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Full Length Article

Venous thromboembolism after surgical treatment of non-spinal skeletal metastases — An underdiagnosed complication

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ABSTRACT

Introduction and aim: Venous thromboembolism (VTE) is a severe complication associated both with major orthopaedic surgery and cancer. However, survival and postoperative complications of skeletal metastases despite their thrombogenic potential, have received little attention in both the clinical management and research setting. This single-centre observational cohort study aimed to evaluate the incidence and impact of VTE in association with cancer surgery targeted to the management of fractures secondary to skeletal metastases.
Methods: Data were collected retrospectively from the medical database. We included consecutive 306 patients operated for 343 non-spinal skeletal metastases during a 15-year period (1999–2014).
The incidence of VTE and its risk factors were assessed using binary logistic regression analysis. Kaplan–Meier and Cox regression analyses were used to evaluate variables affecting survival.
Results: The rate of symptomatic VTE was 10% (30/306) during the 3-month postoperative period, while 79% received thromboprophylaxis. Fatal pulmonary embolism (PE) rate was high, 3.3% (10/306) after surgery. Intraoperative oxygen saturation drop, pulmonary metastases and intramedullary nailing were independent risk factors for VTE. Indicators of decreased survival were lung cancer, intramedullary nailing, multiple skeletal and pulmonary metastases, anaemia, leukocytosis, and PE.
Conclusion: Relationship between fractures secondary to skeletal metastases and VTE needs further clinical attention. Whether the survival of patients with fractures secondary to skeletal metastases can be improved by targeted thromboprophylactic means should be studied further.

1. Introduction

Cancer is a well-known risk factor for venous thromboembolism (VTE) events, including deep vein thrombosis (DVT) and pulmonary embolism (PE). It is estimated that the overall risk of a VTE is increased seven-fold in patients with a malignancy compared with those without malignancy [1]. In patients with cancer, each of the three components of Virchow's triad (blood composition, vessel wall components and blood flow) represents abnormalities that predispose to thrombus formation. Additionally, abnormal angiogenesis is involved in tumour growth, resulting in a prothrombotic state [2]. Several other risk factors for VTE in cancer patients have been reported, including a history of VTE, female gender, older age, leukocytosis, and thrombocytosis [3,4]. Patients who are treated with chemotherapy or have metastatic disease have additional risks for VTE [1,2]. Patients with distant metastases and those undergoing chemotherapy are reported to have a two-fold increased risk compared with those without metastases or not undergoing chemotherapy [1]. One survey found that 5–10% of patients with breast cancer undergoing adjuvant chemotherapy and up to 15% of those with metastatic disease had VTE [5]. Different models for predicting chemotherapy-associated VTE have been developed. One model, the Khorana score, includes the following variables: site of cancer, platelet count, haemoglobin, leukocyte count, and BMI [6].

Trauma and orthopaedic surgery are also well-known risk factors for VTE [7,8]. However, the reported symptomatic VTEs have been few, as during the 90 days after the primary total hip arthroplasty symptomatic DVT occurs in 0.7% and PE in 0.3% of the patients. [9] In one large study including 199,952 patients with pelvic and lower-extremity fracture symptomatic PE was identified only in 0.5% of patients. [10] Cancer surgery seems to significantly increase the risk of postoperative VTE, as well as risk of fatal PE when compared to similar procedures in non-cancer patients (0.33% vs. 0.09%) [11]. Moreover, both cancer and trauma and their management may otherwise contribute to the prothrombotic state, including bed rest, infection, and certain chemotherapies.

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VTE is a severe complication in all hospitalized patients [4]. In a population-based study matched for type of cancer, sex, age, and the year of diagnosis, the 1-year survival of patients diagnosed with VTE and malignancy was 12% compared with those patients without VTE, whose survival rate was three-fold higher [12]. Mortality rates are three times higher in the first 6 months after VTE in patients with cancer than in those without cancer [13]. A necropsy study revealed that 10% (648 of 6197) of patients who died of cancer had PE [14]. After major surgery as much as 10–40% of the deaths were related to PE. [15].

Even though a number of studies have shown the importance of VTE after orthopaedic surgery and disseminated cancer, little attention has been given to the incidence of thrombosis in patients after pathological fractures secondary to skeletal metastases. Therefore, the aim of this observational study was to determine (1) the incidence and impact of symptomatic VTE postoperatively, (2) the risk factors for VTE, (3) whether the Khorana score itself or its haematological elements separately could predict VTE in this surgical patient cohort, and (4) risk factors for decreased survival after operation.

2. Patients and methods

Patients for this observational cohort study were identified from a prospectively maintained database in one referral centre. All consecutive patients, included in the study were treated surgically for non-spinal skeletal metastases, in the vast majority due to pathological fractures, between the 1st of April 1999 and the 31st of July 2014. The institutional ethical review board approved the study. Data were retrospectively collected from the medical records. All patients had metastatic stage IV cancer and all the patients were living independently before surgery. Patients whose survival was estimated to be less than four weeks were not operated. Surgical procedures included osteosynthesis with plate, intramedullary nailing with or without cementing, total arthroplasty, endoprosthetic replacement and Harrington procedure.

Symptomatic DVT was identified by ultrasound scan of lower extremities and PE was diagnosed with computer tomography or autopsy. Data regarding deaths were verified from death certificates or autopsy reports at our institution. Data of patients who died outside the hospital were obtained from Statistics Finland, which is the exclusive Finnish public authority holding data regarding causes of death and post mortem death certificates. Unfortunately, the mortality data are routinely updated 1 year later, thereby underestimating the true rate of occurrence towards the end of the study.

In year 2004 the national guidelines for postoperative thromboprophylaxis were introduced. After this recommendation all major orthopaedic patients had postoperative prophylaxis, enoxaparin 40 mg or dalteparin 5000 IU started 6–12 h postoperatively continuing on once daily basis, unless a bleeding complication or major bleeding risk ensued. No mechanical prophylaxis was used. Surgical techniques and operating times have remained stable in this 15-year period.

2.1. Statistical analysis

Univariate analysis was performed for risk factors of VTE. The chi-square test or Fisher's exact test in the case of proportions and by the *t*-test in the case of continuous variables was used. Using multivariable analysis with binary logistic regression we assessed independent risk factors for VTE and PE. Survival was assessed using the Kaplan-Meier method with a log-rank test for univariate analysis while Cox regression analysis was used to identify independent factors affecting patient survival. In survival analyses we censored patients still alive at the time of study and patients who died for other reasons than cancer. The following variables were evaluated: gender, age, primary diagnosis, number of skeletal metastases (solitary/multiple), metastatic load and sites (lung and liver), intraoperative haemorrhagic events, operation time, intraoperative oxygen saturation drop during application of nails or stems (no vs. minor drop of 5–15% and major drop >15%), fracture localisation (humerus, radius, ulna, scapula, pelvis, femur, or tibia), specific operation method (intramedullary nailing vs. others) and use of low-molecular-weight heparin (LMWH) (28-day period as cut off). The Khorana score as such and its separate haematological variables were analysed to investigate the prediction of VTEs and survival among these patients (6). The variables from the Khorana score are as follows: site of cancer (2 points for very high-risk site, including pancreas and stomach; 1 point for high-risk site, including lung, lymphoma, gynaecologic, and genitourinary organs, excluding the prostate), platelet count ≥350 $\times$ 10^9/L, haemoglobin <100 g/L and/or use of erythropoiesis-stimulating agents, leukocyte count >11 $\times$ 10^9/L, and BMI ≥35 kg/m^2 (1 point each). These variables were analysed both together and independently, in particular to focus on the haematological variables. Specifically, leukocyte count was analysed for different cut-off values (8, 9, 10, and 12 $\times$ 10^9/L). The laboratory parameters were measured preoperatively. *P*-value <0.05 indicated statistical significance. Analyses were conducted with statistical software package IBM SPSS Statistics version 21.0.

3. Results

A total of 343 orthopaedic procedures were performed in 306 patients; 171 females (55.9%) and 135 males (44.1%). The study population comprised several different primary tumours (Table 1). Breast cancer, myeloma and renal cancer were the most common. Patients had a mean age of 67.2 (range 23.4–94.7) years at the time of the operation. Demographics of identifiable risk factors for VTE are reported in Table 2. Altogether 55 patients did not receive thromboprophylaxis. 15 of them were encountered after year 2004, and 13 of them were operated because of upper extremity fracture, one patient had pelvic surgery but because massive intraoperative bleeding complication postoperative thromboprophylaxis was not used. Two patients; one after femoral nailing and one after tibia plating did not have thromboprophylaxis due to unknown reasons.

Symptomatic VTE was identified in 35 patients (11.4%), of which PE was identified in 26 patients (8.5%). In 3-month postoperative period the VTE rate was 10%. Ten out of 306 patients (3.3%) had the diagnosis of PE as the cause of death in post mortem death certificate, established by autopsy. From the 26 patients who had PE, primary tumours were lung cancer ($n = 7$), breast cancer ($n = 6$), renal cancer ($n = 4$), prostate cancer ($n = 3$), myeloma ($n = 2$), lymphoma ($n = 1$), HCC ($n = 1$), primary bone sarcoma ($n = 1$) and in one case tumour origin

Table 1
Distribution of the types of cancer among the study population.

Primary tumour	n	%
Breast cancer	97	31.7
Myeloma	50	16.3
Renal cancer	38	12.4
Prostate cancer	35	11.4
Lung cancer	33	10.8
Colon cancer	8	2.6
Lymphoma	8	2.6
Sarcoma	7	2.3
Unknown	6	2.0
Melanoma	4	1.3
Thyroid cancer	4	1.3
Bladder cancer	3	1.0
GIST	3	1.0
HCC	2	0.7
Squamous cell cancer	2	0.7
Parotid cancer	1	0.3
Merkel cell cancer	1	0.3
Pancreatic cancer	1	0.3
Ventricle cancer	1	0.3
Leukaemia	1	0.3
Chordoma	1	0.3

GIST = gastrointestinal stromal tumour, and HCC = hepatocellular cancer.