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Original Article

Efficacy and safety of postoperative anticoagulation prophylaxis with enoxaparin in patients undergoing pancreatic surgery: A prospective trial and literature review

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ABSTRACT

Background: /Objectives: Enoxaparin is low-molecular-weight heparin that is used for postoperative thromboprophylaxis. The purpose of this study was to evaluate the efficacy and safety of enoxaparin after pancreatic resection. We additionally carried out a literature review regarding venous thromboembolism (VTE) and postoperative bleeding mainly after hepatobiliary-pancreatic surgery.

Methods: This was a prospective, single-arm study. Patients aged 20–79 years who planned to undergo pancreatic resection followed by postoperative anticoagulation therapy with enoxaparin were enrolled from 2013 to 2016. The exclusion criteria were low renal function, active bleeding, clinical signs of VTE at screening, or evidence of thromboembolic disease before surgery. The primary endpoint was the incidence of postoperative VTE. The secondary endpoint was the incidence of postoperative complications. For the literature review, PubMed was searched for relevant articles and the PRISMA guidelines were used.

Results: In total, 103 patients were analyzed. Two patients (1.9%) developed asymptomatic VTE, and no patients developed symptomatic VTE. No in-hospital mortality occurred. Morbidities (Clavien–Dindo grade $\geq$ IIIa) occurred in 29 patients (28.1%). Three patients (2.9%) developed intra-abdominal hemorrhage due to pseudoaneurysm formation after pancreaticoduodenectomy or distal pancreatectomy. The literature review included nine articles, and all indicated that the results of this study were feasible.

Conclusion: This is the first prospective trial to focus on pharmacologic prophylaxis with enoxaparin after pancreatic surgery. Postoperative anticoagulant therapy with enoxaparin was used in patients who underwent pancreatic surgery with a low incidence of VTE and no increase in postoperative bleeding events compared with existing evidence.

1. Introduction

Venous thromboembolism (VTE), such as pulmonary embolism (PE) or deep venous thrombosis (DVT), is a major cause of morbidity and mortality in patients undergoing gastrointestinal surgery for malignancy [1–3]. Pharmacologic prophylaxis is therefore an important and recommended aspect of postoperative care [4–6].

Previous studies of VTE prophylaxis using low-molecular-weight heparin (LMWH) such as enoxaparin in general surgery have indicated that LMWH is significantly associated with a lower incidence of VTE than is elastic compression without an increase in the incidence of severe adverse events and has efficacy and safety similar to those of unfractionated heparin [7]. Two Japanese randomized controlled trials (RCTs) indicated that enoxaparin (20 mg twice daily) is safe and effective for prevention of VTE in patients undergoing knee replacement [8] and surgical treatment of

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abdominal or pelvic cancer [9].

The incidence of VTE in patients with hepatobiliary-pancreatic (HBP) malignancy is relatively high [3,10]. Severe bleeding is a major adverse event that may occur during pharmacologic prophylaxis [3]. Thromboprophylaxis after major HBP surgery such as pancreaticoduodenectomy (PD) or hemihepatectomy is not yet routinely performed, especially in Japan, because these operations have a high risk of operative and postoperative bleeding [8,9,11,12].

The incidence of VTE in patients who have undergone pancreatic surgery is considered highest in those with HBP malignancies [1,12,13]C:\GetARef\Refs\enoxaparin.ref #25;. In addition, postoperative bleeding complications are still an important cause of postoperative mortality in patients undergoing pancreatic surgery [11,14–16]. Several studies of postoperative thromboprophylaxis with enoxaparin in patients who underwent HBP surgery, especially major hepatectomy, have been performed [12,17]. Yamashita et al. showed that postoperative anticoagulant therapy with enoxaparin could prevent portal vein thrombosis in patients who underwent hepatic resection for liver cancers [17]. Hayashi et al. indicated that chemical thromboprophylaxis is beneficial and can be safely used even after major HBP surgery [12]. Their study included 39 patients who underwent PD followed by enoxaparin treatment; however, their study was also retrospective. A prospective RCT about chemical thromboprophylaxis with enoxaparin included only one pancreatic surgery patient [9]. Reinke at al. indicated that the incidence of VTE decreased by preoperative thromboprophylaxis with unfractionated heparin, but not enoxaparin, in their retrospective study of 73 patients who underwent pancreatic surgery [13]. Thus, there is little evidence of the benefit and safety of enoxaparin after pancreatic surgery. Importantly, no prospective study has focused on the impact of enoxaparin after pancreatectomy.

This prospective, single-arm clinical study was performed to investigate the efficacy and safety of postoperative thromboprophylaxis with enoxaparin in patients undergoing pancreatic surgery. In addition, we carried out a systematic literature review regarding VTE and postoperative bleeding mainly after HBP surgery.

2. Material and methods

2.1. Study design

Because the American Society of Clinical Oncology Clinical (ASCO) Practice Guideline recommends consideration of pharmacologic thromboprophylaxis with either unfractionated heparin or LMWH in all patients with malignant disease undergoing major surgical intervention [5,6], we considered that a randomized study of patients with or without pharmacologic thromboprophylaxis should be avoided from an ethical standpoint. Thus, we designed a single-arm trial in which all enrolled patients received treatment. This single-center, single-arm, prospective study was performed at the Department of Gastroenterological Surgery, Kumamoto University Hospital, Japan from November 2013 to September 2016. The study was approved by the Institutional Review Board of Kumamoto University Hospital (#726). All procedures in this study were performed in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients before their participation in the study.

2.2. Patient selection

Male or female patients were eligible for the study if they were aged 20–79 years and undergoing planned, curative pancreatic resection [PD, hepatopancreaticoduodenectomy (HPD), distal pancreatectomy (DP), total pancreatectomy (TP), partial pancreatectomy (PP), or middle pancreatectomy (MP)] for a biliary-pancreatic tumor. Both open laparotomy and laparoscopic surgeries were included in this study.

Patients were excluded from the study if they were aged ≥80 years, had a life expectancy of ≤3 months after surgery, had either a hypersensitivity to heparin or thrombocytopenia due to heparin, had low renal function (defined as a creatinine clearance rate of <30 ml/min), or showed active bleeding. Screening of VTE by enhanced computed tomography (CT) and color doppler ultrasonography (US) was performed for all patients before surgery. Patients who had clinical signs of VTE or evidence of thromboembolic

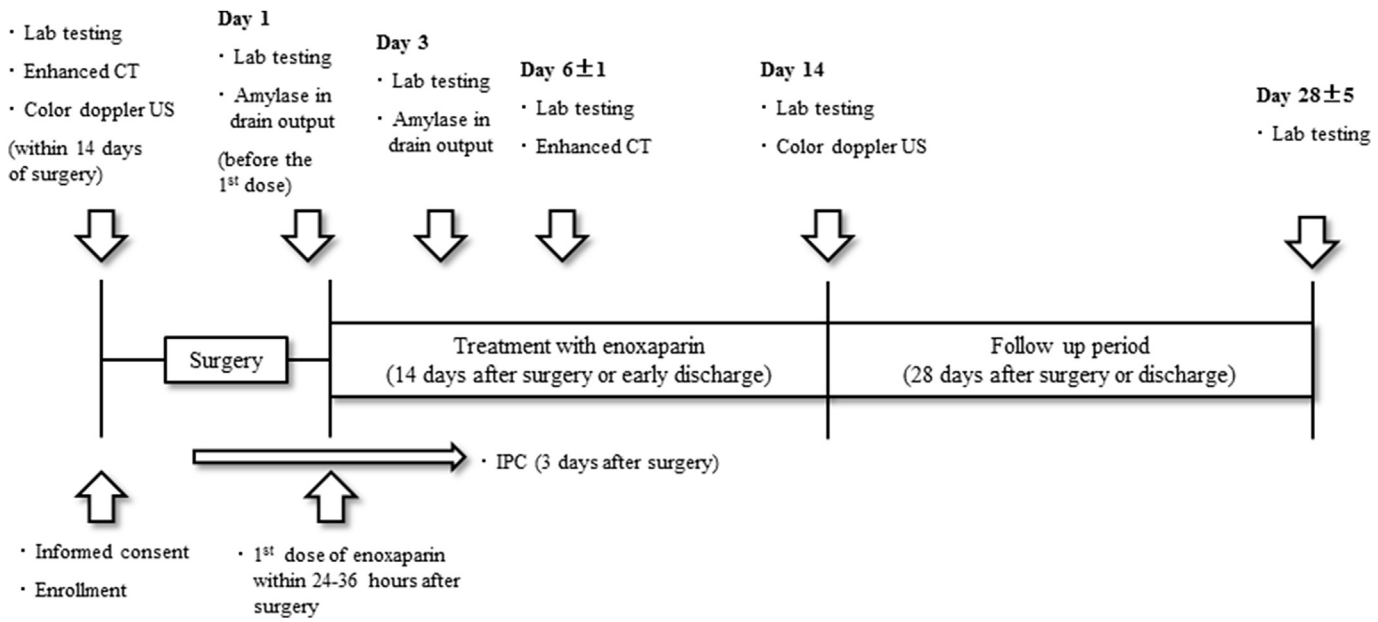

Fig. 1. Study timeline of scheduled observations, tests, evaluations, and interventions.
CT = computed tomography; IPC = intermittent pneumatic compression; US = ultrasonography.

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