

Post-thrombotic syndrome after total hip arthroplasty is uncommon

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Background Deep vein thrombosis (DVT), usually asymptomatic, is common after total hip arthroplasty (THA). Post-thrombotic syndrome (PTS) is a potential late complication of DVT, but there is limited data on its occurrence.

Patients and methods This was a prospective cohort study of subjects at one hospital who had participated in a trial of thromboprophylaxis for THA and who had postoperative venography. Data were collected at baseline and 2–4 years later to ascertain symptoms of PTS using a modification of a validated scoring system. Outcomes were collected without knowledge of baseline characteristics or venogram results. Potential predictors of PTS were explored using exact logistic regression analyses.

Results The cohort (n = 188) had a mean age of 63 years, 51% were male, 35% had a BMI of > 30, and 4% had a prior history of DVT. 25 patients (13%) had DVTs on venography. 12 patients (6%, 95% CI: 3–11) subsequently developed symptoms consistent with PTS, 7 with bilateral symptoms. Most affected limbs (15 of 19) had no postoperative DVT. No statistically significant predictors of PTS were found.

Interpretation Symptoms of PTS are infrequent after THA in patients who receive some form of thromboprophylaxis. Our findings, which are consistent with the existing literature, suggest that there is a potential benefit to giving thromboprophylaxis for reduction of symptomatic PTS.

After total hip arthroplasty (THA), 2–5% of patients have symptomatic deep vein thrombi (DVTs). However, venography performed soon after surgery shows DVT in 40–60% of patients, with approximately half of these being proximal. Effective thromboprophylaxis reduces the risk of DVT by at least 50% (Geerts et al. 2004). The most important reasons for perioperative thromboprophylaxis are prevention of fatal pulmonary emboli and acute symptomatic venous thromboembolic episodes. Prevention of post-thrombotic syndrome (PTS) may be an important additional benefit.

Limited prospective studies have suggested that PTS develops in 20–40% of patients after symptomatic DVT, with severe PTS occurring in 5–10% of patients. The syndrome is usually apparent within 1–2 years (Prandoni et al. 1996, Ginsberg et al. 2001, Kahn and Ginsberg 2002). The reported overall prevalences of PTS after major lower limb arthroplasty vary widely, from < 5% to 26%, and in those with DVT, from 5% to 89% (McNally et al. 1994, Siragusa et al. 1997, Ginsberg et al. 2000, Deehan et al. 2001) (Table 1). Although arthroplasty is now a common procedure, and the high risk of postoperative DVTs is well-recognized, there has been only one prospective cohort study published with more than 100 subjects assessed for PTS following THA. However, this series also included patients who had undergone surgery for total knee arthroplasty (TKA) and hip fracture (Ginsberg et al. 2001) (Table 1). We therefore conducted a study to determine the point prevalence and potential predictors of symptoms consistent

Table 1. Studies of post-thrombotic syndrome after major orthopedic surgery

Study	No. of patients	Study population	DVT diagnosis	DVT (%)	PTS (%)			PTS diagnosis	Years since surgery
					DVT	No DVT	Overall		
McNally et al. 1994	43	THA	V	19	89	13	26	Browse et al. 1980	≥5
Siragusa et al. 1997	98	Mixed	V	49	24	4	14	Villalta et al. 1994	2–4
Ginsberg et al. 2000	255	Mixed	V	36	6	4	5	Ginsberg et al. 2000	2–7
Deehan et al. 2001	405	TKA	Limited ^a	NA	NA	NA	13	Browse et al. 1980	2–10
Warwick et al. 1996	67	THA	FU ± V	100	11	12	NA	Clinical 1996	14–21
Present study	188	THA	V	13	16	5	6	Villalta et al. 1994	2–4

DVT: deep venous thrombosis;

PTS: post-thrombotic syndrome as defined by authors;

THA: total hip arthroplasty;

TKA: total knee arthroplasty;

V: Venogram;

FU: fibrinogen uptake test;

NA: not available.

^a DVT diagnosis by “radiological investigation” only if postoperative symptoms or signs of DVT present.

with PTS 2–4 years after THA. Our study cohort was derived from a larger multicenter randomized trial of perioperative THA thromboprophylaxis, which required venography soon after surgery in all patients. This allowed us to explore the relationship between postoperative DVT and subsequent symptoms of PTS.

Patients and methods

The study subjects who underwent THA at the University of Alberta Hospital (Edmonton, Canada) had previously consented to participate in a multicenter randomized clinical trial of thromboprophylaxis, in which they were randomized to receive either low-molecular-weight heparin or warfarin for 6 ± 2 days. Almost all (88%) of the subjects received epidural or spinal anesthesia. Compression stockings were not used in the trial protocol. Details of the parent North American Fragmin Trials, including anticoagulant prophylaxis, have already been published in detail; this trial required mandatory venography on day 6 ± 2 postoperatively (Hull et al. 2000a, b).

244 patients were randomized into the trial at our hospital. Patients were excluded if they could not be contacted or had declined to participate in our PTS substudy (n = 35), if venography had not been performed or was technically unsatisfactory (n = 20), or if they had had a symptomatic pulmonary

embolism during hospitalization (n = 1). The latter was used as an exclusion criterion as we could not evaluate the patient reliably for the presence or absence of DVT(s) that might have embolized. The final study cohort consisted of 188 patients. Our study was approved by the Health Research Ethics Board of the University of Alberta (File no. 2,533) and performed according to the principles of the Declaration of Helsinki.

Patients were interviewed 2–4 years after their surgery. All outcomes were registered without knowledge of baseline characteristics or venogram results. In addition, as a study center, we remained blinded as to the original treatment allocation. Trained interviewers used a standardized adaptation of an established and validated instrument for ascertainment of PTS published by Villalta et al. (1994). Since we registered symptoms and self-reported signs during a telephone interview, one item of the Villalta instrument could not be scored—namely, pain during calf compression. Otherwise, using this instrument, the interviewer sought for symptoms in each lower limb that had developed or had worsened since hip replacement surgery and that the patient did not consider to be related to the hip itself. Specific enquiry was made regarding the following symptoms and self-reported signs: leg pain or heaviness, cramps in the calf, itching, tingling, persistent swelling (edema), thickening of the skin (induration), brown or red discoloration of the lower leg (hyperpigmenta-

tion), new occurrence of distal small blood vessels (venous ectasia), redness, and distal ulcers. Patients were asked to rate each as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). These points were then summed for each limb and classified as follows: no PTS, 0–4; mild/moderate PTS, 5–14; and severe PTS, ≥ 15 or presence of ulcer (Villalta et al. 1994).

We used case report forms from the clinical trials to determine the patient's baseline (preoperative) demographic and clinical characteristics. Venograms and their concurrent interpretation were performed by one investigator (DBR), who was blinded as to clinical data and to the central consensus interpretations used for the main clinical trial. We did not have access to the latter. Deep vein thrombosis was classified as proximal (popliteal vein and above) or distal (below the popliteal vein). For distal thrombi, only those occurring in the anterior tibial, posterior tibial, or peroneal veins were considered "positive."

Statistics

Our analyses were mainly descriptive in nature. We present our data as means and standard deviations (SD), or proportions. Prevalence (as a percentage over the duration of follow-up) was calculated with exact 95% confidence intervals (95% CIs). We then stratified the data according to the presence or absence of PTS (Villalta instrument score of 5 or greater); thus, our primary outcome was dichotomous in nature. Crude analyses consisted of Student's t-tests, Mann-Whitney U tests, and chi-square tests.

Because of our small sample size (< 200), rarity of events ($n = 12$), and the need to protect against issues related to model overfitting, we conducted only what should be considered exploratory adjusted analyses using exact logistic regression. Age and sex were the only variables forced into models. We considered as potential candidate predictors only those variables that had a crude (unadjusted) odds ratio of greater than 2, or that had greater than 10% absolute differences between those with PTS symptoms versus those without PTS symptoms. We present these exploratory results as crude and adjusted exact odds ratios (ORs) with exact 95% CIs and p-values.

Table 2. Characteristics and outcomes of patients according to the presence or absence of post-thrombotic syndrome

	No PTS (n = 176)	PTS (n = 12)	p-value
Age ^a	63 (11)	59 (13)	0.2
Male ^b	90 (51)	6 (50)	0.9
Weight (kg) ^a	82 (18)	81 (14)	0.9
BMI ≥ 30 ^b	61 (35)	4 (33)	1.0
Days since operation (SD) ^a	1,085 (135)	1,059 (153)	0.5 0.5
Leg operated on ^b			
right	98 (56)	5 (42)	0.4
left	78 (44)	7 (58)	0.4
Previous history of varicose veins ^b	60 (34)	6 (50)	0.4
Previous history of DVT ^b	5 (3)	2 (17)	0.07
Postoperative DVT ^b	21 (12)	4 (33)	0.06
right-sided	12 (7)	2 (17)	0.2
left-sided	13 (7)	3 (25)	0.07
proximal	4 (2)	1 (8)	0.3
distal	17 (10)	3 (25)	0.1

^a Mean (SD)
^b Number (%)

Results

Our cohort consisted of 188 patients (mean age 63 years (SD 12), 51% male, 35% with body mass index of > 30) who were interviewed at a median time of 36 (24–49) months after their surgery. 25 patients (13%) developed a postoperative DVT identified by venography; 4 of these had bilateral DVTs. 20 of the 25 patients had distal thrombi only. 2 of 7 patients who reported a preoperative DVT developed a postoperative DVT (Table 2). All patients with documented postoperative DVTs were therapeutically anticoagulated for 3 months or longer. Few patients had the individual component symptoms and with regard to severity most individual symptoms were relatively mild (Table 3). Except for the presence of ulcers, all symptoms were more common in patients with PTS.

Overall, 12 of 188 patients (6%; 95% CI: 3–11) developed symptoms consistent with PTS over approximately 3 years of follow-up. 7 of these 12 patients had complaints of PTS that were bilateral in nature. Of the 5 patients with unilateral symptoms of PTS, none had ipsilateral thrombosis diagnosed by venogram. Of the 14 affected lower limbs

Table 3. Lower extremity complaints stratified according to the presence or absence of post-thrombotic syndrome (PTS)

	No PTS (n = 176)	PTS (n = 12)	p-value
Leg pain			< 0.001
None	170	6	
Mild	3	0	
Moderate	1	0	
Severe	2	6	
Cramps			< 0.001
None	165	5	
Mild	4	0	
Moderate	1	2	
Severe	6	5	
Itching			0.001
None	164	8	
Mild	7	1	
Moderate	5	1	
Severe	0	2	
Tingling			< 0.001
None	170	8	
Mild	5	0	
Moderate	1	3	
Severe	0	1	
Swelling			< 0.001
None	167	6	
Mild	7	0	
Moderate	2	4	
Severe	0	2	
Thickening			0.01
None	175	11	
Mild	1	1	
Moderate	0	0	
Severe	0	0	
Discoloration			< 0.001
None	172	8	
Mild	3	3	
Moderate	1	1	
Severe	0	0	
Blood vessels visible			< 0.001
None	164	7	
Mild	8	2	
Moderate	4	3	
Severe	0	0	
Redness			0.07
None	172	10	
Mild	3	2	
Moderate	1	0	
Severe	0	0	
Sores			> 0.5
None	176	12	
Mild	0	0	
Moderate	0	0	
Severe	0	0	

of patients with bilateral symptoms consistent with PTS, only 4 had a postoperative venographically documented thrombus. Thus, of 19 lower limbs with symptoms of PTS, thrombi were documented

in only 4. In general, symptoms were mild to moderate. Only 3 patients had scores exceeding 7 and only 1 patient has a score exceeding 11. 54 other patients had minor symptoms that were insufficient for diagnosis of PTS (Villalta score of 1–4); 24 patients had bilateral symptoms and 30 had unilateral symptoms.

We found no statistically significant potential predictors of postoperative symptoms consistent with PTS in either the crude or adjusted analyses (Table 4). Even so, it is noteworthy that in multivariate exact logistic regression analyses (adjusted for age, sex, presence of varicose veins, and venographically confirmed postoperative DVT) the adjusted odds of PTS in subjects with a history of previous DVT was 6 (95% CI: 0.5–50; $p = 0.2$); see Table 4.

Discussion

In this prospective cohort study, we found that 6% (95% CI: 3–11) of patients developed symptoms consistent with PTS following total hip arthroplasty. This fairly low overall frequency is similar to that found by Ginsberg et al. (2000) after THA, TKA, or hip fracture. It is considerably lower than the 13–26% reported by other investigators in the era before routine thromboprophylaxis (McNally et al. 1994, Siragusa et al. 1997, Deehan et al. 2001) (Table 1).

Deep vein thrombosis is usually considered to be the cause of PTS. Some postoperative symptoms of PTS may be due to DVTs that occur after venography has been performed (Ginsberg et al. 2000, Hull et al. 2000b). However, it is unlikely that all of the 4–13% of patients previously reported as developing PTS—with no early DVT detected (Table 1)—had such DVTs as the immediate cause of their PTS symptomatology. As did we, others have also noted symptoms and/or signs of PTS after surgery in substantial numbers of patients or limbs with no documented DVT (Browse et al. 1980, Andersen and Wille-Jorgensen 1991, Warwick et al. 1996, Ginsberg et al. 2000). Other causes of PTS symptoms in patients who have undergone arthroplasty might include more advanced age, relative immobility, other co-morbidities (including previous venous thromboembolism or chronic venous insuf-

Table 4. Crude and adjusted odds ratios for potential predictors of symptoms of post-thrombotic syndrome: exact logistic regression analyses

	Crude odds (95% CI)	Adjusted ^a odds (95% CI)	Adjusted ^a p-value
Varicose veins present	1.9 (0.5–7.5)	2.1 (0.5–8.9)	0.4
Postoperative DVT present	3.7 (0.7–15.1)	3.1 (0.6–13.1)	0.2
Past history of DVT	6.7 (0.6–47.9)	6.1 (0.5–50.1)	0.2

^a Adjusted for age, sex, and all variables presented in the table using exact logistic regression.

iciency), and the sequelae of surgery itself (Ginsberg et al. 2000).

Why is our estimated prevalence of PTS (6% over 2–4 years of follow-up) so much lower than in many previous reports? Although the exact reason is difficult to establish, there are several possible explanations. First, PTS is thought to occur within 2 years of occurrence of DVT (Prandoni et al. 1996, Ginsberg et al. 2001, Kahn and Ginsberg 2002), although it can present later (Kahn and Ginsberg 2002). The incidence of PTS might have been higher with a longer duration of follow-up. However, there is no evidence from prior studies that longer follow-up before assessment for PTS would increase the number of subjects affected (Table 1). Secondly, all of our subjects, and most of those reported by Ginsberg et al. (2000), received perioperative thromboprophylaxis. By contrast, in studies reporting higher frequencies of postoperative PTS (McNally et al. 1994, Siragusa et al. 1997, Deehan et al. 2001), use of thromboprophylaxis was low—occurring in only 2% of patients in one study (Deehan et al. 2001), and probably not at all in another study (McNally et al. 1994). Thirdly, different methods have been used to ascertain and define PTS, which could possibly affect the reported rates of PTS. Unfortunately, at present, there is no methodological “gold standard” for diagnosis of PTS (Kahn et al. 2000, 2006, Kahn and Ginsberg 2002). 4 different methods, sometimes with modifications, were used in the 5 previous studies of PTS after orthopedic surgery (Table 1).

Our study has several limitations. First, some may argue that without physical examination or documentation of venous valvular incompetence, a diagnosis of PTS cannot be made. We contend, as would most clinicians, that patient-reported symptomatic complaints are more important than confir-

mation of PTS using “objective” criteria. Secondly, our cohort was derived from a randomized trial of thromboprophylaxis; it is likely that our population was relatively younger, healthier, and had fewer co-morbidities than patients taken as a whole. Thirdly, we identified DVT venographically and gave patients with positive findings anticoagulation therapy, possibly reducing subsequent PTS. Finally, the small sample size precludes us from drawing statistically robust conclusions regarding predictors of PTS. That said, our study is the largest to examine patients with THA and the third largest study reported in the literature.

We conclude that the frequency of symptoms of PTS following THA is low. There are, however, other compelling reasons for effective thromboprophylaxis in major orthopedic surgery. Indeed, careful attention to thromboprophylaxis may be one of the reasons for the lower than anticipated rates of PTS found in recent studies.

MJM, DBR, and SRM participated in the conception and design of the study. MJM supervised data collection, DBR performed and analyzed the venograms, and DTE and SRM provided statistical expertise. All authors participated in interpretation of the results. The article was drafted by MJM, with revisions regarding important intellectual content by all authors. All authors have read and approved the final manuscript. MJM supervised the study and is guarantor for the findings.

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