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Efficacy of postoperative anticoagulation therapy with enoxaparin for portal vein thrombosis after hepatic resection in patients with liver cancer

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ABSTRACT

Backgrounds: Enoxaparin, low-molecular-weight heparin, has become a routine thromboprophylaxis in general surgery.
Study design: A retrospective cohort study was performed in 281 patients who underwent hepatic resections for liver cancers from 2011 to 2013. These patients were divided into two groups; an enoxaparin (-) group (n = 228) and an enoxaparin (+) group (n = 53). Short-term surgical results including venous thromboembolism (VTE) and portal vein thrombosis (PVT) were compared.
Results: In the enoxaparin (+) group, the patients' age (65 *vs.* 69 years; p = 0.01) and BMI (22.9 *vs.* 24.4; p < 0.01) were significantly higher. According to the symptomatic VTE, symptomatic pulmonary embolism occurred in one patient (0.4%) in the enoxaparin (-) group, but the complication rate was not significantly different (p = 0.63). The complication rate of PVT was significantly lower in the enoxaparin (+) group (10 *vs.* 2%; p = 0.04). The independent risk factors for PVT were an operation time ≥ 300 minutes (Odds ratio 6.66) and non-treatment with enoxaparin (Odds ratio 2.49).
Conclusions: Postoperative anticoagulant therapy with enoxaparin could prevent PVT in patients who underwent hepatic resection for liver cancers.

Introduction

Venous thromboembolism (VTE) represented by pulmonary embolism (PE) or deep venous thrombosis (DVT) is a significant cause of morbidity and mortality in patients undergoing gastrointestinal surgery for malignancy, and pharmacologic prophylaxis is important [1,2]. One of the major cautions regarding pharmacologic prophylaxis is the risk of major bleeding complication, but a recent systemic review reported that bleeding requiring a change of care occurs in less than 3% of cases [3]. It is well known that several hemostatic alternations are present in patients with liver disease; primary hemostasis is often impaired due to thrombocytopenia and secondary hemostasis can be hampered by the reduced synthesis of coagulation factors [4].

Meta-analysis of the use of low-molecular-weight heparin (LMWH) such as enoxaparin in the prevention of venous thromboembolism in general surgery clearly demonstrates that LMWH is associated with lower rates of VTE than elastic compression without compromising patient safety, and similar safety and efficacy in preventing VTE to unfractionated heparin (UFH) [5]. In Japan, two randomized studies demonstrated that 20 mg enoxaparin taken twice daily has a good safety profile and is effective for the prevention of VTE in patients undergoing total hip and knee replacement [6] and abdominal or pelvic cancer surgery [7].

LMWH has potential advantageous properties such as two-fold or three-fold longer plasma half-life when compared with commercially available UFH at therapeutic doses, and a 90-95% bioavailability following subcutaneous administration [8]. These advantageous properties of LMWH obviate the need for serum concentration monitoring and enable single or double daily dosing [8]. LMWH also showed decreased interaction with platelets, and a significantly lower complication rate (0/333 patients) of heparin-induced thrombocytopenia (HIT) than UFH (9/332 patients) (0 vs. 2.7%; p = 0.0018) [9].

Another possible agents for postoperative anticoagulation therapy against VTE is the synthetic factor Xa inhibitor fondaparinux: a randomized clinical trial reported that postoperative fondaparinux (4.6% for VTE) was at least as effective as LMWH (6.1% for VTE) in patients undergoing high-risk abdominal surgery [10]. For prevention against hemorrhagic complications after liver surgery under anticoagulant therapy, we prefer enoxaparin because it has a neutralizer such as protamine.

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Portal vein thrombosis (PVT) is a potentially life-threatening complication that occurs after hepatobiliary pancreatic surgery [11,12]. Theoretically, splanchnic vein thrombosis such as PVT cannot be prevented by mechanical prophylaxis by elastic compression leg stockings and/or intermittent pneumatic compression (IPC). PVT was reported to occur in 12 of 22 (55%) patients who underwent laparoscopic splenectomy [13]. Recently, we reported postoperative PVT after hepatic resection occurred in 19 of 208 patients (9.1%), and closely related to delayed recovery of liver function and delayed liver regeneration [14]. Therefore, making an accurate diagnosis and rapidly initiating treatment for PVT are indispensable. However, there are no detailed reports about prophylaxis against PVT after hepatic resection. Accurate anticoagulation drug therapy could prevent PVT after hepatic resection.

We herein report a series of consecutive patients who underwent hepatic resection for liver cancers with or without postoperative enoxaparin administration. We examined the clinical efficacy of enoxaparin for prevention of VTE and PVT.

Methods

Patients

During the 3 years from 2011 through 2013, 287 hepatic resections for liver cancers were performed at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University. Six patients were excluded from this study, 3 because they had low platelet counts $\leq 10 \times 10^4/\mu l$, 2 because they had low preoperative % prothrombin time (PT) $\leq$ 70%, and one who received perioperative UFH for strict anticoagulant therapy because of a mechanical cardiac valve. Therefore, 281 patients were included in this study of the clinical efficacy of anticoagulant therapy with enoxaparin. The pathological diagnoses for liver tumors of patients in this series were as follows: 181 hepatocellular carcinoma (HCC), 25 intrahepatic cholangiocarcinomas (ICC), 2 cystadenocarcinoma, 1 sarcoma, and 72 metastatic liver cancers (59 colorectal liver metastasis). All patients undergoing hepatic resection had an Eastern Cooperative Oncology Group Performance status of 0-2.

Perioperative mechanical thromboprophylaxis by elastic compression legs stockings and IPC were applied to all patients. From 2011 to 2012, an anticoagulant drug was administered according to the judgment of each patient's physician in charge. From April 2013 on, patients were routinely administered enoxaparin. All 281 patients were divided into 2 groups the enoxaparin (-) group (n = 228), which also had no anticoagulant drug such as UFH or fondaparinux, and the enoxaparin (+) group (n = 53).

Surgical Techniques and Peri-operative Management

Details of our surgical techniques and patient selection criteria for hepatic resection against HCC, ICC, and CRM have been reported previously [15–17]. The key factor concerning the indication for hepatic resection is "remnant liver function" to avoid the fatal postoperative liver failure, and patients with an indocyanine green dye retention rate at 15 minutes (ICGR-15) $\leq$ 40% were selected for hepatic resection [15]. To stabilize the coagulation and fibrinolysis in hepatic resection, 200 mg nafamostat mesilate was given daily, both during and up to 2 days after operation [18], and preoperative steroid (500 mg methylpredonisolone) administration was routinely performed [19]. Intravenous antibiotics for surgical prophylaxis were also given for 2 days after operation.

In almost all hepatic resections, intermittent Pringle's maneuvers, consisting of clamping the portal triad for 15 minutes and then releasing the clamp for 5-minute intervals, or hemivascular occlusions [20] were applied intraoperatively. The CUSA system (Valley Lab, Boulder, CO, USA) has been used with addition of a VIO soft-coagulation system (ERBE Elektromedizin, Tübingen, Germany) [21]. Hepatic venous backflow control [22], which was typically achieved extrahepatically before dividing the liver, and Belghiti's hanging maneuver [23], where a tape was introduced behind the caudate lobe through the groove between the right and middle hepatic vein, were performed as necessary, especially in major hepatic resection. An intraoperative bile leakage test was routinely performed to prevent the postoperative bile leakage [24]. Laparoscopic hepatic resections in the semiprone position were applied to 37 patients in this series [25]. In patients with open hepatic resections (n = 219), an epidural catheter was inserted until the 2nd postoperative day; those with laparoscopic hepatic resection (n = 62) did not receive an epidural catheter and were not administered nafamostat mesilate perioperatively.

Evaluations of Morbidity Including PVT

Morbidity was evaluated by Clavien's classification of surgical complications, and those with a score of Grade II or more were defined as positive [26]. Postoperative liver failure and bile leakage after liver surgery were evaluated according to the definitions of International Study Group of Liver Surgery [27,28].

At 5-7 days after hepatic resection, enhanced abdominal computed tomography (CT) was routinely performed for each patient to check for intra-abdominal problems such as an abscess around the resected stump or abnormality of hepatic blood flow. Postoperative PVT was evaluated using this enhanced abdominal CT [14].

Details of Postoperative Administration of Enoxaparin

The schedule of postoperative administration of enoxaparin is summarized in Fig. 1. To prevent hemorrhagic complications, subcutaneous injections of enoxaparin 20 mg were applied twice daily after the % PT had recovered to over 70%. Patients without an epidural catheter were given the 1st dose of enoxaparin within 24-36 hours after hepatic resection [6,7]. To prevent spinal epidural hematoma related to the decrease of anticoagulant proteins just after hepatic resection or the coexistence of liver cirrhosis, patients with epidural anesthesia were given their 1st dose of enoxaparin 12 hours after the removal of the epidural catheter. Twice-daily administration of enoxaparin was continued until discharge for at most 14 consecutive days [6,7,29].

Statistical Analysis

We compared the background characteristics, surgical outcomes, tumor-related factors, and short-term surgical results including symptomatic PE, symptomatic DVT, hemorrhagic complications, and postoperative PVT between the patients in the enoxaparin (+) and the enoxaparin (-) groups. Risk factors for postoperative PVT were analyzed in this series. Continuous variables are expressed as means $\pm$ SD and were compared using the Student's *t*-test. Categorical variables were compared using either the χ^2 test or Fisher's exact test, as appropriate. Variables at a P value of less than 0.15 on univariate analysis of risk factors for postoperative PVT were subjected to stepwise logistic regression analysis to identify the independent risk factors. All statistical analyses were performed with JMP® Pro 9.0.2 (SAS Institute Inc., Cary, NC). P-values less than 0.05 were considered significant.

Results

Comparisons of Patients' Background Characteristics, Surgical Outcomes, and Tumor-related Factors

The comparison of the patients' background characteristics, surgical outcomes, and tumor-related factors is shown in Table 1. The mean age (65 *vs.* 69 years; p = 0.01) and the mean Body Mass Index (BMI) (22.9 *vs.* 24.4; p < 0.01) were significantly higher in the enoxaparin (+) group. The ratio of females was higher in the enoxaparin (+) group