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Prevalence of Venous Thromboembolism in Patients With Secondary Polycythemia

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Abstract

To investigate an association between secondary polycythemia and venous thromboembolism (VTE) risk, we performed a case–control study to compare the prevalence of VTE in participants with secondary polycythemia due to chronic obstructive pulmonary disease (COPD; N = 86) to that in age- and sex-matched controls with COPD without secondary polycythemia (N = 86). Although there was a significant difference in mean hematocrit between cases and controls (53.5% vs 43.6%, respectively; $P < .005$), we identified no difference in the number of total or idiopathic VTE events in the 2 groups. Patients with VTE, however, had a significantly higher body mass index than patients without VTE. Our findings suggest that secondary polycythemia alone may not be a significant risk factor for VTE but that VTE risk in this population may be related to known risk factors such as obesity. The role of phlebotomy for VTE risk reduction secondary polycythemia is therefore questionable.

Keywords

polycythemia; venous thromboembolism; phlebotomy; obesity

Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) associated with an increased risk of both arterial and venous thromboembolism (VTE). Historically, the increased thrombosis risk in PV has been attributed to hyperviscosity due to increased red cell mass and a generalized poor flow state.[1] Cytoreduction with phlebotomy is frequently performed in high-risk patients, using aspirin as an adjunct for thrombosis risk reduction.[2,3] The observation that patients with PV remain at increased risk of thrombosis despite red cell reduction by phlebotomy, however, led investigators to hypothesize that mechanisms other than altered blood rheology may be involved.[4] For example, studies of coagulation parameters suggest that patients with PV and other MPN have platelet hyperactivation,[5,6] an activated coagulation system,[7-9] impaired coagulation factor inhibition,[10] and defective

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fibrinolysis.[11] Recent data suggest that JAK2 V617F mutation status and leukocytosis may be independent risk factors for thrombosis in patients with MPN via mechanisms that lead to a generalized prothrombotic state.[12-16]

Secondary polycythemia results from an erythropoietin-driven elevation in hematocrit that occurs most commonly as a response to chronic hypoxemia. Obstructive sleep apnea (OSA), obesity hypoventilation syndrome, and chronic obstructive pulmonary disease (COPD) are the most common causes of hypoxemia, leading to secondary polycythemia. The degree to which laboratory markers of coagulation activation are elevated is substantially less in secondary polycythemia than in PV,[9] and there is no clear clinical evidence that secondary polycythemia poses an elevated thrombosis risk. Nevertheless, we have observed that cytoreduction with phlebotomy is frequently recommended for secondary polycythemia patients, likely extrapolating from the PV model.

We undertook the current study to determine whether or not there is an association between secondary polycythemia and increased VTE risk. Polycythemia vera is a clonal neoplasm that appears to confer a prothrombotic state via the dysregulation of numerous coagulation pathways, while such dysregulation is not a feature of secondary polycythemia. Accordingly, we hypothesized that secondary polycythemia does not increase the risk of VTE and performed the case–control study described here to test this hypothesis.

Materials and Methods

Study Design

This was a retrospective case–control study undertaken using a protocol approved by the Committee for the Protection of Human Subjects at Dartmouth College and Dartmouth-Hitchcock Medical Center. The Dartmouth-Hitchcock Medical Center electronic medical record was used to identify all patients admitted with an International Classification of Diseases, Ninth Revision coded diagnosis of COPD, between August 2004 and July 2009. All participants with a documented hematocrit ≥50% on at least 2 separate occasions were included as cases from within the COPD cohort identified from this initial search. Each case was matched with a control from the COPD cohort by sex and age. Controls were required to have hematocrit levels persistently <50%. Participants were excluded from this study if they carried a diagnosis of PV. The medical records of each participant were reviewed by one of the investigators. Data were collected on the history of VTE (including deep vein thrombosis and pulmonary embolism). To be adjudicated as a VTE event, documentation of thrombosis in the medical record was required (progress notes, history, and physical or discharge summaries), with the diagnosis confirmed by lower extremity venous duplex studies, computed tomography of the chest, pulmonary angiography, or ventilation–perfusion scanning. Venous thromboembolism were classified as idiopathic if not associated with surgery, trauma, or hospitalization and were considered provoked if there was an identifiable temporary risk factor unequivocally associated with the VTE event. Data were also collected on body mass index (BMI), comorbid conditions, smoking history, OSA, pulmonary hypertension, home oxygen use, and active malignancy.

Statistical Analysis

Clinical characteristics of participants with and without secondary polycythemia were analyzed using chi-square and *t* test analysis to evaluate the significant differences between the 2 populations. We used a 2-sample *t* test to evaluate the significant mean differences between the 2 populations when the characteristics were a continuous variable, for example age and BMI. For categorical characteristics, such as smoking history and home oxygen use, the chi-square test was used to compare the 2 ratios. All tests used a *P* value of .05 as the

threshold for significance. We calculated odds ratios (ORs) with 95% confidence intervals (CI) as an estimate of relative risk of secondary polycythemia and BMI for VTE events.

Results

Patient Characteristics

Totally, 2802 patients with COPD were admitted to Dartmouth-Hitchcock Medical Center between August 2004 and July 2009. A medical record review of this cohort identified 86 participants with a hematocrit value of ≥50% on at least 2 separate occasions. These patients were included in the case group. In all, 86 age- and sex-matched controls were then selected from the remaining cohort, which now included all patients with a hematocrit value <50%. Thus, a total of 172 patients were enrolled in this study (86 cases and 86 controls). Patient characteristics are summarized in Table 1. Cases and controls were similar in BMI, smoking history, cancer, and prevalence of OSA. Significant differences between cases and controls were identified in mean hematocrit values (53.5% vs 43.6%, $P < .005$), home oxygen use (47% vs 25.6%, $P = .004$), and pulmonary hypertension (15% vs 5%, $P = .04$). Although anticoagulation is frequently prescribed to patients with pulmonary hypertension, no participants with pulmonary hypertension in either group in this study were treated with anticoagulation for this indication unless there was documented VTE.

Prevalence of VTE

Venous thromboembolism events were documented in 29 participants in the entire study population (17%). Venous thromboembolism occurred in 17 cases (19.8%) and 12 controls (14%), a difference that was not statistically significant (OR 1.52, 95% CI: 0.68-3.41; $P = .42$). There was also no difference between the cases and controls as to whether the VTE event was provoked or unprovoked. Provoked VTE events occurred in 7 cases and 8 controls (OR 0.86, 95% CI: 0.3-2.5; $P = 1$), and while there was a trend toward an increase in idiopathic events in cases (N = 10) compared to controls (N = 4), this difference did not reach statistical significance (OR = 2.7, 95% CI: 0.81-8.96; $P = .16$). The BMI in participants with VTE in the study population was increased compared to participants without VTE (34.9 kg/m^2 vs 29.0 kg/m^2, $P = .006$). The difference in average BMI, however, was higher in controls with VTE than in cases with VTE (Table 2).

Discussion

Polycythemia vera is a MPN that is associated with an increased risk of thrombosis for which cytoreduction and low-dose aspirin are commonly performed to reduce this risk.[3,17] Although data to support a role for cytoreduction to lower the thrombosis risk in individuals with secondary polycythemia are lacking, we have observed that phlebotomy is frequently practiced in this population based on the PV model. The conditions most frequently associated with secondary polycythemia (COPD and OSA) are associated with states of oxygen deprivation and thus depend on increased hemoglobin levels for adequate oxygen delivery in response to chronically low oxygen saturation. Accordingly, based on the physiological principles, it may actually be harmful to reduce the compensatory elevated hemoglobin level by phlebotomy in these patients, and the results of the current study suggest that this potential risk is not balanced by a benefit for VTE risk reduction.

Our case–control study compared the prevalence of VTE in age- and sex-matched patients with COPD with and without secondary polycythemia. Our results demonstrated that VTE events did not occur more frequently in patients with secondary polycythemia than in those without, leading us to conclude that polycythemia per se is not an independent risk factor for VTE. Patients with VTE in the entire study population had significantly higher BMI

compared to patients without VTE. This difference was more pronounced in the control group and did not reach statistical significance in the cases group. However, the entire study population as a whole with and without VTE did show a difference, suggesting that the well-established risk factor for obesity may be partially responsible for the high prevalence of VTE in the studied population. Although malignancy is a well-recognized risk factor for VTE, only 4 participants with VTE (10%; 1 case and 3 controls) had documented cancers at the time of the event. Our study has several limitations. First, we noted a trend toward an increase in idiopathic VTE events among participants with secondary polycythemia, but this did not reach statistical significance in this small study, as the total number of events was low and the CIs around risk estimates were wide. A larger study may have identified a significant difference in VTE rates if one exists, but we were limited by the low prevalence of secondary polycythemia in our population (3%). The retrospective nature of the study design restricted us to include only participants who were admitted to an inpatient unit, thus individuals with COPD with and without VTE who were treated as outpatients were not included, potentially leading to bias. We did not evaluate arterial thrombosis as an end point of the study. We deliberately excluded this end point from the study design as we anticipated significant confounding in this high-risk population of smokers. Accordingly, we cannot rule out an effect of phlebotomy on a reduction in arterial thrombotic risk. Finally, although there was a significant difference between cases and controls with respect to mean hematocrit values, we were not able to reliably gather information about which patients with secondary polycythemia underwent therapeutic phlebotomy. We reduced the probability of including patients who underwent phlebotomy, however, by including participants in the case and control groups in whom the hematocrit values ≥50% and <50%, respectively, were documented consistently over time. Finally, there was an increased prevalence of pulmonary hypertension and increased oxygen use in the cases, indicative of a somewhat sicker population compared to controls. It is tempting to speculate that this difference may relate to the slightly higher, albeit not statistically significant, increase in idiopathic VTE events in cases, but the small numbers preclude definitive conclusions.

Despite the limitations, this study has important implications. The results should raise awareness that the mechanism of thrombosis in PV is complex and should not serve as the model for the management of secondary polycythemia with therapeutic phlebotomy for cytoreduction. Although provocative, these results should be regarded as hypothesis generating, and we acknowledge that prospective studies in participants with secondary polycythemia will be required to fully understand the risk of venous and arterial thrombosis in this population.

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Table 1

Characteristics of the Study Population.

	Cases, N = 86	Controls, N = 86	*P* Value
Age, years (range)	68.9 (37-92)	68.9 (37-92)	1
Average hematocrit, % (range)	53.5 (50.1-63.4)	43.6 (32.2-49.7)	<.005
Average BMI, kg/m^2 (range)	30.5 (16.2-52.5)	29.5 (15.2-59.5)	.47
Smoking history, n	83 (97%)	84 (98%)	1
Active malignancy, n	19 (22%)	18 (21%)	1
Obstructive sleep apnea, n	20 (23%)	14 (16%)	.33
Home oxygen use, n	40 (47%)	22 (25.6%)	.004
Pulmonary hypertension. n	13 (15.1%)	4 (4.6%)	.04

Abbreviation: BMI, body mass index.

Table 2

Relationship Between BMI and VTE.

	Average BMI, kg/m^2		
	VTE, n = 29	**No VTE, n = 143**	***P* Value**
Cases (SD)	33.1 (8.4)	30 (8.8)	.17
Controls (SD)	37.1 (12)	28.6 (7.2)	.025
Entire study population (SD)	34.9 (10)	29 (8)	.006

Abbreviations: BMI, body mass index; SD, standard deviation; VTE, venous thromboembolism.