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

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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...
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, 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 (≥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 ± SD       | 57.82 ± 10.86    | 56.63 ± 11.92    | 0.644   |
| Gender                    |                  |                  | 0.352   |
| Male                      | 36               | 37               |         |
| Female                    | 19               | 16               |         |
| Body mass index (kg/m²), mean ± SD | 24.59 ± 3.54 | 23.75 ± 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 ± 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 ± 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 in serted (C & D).
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 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

| 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 | 145.59 ± 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 (%).

| 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/m²) | | | 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 | Yes | 55 | 6 | 0.035 |
| No | 53 | 4 | |

LMWH, low-molecular-weight heparin.
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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