



BRIEF ARTICLES

## A study of pulmonary embolism after abdominal surgery in patients undergoing prophylaxis

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### Abstract

**AIM:** To determine risk factors for pulmonary embolism and estimate effects and benefits of prophylaxis.

**METHODS:** We included 78 patients who died subsequently to a pulmonary embolism after major abdominal surgery from 1985 to 2003. A first, retrospective analysis involved 41 patients who underwent elective surgery between 1985 and 1990 without receiving any prophylaxis. In the prospectively evaluated subgroup, 37 patients undergoing major surgery between 1991 and 2003 were enrolled: all of them had received a prophylaxis consisting in low-molecular weight heparin, given subcutaneously at a dose of 2850 IU AXa/0.3 mL (body weight < 50 kg) or 5700 IU AXa/0.6 mL (body weight ≥ 50 kg).

**RESULTS:** A higher incidence of thromboembolism (43.9% and 46.34% in the two groups, respectively) was found in older patients (> 60 years). The incidence of pulmonary embolism after major abdominal surgery in patients who had received the prophylaxis was significantly lower compared to the subjects with the

same condition who had not received any prophylaxis ( $P < 0.001$ , OR = 2.825; 95% CI, 1.811-4.408). Furthermore, the incidence of pulmonary embolism after colorectal cancer surgery was significantly higher compared to incidence of pulmonary embolism after other abdominal surgical procedures. Finally, the incidence of pulmonary embolism after colorectal cancer surgery among the patients who had received the prophylaxis (11/4316, 0.26%) was significantly lower compared to subjects undergoing a surgical procedure for the same indication but without prophylaxis (10/1562, 0.64%) ( $P < 0.05$ , OR = 2.522; 95% CI, 1.069-5.949).

**CONCLUSION:** Prophylaxis with low molecular weight heparin is highly recommended during the preoperative period in patients with diagnosis of colorectal cancer due to high risk of pulmonary embolism after elective surgery.

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**Key words:** Pulmonary embolism; Surgery; Colorectal cancer; Risk factor; Prevention

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### INTRODUCTION

Pulmonary embolism (PE) is a life-threatening condition or complication and might be one of the worst nightmares for most surgeons. PE is a partial obstruction of the pulmonary arterial tree. The embolus that causes the obstruction usually travels through the venous system from a distant site. PE causes symptoms such as dyspnea, chest pain or collapse. Moreover, the clinical severity of PE can vary, ranging from asymptomatic cases to sudden death. Despite advances in diagnosis and treatment, PE remains a significant cause of morbidity and mortality and is still one of the most common preventable causes of

death, which is easily overlooked<sup>[1,2]</sup>.

Risk factors for deep vein thrombosis (DVT) and PE are prior medical history of DVT or PE, recent surgery, general anesthesia lasting longer than 30 min, pregnancy, prolonged immobilization, age > 40 years, obesity or underlying malignancy<sup>[3,4]</sup>. Moreover, gynecologic surgery, major trauma and indwelling venous catheters are risk factors for DVT at any location. Otherwise, venous thrombosis commonly involves lower limbs, affecting most frequently calf veins, which are involved in virtually 100% of symptomatic, spontaneous lower extremity DVT. Although DVT usually starts in calf veins, it is propagated above the knee in 87% of symptomatic patients before the diagnosis has been made. However, more than 35% of patients who die from PE may have isolated calf vein thrombosis<sup>[5]</sup>.

## MATERIALS AND METHODS

### Subjects

We identified 54690 patients who had surgery between January, 1985 and December, 2003. The study included 39 (50%) females and 39 (50%) males who died subsequently to a PE after major abdominal surgery throughout the study period.

### Retrospective analysis

The database of the Institute for Digestive Disease, Clinical Center of Serbia was reviewed to identify patients who had undergone surgery from January, 1985 to December, 1990. Age, final pathologic diagnosis at autopsy, surgical procedures and venous thromboembolism prophylaxis modalities were recorded.

In a first retrospective evaluation, out of the 15427 patients who had undergone surgery between 1985 and 1990, we included 41 cases (20 men, 21 women) of PE confirmed at autopsy. These patients had not received any prophylaxis prior to elective surgery, as prophylaxis was not performed on a regular basis during that period in our country. The PE patients had undergone the following surgical procedures: total oesophagogastrectomy, 1 case (2.4%); total gastrectomy, 3 (7.3%); Billroth I -type gastric resection, 2 (4.8%); Billroth II-type gastric resection, 4 (9.7%); gastrostomy with jejunostomy, 1 (2.4%); fundoplication, 1 (2.4%); cholecystectomy, 5 (12.1%); ileal resection, 1 (2.4%); nephrectomy, 1 (2.4%); appendectomy, 2 (4.8%); inguinal hernioplasty, 2 (4.8%); adhesiolysis, 1 (2.4%); laparotomic exploration with biopsy of the tumor, 5 (14.6%); right hemicolectomy, 1 (2.4%); left hemicolectomy, 4 (9.7%); coecostomy, 1 (2.4%); splenectomy with distal pancreatectomy, 1 (2.4%); and low anterior resection of the rectum, 3 (7.32%).

### Prospective analysis

In the second part of our study, a total of 39263 patients were admitted to the Institute of Digestive Disease, Clinical Center of Serbia, between January, 1991 and July, 2003, to undergo abdominal elective surgery. All patients

who underwent major surgery received low-molecular weight heparin (LMWH) prophylaxis subcutaneously at a dose of 2850 IU AXa/0.3 mL (body weight < 50 kg) or 5700 IU AXa/0.6 mL (body weight ≥ 50 kg), one hour before the surgery, 12 and 24 h after the main surgery, and once daily each hospital day after main surgery. Prophylaxis did not cause any side effects (e.g. bleeding). Out of this group, a total of 37 patients (19 men, 18 women) died after major surgery due to PE. Diagnosis was confirmed at autopsy. These patients had undergone the following major surgery procedures: total gastrectomy, 5 (13.5%); ulcer suture, 2 (5.4%); gastrostomy, 2 (5.4%); cholecystectomy, 4 (10.8%); hepatico-jejuno anastomosis according to Roux, 2 (5.4%); partial pericystectomy with omentoplasty, 2 (5.4%); ileal resection, 1 (2.7%); appendectomy, 1 (2.7%); hernioplasty, 1 (2.7%); abscess drainage, 1 (2.7%); laparotomic exploration with biopsy of the tumor, 2 (5.4%); total colectomy, 2 (5.4%); right hemicolectomy, 3 (8.1%); left hemicolectomy, 3 (8.1%), Dixon-type resection, 2 (5.4%); Hartman-type resection, 2 (5.4%); Belsey-type resection, 1 (2.7%) and double colostomy, 1 (2.7%) (Table 1).

### Statistical analysis

Results were presented as mean ± SD or as stated. Distribution data were compared by  $\chi^2$  analysis or Kruskal-Wallis test, if data were not normally distributed. In addition, logistic regression tests were conducted. All statistical analyses were performed with the SPSS 10.0 for Windows package (SPSS Inc., Chicago, IL). Values at the  $P = 0.05$  level were considered statistically significant.

## RESULTS

No significant difference as to the gender distribution existed between the two groups ( $\chi^2$  test,  $P > 0.05$ ). No significant difference in the mean age was found between patient groups (Kruskal-Wallis test,  $P > 0.05$ ). However, a higher incidence of thromboembolism (43.9% and 46.34%) was found in older patients (60-69 year range) in both groups of patients.

Forty-one patients out of 15427 (0.27%) who did not receive prophylaxis developed a PE. Among the 39263 patients who received prophylaxis, 37 (0.09%) developed a PE in the postoperative period.

Among the 15427 cases evaluated retrospectively, we identified 4304 patients who underwent colorectal abdominal surgery. Of them, 1562 were cancer cases. Among colorectal cancer patients who underwent major abdominal surgery, 0.64% (10/1562) developed PE postoperatively, while the incidence of PE in all remaining patients was 0.11% (16/13865) ( $P < 0.05$ , OR = 5.577, 95% CI, 2.526-12.311).

Among the 39263 patients who had received prophylaxis before major surgery, 37 (0.09%) were diagnosed as having postoperative PE. Of the 39263 major cases evaluated prospectively, we identified 11735 patients who underwent colorectal abdominal surgery.

Table 1 Characteristics of patients with pulmonary embolism

Clinical data	PE without prophylaxis (n = 41)	PE with prophylaxis (n = 37)
Mean age, yr (range)	64 (26-79)	67 (45-79)
M/F	20/21	19/18
Cause of death (primary)		
Obstruction of right pulmonary artery	10	5
Obstruction of left pulmonary artery	3	5
Obstruction of pulmonary trunk	10	1
Obstruction of both right and left pulmonary arteries	11	20
Obstruction of pulmonary trunk plus both right and left pulmonary arteries	7	6
Cause of death (secondary)		
Colorectal malignancy	11	10
Other malignancy	14	12
Other diagnosis	16	15
Prophylaxis	None	LMWH s.c: 0.3 mL (BW ≤ 50 kg) or 0.6 mL (BW > 50 kg), 1 h before and 12 h after surgery
Time from surgery to death		
0-5 d	12	22
6-10 d	19	8
11-15 d	6	2
16-30 d	4	3
> 30 d	0	2

PE: Pulmonary embolism; LMWH: Low-molecular weight heparin.

Of them, 4316 were cancer cases. Among colorectal cancer patients who underwent major abdominal surgery, 0.25% (11/4316) developed PE postoperatively, while the incidence of PE in all remaining patients was 0.05% (17/34947) ( $P < 0.05$ , OR = 5.250, 95% CI, 2.457-11.216).

The incidence of PE after colorectal cancer surgery among patients who had received prophylaxis was significantly lower compared to that observed in subjects with colorectal surgery due to carcinoma who had not received any prophylaxis, i.e. 0.26% (11/4316) vs 0.64% (10/1562) ( $P < 0.05$ , OR = 2.522; 95% CI, 1.069-5.949). Moreover, incidence of PE after major abdominal surgery of patients who had received prophylaxis was significantly lower compared to that seen in subjects with the same diagnoses who had not received any prophylaxis ( $P < 0.001$ , OR = 2.825; 95% CI, 1.811-4.408).

## DISCUSSION

PE is third most common cause of death in the US, with at least 650 000 cases occurring annually. Furthermore, PE represents the first or second most common cause of unexpected death in most age groups. The highest incidence of recognized PE occurs in hospitalized patients. Autopsy results are showing that up to 60% of patients who die at a hospital have PE, and that diagnosis is missed in about 70% of cases<sup>[6]</sup>. The annual incidence of known DVT and PE in the Western world is 1.0 and 0.5 per 1000, respectively. There are 65 000 cases each year among hospital patients in England and Wales. The prevalence of unsuspected PE diagnosed at autopsy is 3%-8%, and has been unchanged for 3 decades.

PE is common during all trimesters of pregnancy

and puerperium, and incidence of PE is increasing with oral contraceptive or hormone replacement therapy. However, sex alone is not an independent risk factor<sup>[7]</sup>.

Although the frequency of PE increases with age, this is not independent risk factor. Nevertheless, the accumulation of different risk factors, such as underlying illnesses and decreased mobility, increases the frequency of PE in older patients. Unfortunately, diagnosis of PE is often missed, especially in older patients. PE is diagnosed in 30% of all patients who die with massive PE, but only in 10% of those who are 70 years of age or older. Thus, PE still remains the most commonly missed diagnosis in the elderly institutionalized patients<sup>[7]</sup>.

In our study, we found a higher incidence of PE in older patients (> 60 years of age) in both groups (43.9% and 46.34%).

Surgical patients have long been recognized to be at special risk for DVT and PE, but these problems are not confined to surgical patients. Surgeons should always suspect PE in case of a sudden circulatory collapse occurring within one to two weeks after surgery.

The risk of postoperative venous thromboembolism is reported to be twice as high in patients with cancer compared of those without cancer undergoing comparable surgery<sup>[8]</sup>. This risk is also higher in patients undergoing surgery for colorectal cancer as compared to those having abdominal surgery without malignancy. Thromboembolic complications are responsible for about half of deaths following elective colorectal surgery<sup>[9]</sup>. The highest rate (1.8%) of fatal PE was reported in patients following colorectal surgery, with a 3.3-fold increase compared to the overall rate observed among surgical patients, according to a retrospective 10-year review from Switzerland<sup>[10]</sup>. In this study, the increased risk of PE can be explained by a number of factors, such as malignancy-related hypercoagulable

state, postoperative infectious complications, prolonged surgery, pelvic dissection *etc*<sup>[11]</sup>.

Overall, the incidence of PE after general surgery observed in Japan was 0.33%. Fatal PE was reported in 0.08% of the surgical population and the mortality rate of patients with PE was 31%. In addition, the incidence of PE after cancer surgery ranged from 0.57% after colon malignancy to 3.85% after pancreatic cancer surgery, and was significantly higher than in non-cancerous conditions (0.20%)<sup>[12]</sup>.

An increased risk of PE after colorectal surgery has also been showed by Lee *et al* in a study on Chinese patients who underwent colorectal surgery without DVT prophylaxis. The authors demonstrated the occurrence of asymptomatic calf vein thrombosis in 41.7% of patients using serial Duplex ultrasound studies<sup>[13]</sup>.

In our experience, the incidence of PE after colorectal cancer surgery was significantly higher compared with other surgical procedures. However, the incidence of PE after colorectal cancer surgery of patients who received prophylaxis was significantly lower compared to that seen among subjects with colorectal surgery due to carcinoma without prophylaxis.

In the study by Shukla *et al*<sup>[11]</sup>, 99 patients with colorectal cancer selected for surgery were included. Fifty-one patients were randomized to receive LMWH while 48 patients did not receive any prophylaxis. At the end of the study, neither DVT nor PE cases were observed<sup>[12]</sup>.

Anticoagulant prophylaxis is effective in preventing PE in hospitalized patients, since it reduces mortality after surgery. Prophylaxis with LMWH leads to effective reductions in the incidence of DVT after abdominal surgery in patients at risk for thromboembolic complications.

Initial treatment with LMWH following oral anticoagulant therapy with INR ranging from 2 to 3 was associated with an incidence of major bleeding of 3% at 3 mo while the mortality rate was 0.3%<sup>[14]</sup>.

However, Diener *et al*, showed that there may be a dose-dependent risk of bleeding with LMWH therapy<sup>[15]</sup>. Low dose of LMWH was arbitrarily defined as a fixed dose of less than 6000 IU daily, whereas any higher dose of LMWH was considered as LMWH high dose. Concerning weight-adjusted doses of LMWH, 86 IU/kg per day was considered as LMWH low dose, while 86 IU/kg twice a day was considered as LMWH high dose.

In our study, patients who received prophylaxis with low dose LMWH after major abdominal surgery did not have any side effects (such as bleeding). Moreover, incidence of PE was significantly lower compared to subjects with the same conditions who did not receive prophylaxis.

The incidence of PE was four to six times lower in patients who had mechanical prophylaxis, although the difference was not significant. Preoperative prophylaxis for DVT is important, but further research is needed to estimate its effects and benefits<sup>[12]</sup>.

In our study, older age (> 60 years) was identified to be a risk factor for PE. Prophylaxis with LMWH is highly recommended for patients with colorectal cancer before major surgery. As the mortality from PE depends

on correct and timely diagnosis, it is of the utmost importance for clinicians to consider this possibility and perform proper diagnostic tests, especially in patients with colorectal cancer.

## COMMENTS

### Background

Pulmonary embolism (PE) is a life-threatening condition or complication and might be also one of the worst nightmares for most surgeons. Despite advances in diagnosis and treatment, PE remains a significant cause of morbidity and mortality and is still one of the most common preventable causes of death, which is easily overlooked. Risk factors for deep vein thrombosis (DVT) and PE are prior medical history of DVT or PE, recent surgery, general anesthesia lasting longer than 30 min, pregnancy, prolonged immobilization, age > 40 years, obesity or underlying malignancy.

### Research frontiers

PE is the third most common cause of death in the US, with at least 650 000 cases occurring annually. Furthermore, PE represents the first or second most common cause of unexpected death in most age groups. The highest incidence of recognized PE occurs in hospitalized patients. The highlight of this article was to characterize relationship between PE and prophylaxis with a low dose of low-molecular weight heparin.

### Innovations and breakthroughs

The highest rate of fatal PE in previous studies was reported in patients following colorectal surgery. Shukla *et al* described that increased risk of PE has been attributed to a number of factors such as malignancy-related hypercoagulable state of cancer patients, postoperative complications due to infections, prolonged surgery and pelvic dissection. In our experience, incidence of PE after colorectal cancer surgery was also significantly higher compared with other surgical procedures. However, in our study, patients who received prophylaxis with low dose low-molecular weight heparin (LMWH) after major abdominal surgery did not have any side effects (such as bleeding). Moreover, the incidence of PE was significantly lower compared to subjects who did not receive the prophylaxis.

### Applications

The results of this study suggest that prophylaxis with LMWH is highly recommended for older patients (> 60 years) and patients with colorectal cancer before major surgery. As the mortality from PE depends on a correct and timely diagnosis, it is of the utmost importance for clinicians to consider this possibility and perform proper diagnostic tests, especially in patients with colorectal cancer.

### Terminology

Prophylaxis: A low dose of LMWH was arbitrarily defined as a fixed dose of less than 6000 IU daily. A dose of LMWH above 6000 IU was considered high dose LMWH. Concerning weight-adjusted doses LMWH, 86 IU/kg per day was considered as LMWH low dose while 86 IU/kg twice a day was considered LMWH high dose.

### Peer review

This controlled study shows that prophylaxis with low dose of LMWH significantly decreases the incidence of PE after surgery. In addition, our research may foster new therapeutic developments in the treatment of PE.

## REFERENCES

- 1 Idiz M, Konuralp C, Ates M. Under diagnosis of pulmonary embolism: a recurrent nightmare for surgeons. *Eastern J Med* 2003; **8**: 1-6
- 2 Wolfe TR, Hartsell SC. Pulmonary embolism: making sense of the diagnostic evaluation. *Ann Emerg Med* 2001; **37**: 504-514
- 3 Robinson GV. Pulmonary embolism in hospital practice. *BMJ* 2006; **332**: 156-160
- 4 McAlister FA, Bertsch K, Man J, Bradley J, Jacka M. Incidence of and risk factors for pulmonary complications after nonthoracic surgery. *Am J Respir Crit Care Med* 2005; **171**: 514-517
- 5 Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. *J Thromb Thrombolysis* 2006; **21**: 23-29



- 6 **Klok FA**, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. *Am J Respir Crit Care Med* 2008; **178**: 425-430
- 7 **Konstantinides SV**. Massive pulmonary embolism: what level of aggression? *Semin Respir Crit Care Med* 2008; **29**: 47-55
- 8 **Prandoni P**. Antithrombotic strategies in patients with cancer. *Thromb Haemost* 1997; **78**: 141-144
- 9 **Huber O**, Bounameaux H, Borst F, Rohner A. Postoperative pulmonary embolism after hospital discharge. An underestimated risk. *Arch Surg* 1992; **127**: 310-313
- 10 **Wille-Jorgensen P**, Kjaergaard J, Jorgensen T, Korsgaard Larsen T. Failure in prophylactic management of thromboembolic disease in colorectal surgery. *Dis Colon Rectum* 1988; **31**: 384-386
- 11 **Shukla PJ**, Siddachari R, Ahire S, Arya S, Ramani S, Barreto SG, Gupta S, Shrikhande SV, Jagannath P, Desouza LJ. Postoperative deep vein thrombosis in patients with colorectal cancer. *Indian J Gastroenterol* 2008; **27**: 71-73
- 12 **Sakon M**, Kakkar AK, Ikeda M, Sekimoto M, Nakamori S, Yano M, Monden M. Current status of pulmonary embolism in general surgery in Japan. *Surg Today* 2004; **34**: 805-810
- 13 **Lee FY**, Chu W, Chan R, Leung YF, Liu KH, Ng SM, Lai PB, Metreweli C, Lau WY. Incidence of deep vein thrombosis after colorectal surgery in a Chinese population. *ANZ J Surg* 2001; **71**: 637-640
- 14 **Nijkeuter M**, Sohne M, Tick LW, Kamphuisen PW, Kramer MH, Laterveer L, van Houten AA, Kruip MJ, Leebeek FW, Buller HR, Huisman MV. The natural course of hemodynamically stable pulmonary embolism: Clinical outcome and risk factors in a large prospective cohort study. *Chest* 2007; **131**: 517-523
- 15 **Diener HC**, Ringelstein EB, von Kummer R, Langohr HD, Bewermeyer H, Landgraf H, Hennerici M, Welzel D, Grve M, Brom J, Weidinger G. Treatment of acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the TOPAS trial. Therapy of Patients With Acute Stroke (TOPAS) Investigators. *Stroke* 2001; **32**: 22-29

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