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ORIGINAL ARTICLE

Does the use of postoperative low-molecular-weight heparin in patients with lung cancer increase tube drainage?

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KEYWORDS
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Summary *Background:* The objectives of this study are to assess the chest drainage volumes of patients undergoing anatomic resection of non-small cell lung carcinoma and to determine the safety and effectiveness of administering enoxaparin for thromboprophylaxis.
Methods: A total of 77 patients were included in the study. A study was conducted on the first group of 42 patients in which enoxaparin prophylaxis (enoxaparin, 40 mg) was subcutaneously injected once a day for a period of three days after the patients underwent anatomic pulmonary resection between March 2016 and March 2018. An enoxaparin-free group was identified and included 35 patients who received no enoxaparin prophylaxis after undergoing anatomic pulmonary resection between February 2013 and February 2016. We compared the changes in hemoglobin (Hb) levels, postoperative 3-day drainage volume, transfusion volume, pulmonary complications and length of stay between the two groups.
Results: No differences in postoperative Hb levels, chest drainage volume, transfusion volume, postoperative complications, and length of stay were observed between the two groups. Deep-vein thrombosis was noted in a patient in the enoxaparin-free group. No major bleeding was noted in either group.
Conclusion: We found that for patients undergoing anatomic resection of primary lung cancer, the blood transfusion and chest drainage volumes did not differ, regardless of whether the patients were given enoxaparin. To the best of our knowledge, the impact of low-molecular-weight heparin on chest tube drainage volume for patients undergoing anatomic resection of non-small cell lung carcinoma has not been investigated before.

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1. Introduction

Cancer is generally associated with hypercoagulability and thereby an increased risk of venous thromboembolic events (VTEs). It has been reported that the risk of developing VTEs in cancer patients is five-to seven-fold higher than that in the normal population.[1] It has also been demonstrated that cancer patients undergoing surgery have at least double the risk of postoperative VTEs and more than three times the risk of encountering a fatal pulmonary embolism over noncancer patients undergoing similar procedures.[2]

Low-molecular-weight heparin (LMWH) thromboprophylaxis is widely recommended for patients undergoing lung cancer surgery.[3,4] However, the rate of bleeding associated with the use of LMWH for thromboprophylaxis in patients without any previous risk factors has been reported to be as high as 10%.[5] The objectives of this study were to assess the chest drainage volumes of patients undergoing anatomic resection of non-small cell lung carcinoma and to determine the safety and effectiveness of administering enoxaparin for thromboprophylaxis.

2. Methods

We retrospectively analyzed the medical records of all patients who underwent anatomic lung resections for non-small cell lung carcinoma between February 2013 and March 2018. A total of 77 patients were included in the study. The following data were collected: age, sex, body mass index, previous history of VTEs, American Society of Anesthesiologists (ASA) score, major comorbidities (ischemic heart disease, cerebrovascular event, liver cirrhosis, end-stage renal disease), preoperative concomitant medications that may interact with enoxaparin (nonsteroidal anti-inflammatory drugs, low dose acetyl salicylic acid, clopidogrel, ticlopidine, limaprost alfadex, warfarin), prothrombin time (PT), activated partial thromboplastin time (APTT), International Normalized Ratio (INR), platelet count, volume of bleeding during surgery, operative time, preoperative hemoglobin values (Hb) and hemoglobin values on postoperative days 1 (Hb1) and 4 (Hb4), amount of postoperative blood transfusion, postoperative use of enoxaparin, total 3-day drainage volume from the chest tubes, length of stay, and postoperative complications and mortality.

A study was conducted on the first group of 42 patients who received enoxaparin prophylaxis in which "enoxaparin (40 mg)" was subcutaneously injected once a day for a period of 3 days after the patients underwent anatomic pulmonary resection between March 2016 and March 2018. We monitored the dose of LMWH with clinical follow-up and Activated partial thromboplastin time. Perioperative elastic stockings and postoperative early ambulance (first day) are routine procedures for patients undergoing lung cancer surgery in our institution. An enoxaparin-free group was identified and included 35 patients who received no enoxaparin prophylaxis after undergoing pulmonary anatomic resection between February 2013 and February 2016. The patients were classified into two groups, the "enoxaparin" group and the "enoxaparin-free" group.

We excluded patients who had a past history of deep-vein thrombosis, thrombocytopenia, or anemia; who were drugs taking that may interact with enoxaparin; who had coagulopathy; who received neoadjuvant chemo-and/or radiation therapy prior to surgery; and who had major comorbidities (ischemic heart disease, cerebrovascular event, liver cirrhosis, end-stage renal disease). We compared the changes in hemoglobin (Hb) levels (preop Hb, postop Hb1 and 4), postoperative 3-day drainage volume, transfusion volume, postoperative complications, and length of stay between the two groups.

We compared the differences in age, body mass index, preoperative Hb and postoperative Hb1 and Hb4 levels, 3-day chest tube drainage volume, surgical bleeding, operative time, blood transfusion volume and length of stay between the groups using independent *t*-tests. We compared the differences in ASA score and postoperative complications using the Chi-square test. All the statistical comparisons were made using the Statistical Package for Social Science (SPSS) software (version 16; SPSS Inc., Chicago, IL, USA).

3. Results

A total of 77 patients were enrolled in this study, of which 42 received enoxaparin prophylaxis after undergoing anatomic resection for non-small cell lung carcinoma. The mean age of the patients was 61.4 years (range, 42—76 years). Twelve percent of the patients were male. No major adverse events (death, neurologic injury, severe infection, or chylothorax) were observed. The pathological analysis included squamous cell carcinoma, adenocarcinoma and other types of non-small cell lung carcinoma. Patients had undergone an elective lobectomy or bilobectomy. In the postoperative period; Activated partial thromboplastin time (aPTT) test was performed to monitor LMWHs. APTT significantly prolonged with LMWH compared to preoperative values, but no significant difference was found in tube drainage between the two groups during clinical follow-up ($P > 0.05$). Table 1 summarizes the patient characteristics. The two groups were similar in terms of age, ASA score, body mass index, preoperative Hb level, operative time, and surgical bleeding. No significant differences were found between the two groups.

Table 1 Patient characteristics.

	Enoxaparin group (n = 42)	Enoxaparin-free group (n = 35)
Age	63,65 ± 9,32	59,64 ± 7,45
Gender (female/male)	18/24	16/19
ASA score	2,90 ± 0,57	2,45 ± 0,45
Body mass index	22,35 ± 1,35	24,42 ± 1,95
Preoperative Hb	14.04 ± 1,61	13.70 ± 1,64
Postoperative Hb 1	12.65 ± 1,31	12.78 ± 1,57
Postoperative Hb 4	11.80 ± 1,63	10.92 ± 1,43
3 day drainage (mL)	652.85 ± 32,56	791.42 ± 30,32
Blood transfusion (mL)	395.40 ± 25,35	374.20 ± 22,89
Surgical bleeding (mL)	205,24 ± 45,35	179,45 ± 37,85
Operative time (min)	156,35 ± 24,20	171,24 ± 25,70
Length of stay	9.60 ± 3,20	8.92 ± 2,75

Table 2 summarizes the perioperative and postoperative data. There were 7 patients who had postoperative complications, including pneumonia (n = 4), arrhythmia (n = 2) and deep-vein thrombosis (n = 1). Analysis of the data showed no statistically significant differences between the two groups (P > 0.05). Patients experiencing atrial fibrillation in the enoxaparin-free group were converted to sinus rhythms using amiodarone, and no additional antithrombotic treatment was provided. One patient in the enoxaparin-free group developed deep-vein thrombosis on postoperative day six. The patient who developed deep-vein thrombosis was treated, and pulmonary embolisms did not develop during follow-up visits.

4. Discussion

Many patient factors, such as immobility, dehydration, age, obesity and insertion of central venous catheters, could increase the risk of VTEs in patients with lung carcinoma.[6] Almost all hospitalized patients have at least one risk factor for VTEs, and the incidence of in-hospital VTE has been shown to be 10—40% among medical patients and as high as 40—60% following major operations. The routine use of thromboprophylaxis has resulted in a significant reduction in the incidence of VTEs, and LMWH has been considered the standardized prophylactic regimen for a long time. LMWH has many effects on the coagulation cascade, but its main effect is the inhibition of factor Xa and, to a lesser extent, factor IIa.[6]

Recommendations on the dosage and the timing for the administration of LMWH have remained very unclear. The most recent of these guidelines, by the American College of Chest Physicians,[7] recommends the use of routine thromboprophylaxis with LMWH (grade 1C evidence) for patients undergoing major thoracic surgery but gives no advice on the dosage or the timing of its administration. Enoxaparin sodium, a low-molecular weight heparin, has been used to prevent VTEs and has been shown to be effective in clinical trials.[8,9] Generally, enoxaparin has a predictable pharmacokinetic profile and dose response curve, allowing for simplified dosing without the need for careful monitoring through laboratory tests.[10] We used enoxaparin in our study and did not observe VTEs in the enoxaparin group.

It is well-understood that anticoagulants that reduce the incidence of DVT (chemoprophylaxis) are associated with increased risks of postoperative bleeding.[11,12] The incidence of major hemorrhagic complications has been reported to be between 0.5% and 4%, with a higher incidence in elderly patients with renal and liver disease and patients who receive other forms of anticoagulants, such as acetyl salicylic acid and clopidogrel. In addition, several cases of epidural hematomas have been reported with the use of LMWH and epidural catheters in patients who underwent thoracic surgery.[13] As most patients undergoing thoracic surgery for malignancies are elderly with other comorbidities, the risks of bleeding are serious. We did not observe major bleeding in either group.

We acknowledge the limitations of this study. First, we preoperatively excluded patients with a high risk of coagulopathy or thromboembolism. Second, this study was a retrospective review. Further randomized controlled clinical trials are necessary to assess the efficacy and safety of using enoxaparin in clinical practice.

Table 2 Perioperative and postoperative data.

	Enoxaparin group (n = 42)	Enoxaparin-free group (n = 35)	*P* values
Preop Hb	14.04	13.70	0.880
Postop Hb1	12.65	12.78	0.210
Postop Hb4	11.80	10.92	0.174
3 days drainage (ml)	652.85	791.42	0.510
Blood transfusion (ml)	395.40	374.20	0.068
Postoperative complication	3	4	0.156
Length of stay (day)	9.60	8.92	0.421

5. Conclusion

The chest drainage volume substantially determines the duration a patient needs to have a chest tube and thereby contributes to the postoperative morbidity. In this retrospective trial, we found that in patients undergoing anatomic resection of primary lung cancer, the blood transfusion and chest drainage volumes did not differ whether the patients were given LMWH. In patients who underwent resection due to non-small cell lung carcinoma, LDWH should be given postoperatively. To the best of our knowledge, the impact of LMWH on chest drainage volumes in patients undergoing anatomic resection of non-small cell lung carcinoma has not been investigated before.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest

The authors declares that there is no conflict of interest regarding the publication of this paper.

Author's contributions

H.E. was responsible for the research idea, study design, collecting the data, reviewing the literature, writing the manuscript, and approving the final version of the study. A. S. was responsible for reviewing the literature, collecting the data, writing the manuscript, and approving the final version of the study. A.C. was responsible for reviewing the literature, performing statistical analyses for the results, writing the manuscript, and approving the final version of the study.

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Appendix A. Supplementary data

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