Original article

Incidence of pulmonary thromboembolism in gastric cancer surgery using routine thromboprophylaxis

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Abstract

Background. There is a lack of published data on the incidence of pulmonary thromboembolism (PTE) after resections for gastric cancer. We report the incidence of PTE after gastric cancer surgery with routine thromboprophylaxis from a high-volume center.

Methods. Between October 2002 and December 2008, 3262 patients underwent gastric cancer surgery with routine thromboprophylaxis using low-dose unfractionated heparin, intermittent pneumatic compression, fluid infusion, and graduated compression stockings. Patients diagnosed with PTE were identified from a prospectively collected database that included complications related to thromboprophylaxis.

Results. Seven patients (0.2%) developed symptomatic PTE in this series. Multivariate analysis demonstrated that female sex ($P = 0.029$) and high body mass index ($P = 0.025$) were significant risk factors for PTE. The most common symptom was dyspnea (57%). Five patients (71%) developed PTE by the second postoperative day. All patients were treated successfully with medical treatment and no hospital deaths were recorded. Adverse events related to thromboprophylaxis included major postoperative bleeding in 10 (0.3%) of the 3262 patients. There were no cases of hematoma related to the insertion of epidural catheters for analgesia.

Conclusion. The routine use of thromboprophylaxis in Japanese patients undergoing gastric resection is safe and effective in reducing the incidence of pulmonary thromboembolism.

Key words Pulmonary thromboembolism · Thromboprophylaxis · Gastric cancer surgery · Low-dose unfractionated heparin · Intermittent pneumatic compression

trast to Western countries, the incidence of PTE has been very low in Japan. An autopsy study conducted in the 1960s revealed that PTE was found 20 times less frequently in the Japanese population compared to findings in the United States [1]. In keeping with a transition towards a more Western lifestyle in Japan, the risk of PTE has been increasing. A recent survey suggested that the age-adjusted mortality rate of PTE has increased markedly over the past five decades [2]. Japanese guidelines for the prevention of venous thromboembolism (*The guidelines for PTE prophylaxis in Japan*) were established in 2004, and they categorized patients undergoing major cancer surgery as a high-risk group, for whom routine thromboprophylaxis was recommended [3]

At our center, between January 1999 and September 2002, 13 of 1706 patients (0.8%) developed PTE after gastric cancer surgery. Thromboprophylaxis in this cohort was performed selectively for overweight patients (body mass index > 25). From October 2002, we have performed routine thromboprophylaxis in patients undergoing gastric resection for cancer and have prospectively recorded the incidence of PTE. Although the incidence of PTE in Japanese patients undergoing gastric cancer surgery without thromboprophylaxis was reported to be about 1%, the incidence of PTE with routine thromboprophylaxis has not been reported.

The aim of this study was to elucidate the incidence of PTE and the safety of routine thromboprophylaxis in gastric cancer surgery.

Introduction

Pulmonary thromboembolism (PTE) is a cause of morbidity and death after major abdominal surgery. In con-

Patients and methods

Patients

The study group consisted of 3262 patients who underwent gastric cancer surgery with routine thromboprophylaxis at the National Cancer Center Hospital, Tokyo, between October 2002 and December 2008.

Table 1. Patients' characteristics

	Patients undergoing gastric cancer surgery (<i>n</i> = 3262)		<i>P</i> value
	PTE (<i>n</i> = 7)	Without PTE (<i>n</i> = 3255)	
Median age, years (range)	68 (23–80)	63 (21–90)	0.873
Sex male:female (M/F)	2:5 (0.4)	2175:1080 (2.0)	0.054
Median body mass index (range)	24 (22–29)	23 (13–44)	0.119
Gastric cancer			0.225
Early (T1) disease	3 (43%)	1707 (52.4%)	
Advanced (>T2) disease	4 (57%)	1548 (47.6%)	

PTE, pulmonary thromboembolism

Table 2. Surgical procedures

	Patients undergoing gastric cancer surgery (<i>n</i> = 3262)		<i>P</i> value
	PTE (<i>n</i> = 7)	Without PTE (<i>n</i> = 3255)	
Type of surgery			0.501
Total gastrectomy	2 (28%)	901 (27.7%)	
Partial gastrectomy	4 (57%)	2107 (64.7%)	
Laparoscopic gastrectomy	0 (0%)	178 (5.5%)	
Others	1 (14%)	69 (2.1%)	
Median duration of surgery, min (range)	220 (145–291)	225 (17–661)	0.549
Median intraoperative blood loss, ml (range)	214 (97–553)	241 (10–2980)	0.621

Table 3. Multivariate analysis of risk factors for PTE

	RR	95% CI	<i>P</i> value
Age	1.002	0.940–1.068	0.958
Sex (male:female)	0.154	0.029–0.827	0.029
Body mass index	1.237	1.027–1.491	0.025
Gastric cancer (T1: ≥T2)	3.185	0.610–16.628	0.169
Duration of surgery	0.996	0.984–1.008	0.488

RR, relative risk; CI, confidence interval

Surgical procedures (Table 2)

Of the patients with PTE, two (28%) had a total gastrectomy; four (57%) had partial gastrectomies, including distal, proximal, and pylorus-preserving gastrectomy; and 1 (14%) had bypass surgery for an unresectable tumor. The median duration of surgery was 220 min (range, 145–291 min) and the median intraoperative blood loss was 214 ml (range, 97–553 ml).

Multivariate analysis of risk factors for PTE (Table 3)

Multivariate analysis was performed with the variables age, sex (M/F), body mass index, cancer T stage (T1 or ≥T2), and duration of surgery. Female sex (*P* = 0.029) and high body mass index (*P* = 0.025) were significant risk factors for the development of postoperative PTE.

Table 4. Patients with PTE (*n* = 7)

Symptoms	
Dyspnea	4 (57%)
Loss of consciousness	1 (14%)
Low arterial oxygen saturation	1 (14%)
Nonspecific lack of wellbeing	1 (14%)
Day of development	
1 st postoperative day	3 (43%)
2 nd postoperative day	2 (28%)
4 th postoperative day	1 (14%)
12 th postoperative day	1 (14%)
Severity	
Massive	1 (14%)
Submassive	2 (28%)
Nonmassive	4 (57%)
Therapy	
Therapeutic dose of unfractionated heparin	7 (100%)
Thrombolytic agent	4 (57%)
Inferior vena cava filter	3 (43%)
Artificial ventilator	1 (14%)
Median hospital stay, days (range)	35 (17–82)
Mortality of PTE	0 (0%)

Patients with PTE (Table 4)

The most common symptom in patients with PTE was dyspnea (57%) followed by loss of consciousness (14%), low arterial oxygen saturation (14%), and a nonspecific lack of wellbeing (14%). Five patients (71%) developed PTE by the second postoperative day. One patient

(14%) developed massive PTE on the twelfth postoperative day. This patient had a pancreatic fistula with active ongoing inflammation. Submassive PTE was diagnosed in two patients (28%), and nonmassive PTE in four patients (57%).

All patients with PTE were treated successfully with medical therapy using therapeutic-dose unfractionated heparin followed by warfarin. Four patients (57%) needed treatment with thrombolytic agents and 3 (43%) had an inferior vena cava filter inserted. Artificial ventilation was needed for the one patient with massive PTE. There were no mortalities after PTE.

Safety of routine thromboprophylaxis

Intermittent pneumatic compression and fluid infusion were performed in all the study patients ($n = 3262$). Low-dose unfractionated heparin was administered in 3102 patients (95.1%) but was omitted in the remaining 160 patients (4.9%) because these patients were assessed as having a high risk of postoperative bleeding. Of the 3102 patients who received low-dose unfractionated heparin, the drug was discontinued in 179 patients due to minor bleeding, heavily blood-stained discharge from drains, or wound hematomas.

Postoperative major bleeding was found in 10 (0.3%) of the 3262 patients who underwent gastric cancer surgery with routine thromboprophylaxis. These patients had localized bleeding from an artery, which was considered to be a surgical problem. None of these patients had diffuse-type bleeding related to a possible coagulopathy. Although all the study patients had epidural catheters for analgesia, no epidural hematomas were recorded.

Discussion

The incidence of PTE in gastric cancer surgery with routine thromboprophylaxis was low (0.2%) in the present study. A Japanese literature review by Sakon et al. [5] reported that the incidence of PTE in postsurgical patients without thromboprophylaxis was 1.11%. At our center, between January 1999 and September 2002, 13 (0.8%) of 1706 patients developed PTE after gastric cancer surgery. At that time, thromboprophylaxis using low-dose unfractionated heparin, intermittent pneumatic compression, and fluid infusion was reserved for overweight patients (body mass index > 25). Since October 2002 we have performed routine thromboprophylaxis in patients undergoing resection for gastric cancer and have now shown a significant reduction (from 0.8% to 0.2%; $P = 0.004$) in the incidence of PTE.

The mortality rate in Japanese patients with PTE after surgery has been reported as 31% in one literature

review [5]. Although seven patients in the present series developed PTE, there were no deaths related to this potentially fatal condition. The intensive thromboprophylaxis in our series may have prevented the propagation of pulmonary clots, and in turn, contributed to the lack of mortality. In addition, we have a low threshold for investigation and treatment of suspected PTE during the postoperative period. Patients are routinely monitored with an oxygen-saturation monitor during the first walk after surgery, and those with acute respiratory symptoms and/or a drop in arterial oxygen-saturation undergo immediate evaluation. As a result, prompt detection and treatment may have prevented mortality.

Risk factors for PTE in general surgical patients include the type of surgery, cancer, previous venous thromboembolism, obesity, delayed mobilization, increasing age, female sex, prolonged duration of surgery, and postoperative infection [6, 7]. Multivariate analysis in the present series demonstrated that female sex and high body mass index were significant risk factors for PTE. It has been reported that PTE occurs more frequently in females than in males in the Japanese population [8, 9], while many Western studies demonstrate a slightly higher risk of PTE in males [10, 11]. The reason for this discrepancy is still unclear. The increased risk of PTE related to obesity is less controversial. The proportion of obese patients with gastric cancer has been rising in Japan [12] and this is probably contributing to the increasing incidence of PTE.

Evidence from numerous randomized clinical trials and meta-analyses suggests that patients should receive routine thromboprophylaxis following major general surgical procedures [13]. For patients undergoing major cancer surgery, the 8th American College of Chest Physicians guidelines (2008) recommended thromboprophylaxis with low-molecular-weight heparin, low-dose unfractionated heparin, or fondaparinux [6]. Both low-dose unfractionated heparin and low-molecular-weight heparin reduce the risk of PTE after general surgery compared with no thromboprophylaxis [13, 14], and the therapeutic equivalence of the drugs in terms of both efficacy and safety has been reported previously [15–18]. The *guidelines for PTE prophylaxis in Japan* (2004) categorized patients undergoing major cancer surgery as a high-risk group, for whom thromboprophylaxis with intermittent pneumatic compression or low-dose unfractionated heparin was recommended [3]. PTE is a relatively uncommon postoperative complication, but the risk of a potentially fatal outcome is high. In light of this we have adopted an intensive thromboprophylaxis regimen; combining low-dose unfractionated heparin with intermittent pneumatic compression, fluid infusion, and graduated compression stockings. Although our protocol exceeds the current Japanese guidelines, the

cost of the treatment is fully covered by the national insurance system.

The optimal timing for the initiation of thromboprophylaxis is not well established. In most studies of thromboprophylaxis using low-dose unfractionated heparin or low-molecular-weight heparin, subcutaneous administration of these drugs is started 1 to 2 h before surgery [19]. However, in a study comparing the administration of 5000 units of dalteparin (a low-molecular-weight heparin) the evening before surgery to administration 2 h before surgery, the incidence of postoperative deep venous thrombosis was reduced in the group given heparin the evening before [20]. PTE usually occurs in the early postoperative period. In our series, five patients (71%) developed PTE by the second postoperative day. During the period between January 1999 and September 2002, when we were using selective thromboprophylaxis, 12 (92%) of 13 patients developed PTE by the second postoperative day (data not shown). These findings suggest that venous thrombi develop during or just after surgery, and thromboprophylaxis should therefore be started prior to surgery. We have not used heparin preoperatively because of the potential risk of increased intraoperative bleeding. We have adopted an alternative strategy of preoperative fluid infusion from the evening prior to surgery in order to avoid dehydration. There is supporting evidence that adequate hydration reduces the incidence of venous thromboembolism in air travelers [21].

The optimal duration of thromboprophylaxis is controversial. In the early studies of thromboprophylaxis with unfractionated heparin, the drug was administered for approximately 1 week [19]. However, it has recently been clear that late thrombotic events can occur up to 6–7 weeks after surgery [22, 23]. A literature review of the frequency of late thrombotic events suggests that clinically diagnosed late deep venous thrombosis and/or PTE (outside the normal period of hospitalization) occurs in approximately 1% of patients [24]. The Enoxaparin and Cancer II study has shown, at least in high-risk patients (such as those with cancer), that there is a significant benefit of an extended 4-week prophylactic period compared with the standard 1-week regimen [25]. However, these evidences are derived from observations and studies in the West. Given the rarity of PTE in Japan as evidenced in the current case series, frequent manifestation within the first two days postoperatively, and high cost of relevant medical resources, prolonged thromboprophylaxis extending for several weeks may not be recommended for the Japanese population in general and could be reserved for patients who suffer from morbid surgical site infection.

The present study revealed that our regimen of routine thromboprophylaxis is safe, with a low incidence of bleeding complications. The incidence of major bleed-

ing after gastric cancer surgery was 0.3% in this series and it was not higher than the incidence in a previous cohort when thromboprophylaxis was used selectively in overweight patients only (0.3%; 5 of 1706 patients, data not shown). A similar finding was observed in a previous report (0.3% in both control and low-dose unfractionated heparin groups) [13]. The incidence of minor bleeding that required discontinuation of heparin was also low in the present series (5.8%; 179 of 3102 patients). In spite of the routine use of epidural catheters for postoperative analgesia, none of the patients in this series developed epidural hematomas. Because epidural catheters are inserted just prior to surgery and removed on the third postoperative day, low-dose unfractionated heparin is avoided at these times. Thus, the careful use of pharmacological thromboprophylaxis did not increase bleeding complications.

Heparin-induced thrombocytopenia develops in 2.7% of patients receiving unfractionated heparin therapy and typically appears 5 or more days after the start of the therapy [10]. No patients in the present series developed clinically relevant thrombocytopenia. This could be explained by the short duration of treatment with unfractionated heparin in our regimen.

In conclusion, the incidence of PTE in patients undergoing resection for gastric cancer with routine thromboprophylaxis was very low. Intensive thromboprophylaxis is safe and should be used routinely for the prevention of PTE.

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