STUDY PROTOCOL

Optimal Prophylactic Method for Venous Thromboembolism After Gastrectomy in Korean Patients

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1. Title of the study

Optimal Prophylactic Method for Venous Thromboembolism After Gastrectomy in Korean Patients: the PROTECTOR Randomized Controlled Trial

2. Institute’s name and address

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3. Person in charge and collaborators

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4. Background of this study and objectives

- Objectives
  - The primary outcome: to examine the VTE incidence rate within 30 days of surgery and to determine the rate of symptomatic VTE requiring interventional treatment.
  - The secondary outcome: identification of postoperative complications, particularly those related to the method of VTE prophylaxis.

- Backgrounds:
  - Venous thrombosis is found in a variety of patients, and can be a cause of morbidity and mortality, especially in patients who undergo surgical treatment. Venous thrombosis accompanying pulmonary embolism can be fatal to patients [1]. Recent studies have
shown that the incidence of venous thromboembolism in patients with cancer, associated with systemic therapies, or surgery has increased from 23% in 1995 to 2003 [2]. The incidence of venous thromboembolism in patients with general anesthesia without prophylactic methods has been reported to occur in about 25% of all patients though checking radioisotope labeled fibrinogen level [3], and the incidence of high-risk patients with venous thrombosis was 20 ~ 80%. [4]. Gastrointestinal cancer is a high risk factor for venous thromboembolism, and long-period immobilization during the stomach cancer surgery and persistent intraperitoneal pressure and Trendelenburg position in the laparoscopic surgery are also risk factors for venous thromboembolism [5, 6]. It is known that venous thromboembolism is caused by the hypercoagulability and decrease tension of the muscles during surgery under the general anesthesia, and the enlargement of the internal diameter of the vein due to the posture during surgery following the micro damage on the endothelium [7, 8]. Prevention of venous thromboembolism can be divided into three methods: drug-based, mechanical, and a combination of both. Subcutaneous injection of low molecular weight heparin is easy to use once a day and the incidence of heparin-induced thrombocytopenia is also low, which is widely used for prevention of venous thrombosis. Mechanical methods include pressure tights or intermittent pneumatic compressors. This increases pressure on the relaxed intravenous lumen to narrow the venous diameter and increase blood flow velocity to prevent venous retention. In particular, intermittent pneumatic compressors are effective in preventing thrombosis due to fibrinolysis effects [9]. Prevention of thrombosis in digestive cancer surgery has standardized based on many research in the West. On the other hand, the incidence of thrombosis in the Asian countries is relatively lower than that of the Western [10]. However, recent studies have shown that the incidence of venous thrombosis in Asia is increasing, but still, the results of the studies are limited to specific research designs or to specific races [11, 12]. As the studies’ results are being contrary, there is no exact evidence for the prevalence of thrombosis after gastric cancer surgery or standardized prophylactic methods in Asia. Some reports showed that single dose of low molecular weight heparin which is recommended by most of guidelines might be excessive for Asian patients and may lead to complications such as postoperative bleeding; so that it is appropriate to choose a preventive method differently from Western ones. Therefore, it is meaningful to investigate the best way to prevent thrombosis in gastric cancer patients in Asia. The aim of this study is to investigate the incidence of venous thrombosis in Korean gastric cancer patients. In addition, we aimed to compare the efficacy and the complications of the combination of low molecular weight heparin and intermittent pneumatic compressors through a prospective clinical study, through randomly assigned patients to use the above method and intermittent pneumatic device only. We also hope that this study will contribute to the establishment of the optimal prevention method to
help patients by confirming the effect of mechanical thrombosis in Korean gastric cancer patients.

5. General name of pharmaceuticals for clinical trials, drug substance and its amount, dosage form, etc.

None

6. Disease indications

Gastric cancer

7. Inclusion and exclusion criteria

7.1 Inclusion Criteria

1. Gastric adenocarcinoma, confirmed by pathologic result
2. Aged 20-75
3. ECOG ≤ 2
4. ASA ≤ 3
5. Patients who signed the written consent of the institutional ethics review committee to participate in this study with full understanding of the purpose and contents of the research prior to the participation.

7.2. Exclusion criteria; patients with...

1. Active status of other cancer
2. Diagnosed or treated with DVT or PTE within 1 year.
3. Preoperative prolonged immobilization or being wheelchair-dependent
4. Disease with hemorrhagic tendency
5. Currently taking anticoagulants
6. Underwent surgery under general anesthesia for more than 4 hours within the last 6 months
7. History of stroke within the last 3 months
8. Allergy to heparin or history of heparin-induced thrombocytopenia
9. Varicose veins or chronic venous insufficiency, peripheral vascular disease, skin ulcer
10. History of anticancer or radiation therapy in the past
11. BMI ≤ 18.5 kg/m2
12. Pregnant patients

8. Period of Clinical trial

After IRB approval, 3 years for the registration and 6 months of follow-up period is 6 months, total 3 years and 6 months.
9. Randomization
- Using sequential sealed envelopes containing computer-randomized treatment assignments, the enrolled patients will be assigned to the IPC only group or the IPC + LMWH group.

10. Registration and data collection
- This study should be conducted in the direction of maximum protection of the patient according to the Helsinki Declaration and legal regulations. Researchers should ensure that the patient is suitable for the study and receive consent before consultation. The content form should include explanations about the possibility of venous thrombosis after gastrointestinal cancer patients and general anesthesia surgery, the necessity and purpose of this study, pros and cons of each prevention method, and explanations that emphasize the spontaneity of participation in research. If the inclusion criteria are met, the practitioner will be informed assigned group by the randomization according to pre-written assignment plan

11. Protocol for DVT prophylaxis
- **group A : IPC only**
  The IPC will be initiated preoperatively and continued until postoperative discharge. Patients will be monitored by their medical team for compliance and encouraged to use IPCs at all times unless the patients are ambulating.
- **group B : IPC+LMWH**
  For patients in the IPC plus enoxaparin group, enoxaparin should be administered postoperatively at 24-hour intervals in a daily dose of 40 mg beginning on the day of surgery.

Flow chart of study
12. Clinical outcomes

12.1. Operative outcomes
- Operative time: time of first incision to the end of wound closure
- Estimated blood loss: blood from the abdominal cavity that removed with an suction and the total amount should be checked after the operation.
- gas out: when the day after surgery is the first postoperative day, first gas out day should be checked.
- diet: when the day after surgery is the first postoperative day, first liquid and soft diet starting day should be checked.
- Hospital stay length

12.2. Postoperative complications
- Bleeding: Major and minor bleeding after surgery was defined according to the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. It defines major bleeding for patients undergoing surgery as fatal bleeding and/or extrasurgical site bleeding causing a fall in hemoglobin level of ≥ 2 g/dL, bleeding requiring transfusion of ≥ 2 units of whole blood or red cells, or surgical site bleeding that requires a second intervention.
- Wound complications: seroma, hematoma, wound infection, wound dehiscence, wound evisceration, etc.
- Leakage: anastomosis leakage, duodenal stump leakage, etc.
- Pulmonary complications: atelectasis, pleural effusion, empyema, pneumonia, pneumothorax, etc.
- Bowel obstruction: no gas passage until postoperative day 5, mechanical ileus on simple x-ray, paralytic ileus symptoms, A-loop syndrome, other evidences of bowel obstruction sign
- Urinary complications: UTI, urgency, dysuria, etc.
- Intraabdominal infection: abscess formation in abdominal cavity on CT or ultrasound
- Pancreatitis: clinical symptoms of pancreatitis with significantly elevated serum amylase
- Pancreatic fistula: elevated drain amylase over 1,000 after postoperative day 3.
- Enteric fistula: confirmed by fistulography

12.3. Diagnosis of venous thrombosis
- Laboratory findings: serum protein C, protein S, anti-thrombin III, homocystein, Factor Va, antiphospholipid antibody – at admission (the day before surgery)
- Postoperative DVT screening
197 (A) clinical symptoms: leg edema, leg pain, superficial venous congestion, Changes in
198 circumferential length before and after surgery
199 (B) D-dimer check at OP day, postoperative day 1, and 4
200 (C) duplex ultrasonography (DUS) of both leg,
201 - using the two-point compression method
202 : proximal venous system of the common and superficial femoral veins to below the
204 popliteal vein
205 - findings:
206 1) non-compressibility of veins
207 2) echogenic thrombus
208 3) diminished/absent venous flow
209 4) absence of respiratory phasicity
210 5) absent or incomplete color filling

13. Criteria for withdrawing clinical research
213 - allergic to heparin/ heparin induced thrombocytopenia
214 - poor compliance to IPC, failed to use IPC for 4 hours a day
215 - by the patient of their legal representative's request

14. The judgment criteria for the effect
217 14.1. Collecting CRF
219 - The original CRF will be kept by the researchers, and a copy will be sent to the executor.
220 The CRF will be automatically locked to prevent further modifications
221 - The staff will carry out the test items listed on the case report periodically.
222 - Confirm forms and data content: Executives should review the forms submitted by each
223 research team to identify missing parts, and contact the researchers to improve the quality of
224 the basic data.
225 - Interim analysis: After 6 months from the start of the study, analysis of adverse events and
226 mortality will be conducted to determine the possibility of the research progress or the early
227 termination of the study.
228 - In particular, if the Maternal Mortality rate exceeds 5% in the interim analysis, the clinical
229 trial should be stopped immediately and the specific group should be eliminated if the
230 specific complication rate is significantly higher in the specific group (difference of 30% or
231 more).

14.2. Calculated sample size and statistical analysis
233 The overall purpose of this trial is to determine whether singular IPC is comparable to the
current heparin-based standard treatment for VTE prevention. A primary noninferiority analysis is
based on a 95%(two-sided) confidence interval (CI) computed on the difference between the two
groups with the power of 80%. To prove noninferiority, the upper limit of this CI was to be within
the preestablished noninferiority margin of 2%, and we presumed a baseline event rate of 1% for
the standard treatment group (LMWH) as observed in the previous trials. We determined that a
sample of 341 patients was required for each group, assuming a 10% drop rate. The Wald method
(without continuity correction) will be used to compute the CI. Pearson’s Chi square test will be
used to identify categorical variable differences, and the Wilcoxon rank sum test will be used to
identify the continuous variable differences. The data will be analyzed on intent-to-treat (ITT) and
per-protocol (PP) bases. If data for a given visit are missing, cases that are missing on the
secondary outcome simply will be deleted. All of the reported P values are two-sided; 0.05 will be
considered statistically significant. All of the statistical analyses will be performed using SAS
software (SAS Institute, Inc., Cary, NC).

Gastric cancer patients who are planning to undergo gastrectomy: 682

Group A: Intermittent pneumatic compressor (IPC) only: 341

Group B: IPC + LMWH: 341

\[ H_0 : p_1 = p_0 \quad \text{vs} \quad H_1 : p_1 > p_0 - \delta \]

- \( \delta \): noninferiority margin, \( \delta = 0.02 \)
- \( \alpha = 0.05, \beta = 0.2 \)
- \( p_0 = 0.01(1\%), p_1 = \) same as the VTE incidence of IPC+LMWH group

\[ Z_{1-\alpha} = Z_{0.95} = 1.645, \quad Z_{1-\beta} = Z_{0.8} = 0.84, \]

\[ n = \frac{(z_{1-\alpha} + Z_{1-\beta})^2 [p_0 (1 - p_0) + p_1 (1 - p_1)]}{(p_1 - p_0 - \delta)^2} = 306.04 \]

- Considering 10% drop rate, 341 for each, total 682 patients are needed.

15. Criteria of safety including side effects, evaluation method and reporting method

Low-molecular-weight heparin or intermittent pneumatic compressors to be used in this clinical
trial will be performed under the same conditions as the existing thrombosis prevention method,
and the side effects or complications will be treated according to the treatment principle as in the
case of non-clinical trials. Stability is assessed as complications that occur. During the trial period,
the clinical investigator will ensure the safety of the patient and report serious adverse events to
the clinical trial review committee (IRB).
16. Statute of Compensation for Victims
This study is a clinical trial comparing conventional methods to prevent venous thromboembolism after gastric surgery. Therefore, the present researchers will not be compensated for the occurrence of complications related to surgery, and the study will be conducted only if the subject agrees.

17. Measures for the treatment after clinical trials and measures to protect the safety of subjects
The surgery in this study is routine treatment already performed in the clinic and there is no additional procedure or examination due to the clinical trial. Therefore, the treatment and follow-up method of the patients will be preceded according to the treatment guidelines of general gastric cancer patients.

18. All clinical information required for statistical data will be used excluding the personal information of the patient, and the personal information is not leaked through a separate two-step coding process.

21. References


### Investigator-Initiated Research Proposal

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<tr>
<th>Title</th>
<th>Optimal prophylactic method of venous thrombo-embolism for gastrectomy in Korean patients</th>
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| **Reason for conducting the proposed study** | - There are only a few reports for the incidence of VTE in Asian patients.  
- **Most Korean surgeon** concerns regarding the increased postoperative bleeding associated with LMWH prophylaxis.  
- **Gastric cancer** is the most frequent cancer in Korea.  
- : 500-600 patients underwent surgery in One year  
- There is no consensus  
  1. True incidence of VTE  
  2. Optimal methods of prophylaxis in Korean patients. |
| **Objectives of the study** | To define the optimal method of prophylaxis for surgical patients in Korea |
| **Research Sites** | Single Center |
| **Outcome measures** | - Clinical symptoms  
  - leg swelling, pain around leg deep vein, congestion of superficial vein  
  - Serum D-dimer, protein C,S, Anti-thrombin III, homocystein, Factor Va, antiphosholipid antibody  
  - Duplex ultrasonography  
  - Operative outcomes |
| **Type of study design** | Randomized prospective controlled trial (non inferiority test) |
| **Study groups and number** | Control IPC group (n=341)  
Interval IPC+LMWH group (n=341) |
| **Duration of treatment** | From one day before surgery to discharge from hospital |
| **Duration of follow-up and methodology for conducting follow-up examinations** | f/up will be continued until discharge screening : d-dimer study  
confirmation : duplex ultrasound or embolism scan |
| **Patient population** (i.e., briefly describe enrollment criteria or type of patient intended) | Patients diagnosed as gastric cancer  
- Age ; 20 ~ 75 year old  
- Elective and curative under general anesthesia  
- ECOG score 0-1  
- ASA score <3 |
| Total number of patients | N=682  
A primary non-inferiority analysis was based on a 95% (two-sided) confidence interval (CI) computed based on the difference between the two groups with the power of 80%. To prove non-inferiority, the upper limit of this CI was set within the preestablished non-inferiority margin of 2%, and we presumed a baseline event rate of 1% for the standard treatment group, as observed in previous trials. We determined that a sample of 341 patients was required for each group, assuming a 10% drop rate, and therefore a total 682 patients were enrolled. The Wald method (without continuity correction) was used to compute the CI. The Pearson chi-square test was used to identify the categorical-variable differences, and the Wilcoxon rank sum test was used to identify the continuous-variable differences. The data were analyzed on per-protocol base. If data for a given visit were missing, cases that were missing on the secondary outcome simply were deleted. All the reported P values are two-sided, and P<.05 was considered statistically significant. All the statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, NC). |
| Study duration | 3 and half year |
| End point | Primary : incidence of VTE  
Secondary : complication |
| Ethics Committee Approval | IRB Approved (KC11OSSI0608) |
| Clinical trial.gov | Approved (NCT01448746) |
| Publication and/or Presentation Plan | We are planning to present the interim and final result to associate meeting and will submit the paper. |