried to compare with the outcomes of intermittent pneumatic compression (IPC) device without LMWH.

## METHODS

From July to October 2011, we reviewed 108 patients' medical records; diagnosed with histologically confirmed primary gastric adenocarcinoma, and who showed no evidence of distant metastasis upon preoperative evaluation. The patients divided into two groups: LMWH + IPC (group A) and IPC alone (group B). Use of enoxaparin depended on the surgeon's preference. We had two gastric surgeons in our hospital during this study, and only one surgeon (K.Y.S.) used enoxaparin. The Institutional Review Board of Seoul St. Mary's Hospital approved this study.

All patients had curative intent (R0) gastrectomy with extragastric lymph node dissection. We screened all patients' coagulation profiles, including bleeding time, prothrombin time, activated partial thromboplastin time, and platelet count. In order to screen the disease conditions related to hypercoagulability or bleeding tendency, the levels of protein C, protein S, antithrombin, homocysteine, factor Va, and antiphospholipid IgG/IgM were determined. All patients were managed by the critical pathway protocol; based on this, patients were encouraged to walk early on postoperative day 1 and resume diet no later than postoperative day 3.

### LMWH prophylaxis regimen

All patients wore an IPC device to prevent VTE. IPC device was mandatory before going to the operation room and until discharge. A 40 mg of enoxaparin sodium (Clexane, Sanofi-Aventis Ltd., Seoul, Korea) was administered to patients if they were allotted to group A. Enoxaparin was injected subcutaneously at least 12 hours before surgery and continued once daily until discharge. A serum D-dimer assay was performed on postoperative days 1 and 3 to rule out VTE. Duplex ultrasonography or embolism computed tomography (CT) scan performed if there was any clinical suspicion of deep vein thrombosis or pulmonary embolism (PE).

### Outcome measures

For both groups, we prospectively collected data regarding surgical outcomes including morbidity and mortality, and hospital courses in our data-recording system.

Regarding bleeding indices, luminal bleeding was diagnosed when there was melena or hematochezia accompanied by a decrease in serum hemoglobin levels ( $\geq 2$  g/dL over 24 hours)

or by endoscopic findings. Intra-abdominal bleeding was suspicious, when there was bloody drainage with significant hemoglobin changes, and required radiologic confirmation; such as CT or ultrasonography. Regarding demographic characteristics, the following parameters; such as age, sex, body mass index (BMI), and comorbid medical conditions were compared. For surgical outcomes, local and systemic complications, hospital stays, postoperative fever, and diet resumption time were compared between the two groups. Postoperative complications graded by the Clavien-Dindo Classification system [8].

### Statistical analysis

All statistical analyses were performed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). The  $\chi^2$  test or Fisher exact test and independent 2-tailed t-tests were used to compare the clinicopathological parameters and surgical outcomes between groups A and B, wherever appropriate. Continuous variables were stratified and analyzed as categorical data. Therefore, univariate analysis was performed using the  $\chi^2$  test or Fisher exact test to determine the associations between variables and bleeding complications. Moreover, backward stepwise multivariate logistic regression analysis incorporating all variables in the univariate analysis was performed. The level of statistical significance was set at  $P < 0.05$ .

**Table 1.** The specific biological pathways regulated by up-regulated microRNA

Characteristic	Group A (n = 55)	Group B (n = 53)	P-value
Age (yr), mean $\pm$ SD	57.82 $\pm$ 10.86	56.63 $\pm$ 11.92	0.644
Gender			0.352
Male	36	37	
Female	19	16	
Body mass index (kg/m <sup>2</sup> ), mean $\pm$ SD	24.59 $\pm$ 3.54	23.75 $\pm$ 2.76	0.259
Medical comorbidity			0.161
Yes	15	10	
No	40	43	
Operation procedures			0.877
Subtotal	41	40	
Total gastrectomy	14	13	
Approach			0.028
Laparoscopic	44	37	
Open	11	16	
TNM stage			0.989
I	39	36	
II	10	10	
III	6	7	

SD, standard deviation.

## RESULTS

### Patient demographics

There were 73 male and 35 female patients; their mean age was  $57.1 \pm 10.9$  years. There were no significant differences between the groups with respect to age, gender, BMI, operation type, or medical comorbidities (Table 1).

Operative results showed that 81 of the subjects (75%) underwent subtotal gastrectomy, 27 (25%) underwent total gastrectomy, and 71 (65.7%) underwent laparoscopic gastrectomy. Out of 108 patients, 66 (61.1%) underwent D2 lymph node dissection with a mean operation time of  $156.5 \pm 45.5$  minutes. No significant intergroup difference was found with respect to the type of resection, surgical approach, lymph node dissection, or operation time. Stage distribution did not differ significantly between groups.

### Surgical outcomes and complications

During the postoperative period, 1 female patient from group B presented with symptomatic VTE on postoperative day 14; she underwent curative subtotal gastrectomy using an open approach and experienced sudden swelling with pain in her left lower calf. CT venography revealed massive thrombotic occlusion in her left femoral vein. We performed mechanical thrombolysis followed by heparinization and inferior vena cava filter placement (Fig. 1).

In this study, 33 complications occurred in 27 patients. According to the Clavien-Dindo classification, 15 and 2 complications were grade II and IIIa, respectively.

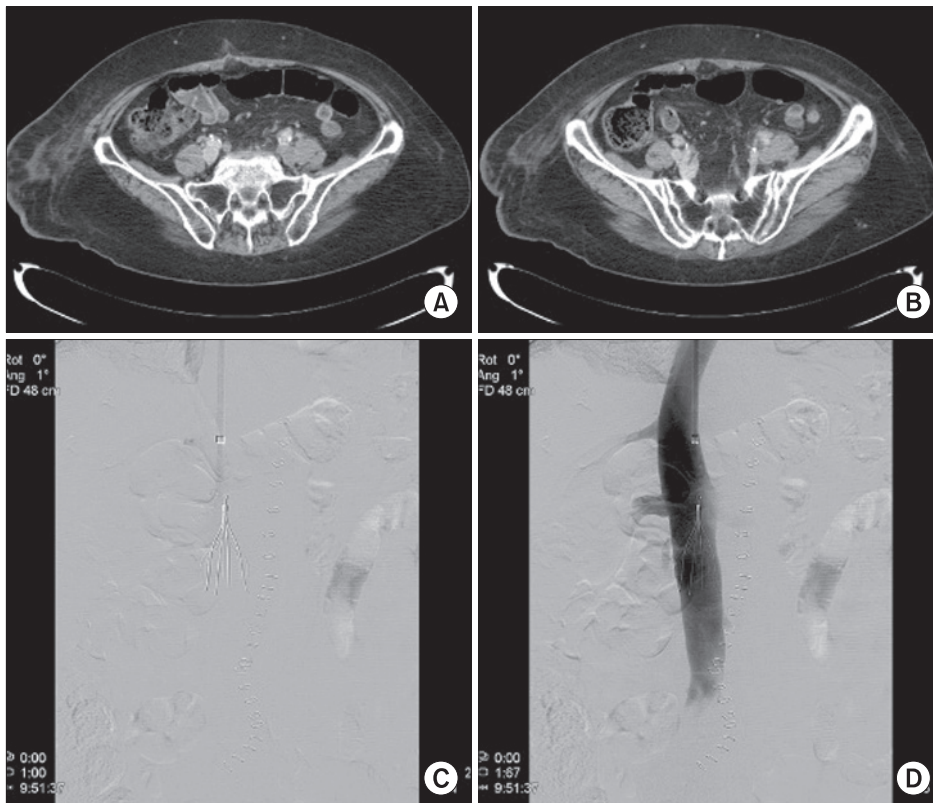
Postoperative complication rates tended to be higher in group A than that in group B, but were not statistically significant (30.9% vs. 18.9%,  $P = 0.091$ ) (Table 2). Although the incidences of intra-abdominal and luminal bleeding after operation were not significantly different between groups ( $P > 0.05$ ), skin hematoma was significantly higher in group A than that in group B (group A vs. group B, 7.2% vs. 0%;  $P < 0.05$ ).

### Risk factors for bleeding complications

Univariate analysis revealed that LMWH usage and high BMI significantly increased the risk of bleeding complications ( $P = 0.047$  and  $P = 0.035$ , respectively). After using multivariate analysis, these factors were not significant risk factors of postoperative bleedings. The BMI showed tendency of increasing risk of postoperative bleeding (odds ratio, 1.45; 95% confidence interval, 1.12–2.43;  $P = 0.051$ ) (Table 3).

## DISCUSSION

The American College of Chest Physicians guidelines for thromboprophylaxis classify cancer surgery as a "high-risk" procedure for the development of VTE and recommend active prophylaxis including LMWH or unfractionated heparin [9].



**Fig. 1.** Computed tomography image revealed extensive deep vein thrombosis along the left iliac and femoral veins (A & B). An inferior vena cava filter was inserted (C & D).

**Table 2.** Surgical outcomes and postoperative complications

Variable	Group A (n = 55)	Group B (n = 53)	P-value
Operation time (min)	155.8 ± 28.0	165.19 ± 46.9	0.071
Estimated blood loss (mL)	114.8 ± 77.5	145.5 ± 98.8	0.056
Hospital stays (day)	7.5 ± 2.4	7.0 ± 2.8	0.418
Diet start (day)	3.5 ± 0.9	3.2 ± 1.7	0.060
Transfusion required	9 (16.3)	5 (9.4)	0.066
Complications (event/person)	20/17	13/10	0.091
Bleeding (abdominal/luminal)	5/1 (10.9)	3/1 (7.5)	0.055
Abdominal fluid collection	2 (3.6)	2 (3.7)	0.271
Skin hematoma	4 (7.2)	0 (0)	<0.050
Wound	1 (1.8)	1 (1.9)	0.987
Gastric stasis	3 (5.4)	1 (1.9)	0.248
Pancreatitis	0 (0)	1 (1.9)	0.640
Anastomotic complication	1 (1.8)	1 (1.9)	0.984
Pneumonia	2 (3.6)	1 (1.9)	0.660
Pleural effusion	1 (1.8)	2 (3.7)	0.660

Values are presented as mean ± standard deviation or number (%).

The estimated incidences of deep vein thrombosis (DVT) and fatal PE in this group are 20%–40% and 0.4%–1.0% respectively [6,9]. However, in Korea, the routine use of LMWH to prevent VTE in preoperative periods was not common. Surgeons are afraid of risks of unexpected intraoperative or postoperative bleeding. Many Korean surgeons are more concerned about the postoperative bleeding than prevention of rare risk of VTE with LMWH, compared with the high incidence of VTE in the western countries [10,11].

The rate of thromboprophylaxis with LMWH is significantly lower in Asian countries than that in the Western countries because the true incidence and risks of VTE after cancer surgery in Asian patients remain uncertain. The incidence of VTE in Asian patients was approximately 3- to 5-fold lower in a previous report, although the incidence of asymptomatic VTE may be higher without thromboprophylaxis. An increased risk of postoperative bleeding is another issues related to LMWH usage.

Meta-analyses and randomized controlled trials conducted in the West revealed little or no increase in the rates of clinically significant postoperative bleeding with the use of prophylactic doses of LMWH [12-15]. However, few studies have evaluated the feasibility of LMWH prophylaxis in Asia. We are planning to determine the optimal thromboprophylaxis method during gastric cancer surgery. Before starting a prospective clinical trial, we tried to evaluate the safety of using LMWH in the present

**Table 3.** Predictive factors for risk of postoperative bleeding

Variable	Total patients (n = 108)	Bleeding complication (n = 10)	P-value
Age (yr)			0.808
<65	77	6	
≥65	31	4	
Gender			0.464
Male	73	6	
Female	35	4	
Body mass index (kg/m <sup>2</sup> )			0.047
<23	34	3	
23–25	49	5	
≥26	25	2	
Comorbidity			0.341
No	83	7	
Yes	25	3	
Surgical approach			0.230
Open	27	4	
Laparoscopy	81	6	
Type of operation			0.251
Subtotal gastrectomy	81	6	
Total gastrectomy	27	4	
Lymph nodes dissection			0.351
D2	72	6	
D1+	36	4	
LMWH			0.035
Yes	55	6	
No	53	4	

LMWH, low-molecular-weight heparin.

study. The LMWH tended to increase the risk of postoperative bleeding in patients with gastric cancer in our patients. However, most of the bleeding complications were minor events unrelated to mortality and mostly managed conservatively.

The surgical procedures and extent of surgery might influence bleeding risks, such as open versus laparoscopy and extent of lymph node dissection. Extensive lymph node dissection, which could increase the risk of bleeding complications, is a routine procedure for radical gastrectomy in Korea in contrast to surgery in the West [16]. Nonetheless, there was no significant difference in bleeding episodes with respect to the resection type, extent of lymph node dissection, or type of surgical approach (i.e., laparoscopic and open) between groups. Only high BMI was an independent risk factor for an increased risk of bleeding, probably because the surgical plane is more difficult to find and more friable for dissection in obese patients [17].

In order to examine the hypercoagulability status of Korean

patients, we measured protein C, protein S, antithrombin, homocysteine, factor Va, and antiphospholipid IgG/IgM levels, which are well-known factors related to hypercoagulability. Interestingly, most factors were within normal limits, implying that hereditary causes of coagulopathy are not prominent among Korean patients. On postoperative day 1, 50 patients (46.2%) exhibited elevated D-dimer levels; of these patients, 3 (2.7%) who presented with asymmetric leg swelling underwent duplex ultrasonography to rule out DVT. None of these patients showed DVT.

The risk of bleeding associated with LMWH usage is hypothetically dependent on several factors including LMWH dosage and injection timing. A previous intervention study comparing the administration of 2,500 and 5,000 U LMWH in general surgical patients revealed that the incidence of DVT was significantly lower in those administered 5,000 U; however, the incidence of bleeding was significantly higher in these patients than that in patients administered 2,500 U [18]. In the present study, we used 40 mg of enoxaparin sodium, which recommended dosage in the previous trials [19,20]. We just followed this dosage, which is sufficient to prevent VTE and

to have reasonable rate of bleeding complications in Korean patients, but in future trial will also confirm it.

In this study, LMWH seems to increase bleeding risks, but it does not significantly alter the patients' clinical course. LMWH seemed to have a tendency to increase the risks of bleeding in patients with high BMI.

In Asia, due to the low-reported incidence of VTE, surgeons in Asia rather not interested in VTE prophylaxis as in Western surgeons. However, the patients' population were aged and got overweight. The real incidence of VTE or LMWH related risks of bleeding were uncertain.

Based on this study, we will launch a prospective randomized clinical trial to investigate the clinical efficacy of LMWH thromboprophylaxis by comparing LMWH plus IPC prophylaxis with IPC alone in Korean gastric cancer patients after surgery.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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