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Deep vein thromboses in users of opioid drugs:

incidence, prevalence, and risk factors

Abstract

Background
Users of illicit opioids are at increased risk of hospital admission for deep vein thromboses (DVTs); however, the community prevalence, risk factors, and complications of DVTs in this group are poorly understood.

Aim
This study aimed to describe the prevalence of previous DVT for users of opioids in primary care; provide age- and sex-adjusted annual incidence rates of DVT; and explore factors associated with DVT, concordance with subsequent treatment, and complications.

Design
A retrospective analysis of DVT prevalence and incidence, and analysis of risk factors for DVT using Poisson regression of incidence rates.

Method
A review of 734 patients in treatment for opioid addiction, who were registered to a single, specialised primary care practice in Middlesbrough, England.

Results
The prevalence of previous DVT in users of opioids was 13.9% (95% confidence interval [CI] = 11.5 to 16.6) with an annual incidence rate of 3.2% (95% CI = 2.6 to 3.7). The incidence rate increased with age and for female users; an exploration of risk factors suggests that rising age, female sex, sex-worker status, and intravenous delivery all independently increase the risk of DVT. Concordance with treatment appeared reasonable and, compared with DVT in groups of people who do not use drugs, there was no evidence of increased risk of pulmonary embolism. Participants with previous DVT reported lower health and wellbeing scores.

Conclusion
Primary care providers should be aware of the considerably increased risk of DVT and its sequelae in users of intravenous drugs. Evidence for effective primary care prevention and the effective management of DVT complications is lacking; until this emerges, vigilance on the part of clinicians may help to minimise harm.

Keywords
heroin dependence; primary care; substance abuse; venous thrombosis.

INTRODUCTION

Deep vein thromboses (DVTs) are common in users of intravenous drugs. Although recognised as an important problem among professional healthcare workers who treat drug users, there is surprisingly little published research in this area and anything that has been published relates to the hospital rather than the community setting. As such, it is not understood which groups of users of opioid drugs are predisposed to DVT and what preventative measures would be effective in the primary care setting.

Once users of opioid drugs have been diagnosed with DVT, their concordance with treatment regimes in community settings is unreported and potentially problematic.[1] Venous access to monitor coagulation is difficult in many patients because of damage caused to veins from drug use. As regular attendance — which is necessary when medications such as warfarin are prescribed — is likely to be compromised in chaotic groups (such as, users of intravenous drugs), many professionals offer self-administered heparin injections; this method reduces the problem of attendance[2] but does not necessarily ensure regular, reliable administration.

Intravenous drug-related DVT has substantial resource implications for the NHS. In one published study of 182 females aged 16–70 years who were admitted to hospital with DVT, the cause of DVT in 20% of cases was intravenous drug use;[1] this figure rose to 52% for those aged <40 years. In a further study of 109 patients presenting to an emergency department with possible DVT, a third were users of intravenous drugs.[3]

DVTs resulting from intravenous drug use differ in a number of ways from those arising from other causes. They are: more likely to be situated in the femoral vein (more commonly the right than the left)[4] and probably easier to diagnose clinically.[3] In addition, intravenous drug use is more likely to be the cause of DVT in younger patients,[1,4] who are more likely to be admitted and have longer hospital stays.[3]

There is debate about the aetiology of DVT in the general population, with possibilities including blood hypercoagulability, stasis, blood-vessel injury, and anoxic damage to venous valves.[5] However, the aetiological factors in users of intravenous drugs are likely to be different; possible causes include reduced blood flow from inactive muscle pumps during periods of intoxication, endothelial damage from injections, and elevated coagulation factors from infection introduced via injections.[1,6]

Although 3 months' anticoagulation is now established as the optimum treatment for patients with DVT who have an 8% chance of developing further DVT or pulmonary emboli over 1 year,[7,8] there is a lack of evidence about the risk of long-term complications and the optimum treatment approach for DVT resulting from intravenous drug use: for instance, taking anticoagulants may be more risky if intravenous drug use is continuing.[1] There

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Submitted: 16 June 2011; **Editor's response:** 7 July 2011; **final acceptance:** 18 August 2011.

This is the full-length article (published online 28 Nov 2011) of an abridged version published in print. Cite this article as: **Br J Gen Pract 2011; DOI: 10.3399/bjgp11X613115**

How this fits in

Hospital studies show that users of intravenous opioid drugs are at considerably increased risk of deep vein thromboses (DVTs), although data are lacking from primary care. At 3%, the annual incidence of DVTs in users of opioid drugs is some 100 times greater than in the general population of comparable age; the risk is higher in the those who inject intravenously, are sex workers, are older, and are female. Users of opioids who have previously had a DVT report poorer physical and psychological health status than users of opioids who have not had a DVT; this is consistent with the long-term morbidity associated with DVT in the general population. In those experiencing DVT, as it may be difficult to provide optimal management to prevent complications, particular vigilance by primary care physicians is required.

has been no systematic study of post-thrombotic complications following DVT in users of intravenous drugs; however, long-term complications are significant in people who do not use drugs[9] and may be prevented by specific treatments such as exercise.[10]

METHOD

The primary aim of the study was descriptive: to provide crude, and age- and sex- adjusted prevalence estimates for previous DVT in users of illicit opioids (injecting and non-injecting) in a community care setting. Annualised incidence data were estimated from DVT documented in the 5 years preceding the review census date (1 March 2009) for each complete year that each patient was registered to the practice. DVT in users of illicit opioids is characterised in this study using crude and adjusted estimates of DVT incidence and prevalence, identifying risk factors, describing concordance with treatment, and reporting complication rates.

The secondary aims were descriptive and analytic. The descriptive aims were to ascertain DVT complication rates and concordance with treatment; the analytic aim was to explore the determinants of DVT using multiple regression, including a range of measured demographic, comorbidity, and behavioural variables.

Sample and setting

The study sample comprised 734 patients who were receiving treatment for opioid addiction and who were registered for general medical services at the Fulcrum Medical Practice in Middlesbrough, which serves a region of relative deprivation in the north of England. The group studied was defined as those patients both receiving treatment for opioid addiction (methadone or buprenorphine) and registered for general medical services at a single point in time. The practice provides treatment services of opioid addiction for all patients in the surrounding area. A further 627 patients, who were receiving treatment at the practice but registered elsewhere, were not included because of practicalities regarding gaining access to their full medical records.

Measures

The Treatment Outcomes Profile (TOP) measure is a validated self-report tool;[11] it includes measures such as frequency, mode, and type of illicit drug use; social functioning (housing, employment, and education status); subjective health and psychological status; and criminal activity, and records activities and behaviours that have occurred in the preceding 4 weeks. A TOP measure was completed for each patient every 3 months, with the most recent being used in the analysis.

Data from the National Drug Treatment Monitoring System form were also available for all patients in treatment; these included information such as ethnicity, hepatitis B vaccination status, hepatitis C testing status, illicit drugs used, and sex-worker status. Data were extracted from the practice records using a Read code search, including: DVT frequency, location, timing, scan confirmation, management, and complications. Compliance with anticoagulant use was estimated as a percentage of the treatment time period for which the prescribed drug was issued. Whether a further DVT represented a complication of the first DVT or was a new DVT was a pragmatic decision, which was based on the presentation and scan results, if available.

Analysis

Data capture was piloted by reviewing the notes of 10 eligible patients to identify data-recording issues. Subsequently, data from sources were combined and anonymised before analysis; no individual patient characteristics were identifiable within the analyses. Analysis was conducted using SPSS (version 19).

Exact confidence intervals (CIs) were estimated for proportions; parametric CIs were estimated for continuous measures

and verified using bootstrapped estimation. Explorations of risk factors for DVT were modelled using 5-year counts of DVTs as the dependent variable within a Poisson regression, conservatively using the negative binomial with log link to manage potential over-dispersion. Model coefficients were expressed as incident rate ratios, taking the exponential values of parameter estimates. Simple univariate modeling, using the full range of potential explanatory variables, was followed by stepwise addition iterating to the best model. The reported model was tested for all two-way interactions and checked qualitatively by simple logistic modelling (DVT or no DVT during the 5-year period). All estimates of test probabilities are reported for the purpose of hypothesis generation, with a 5% threshold for significance.

The study power calculation estimated that approximately 10% of 800 patients would have a history of DVT, providing a crude prevalence estimate with 95% CI = 8% to 12%.

RESULTS

Demographic characteristics

Data were available for 734 participants who were receiving treatment for illicit opioid addiction and registered at Fulcrum Medical Practice; the mean age was 34 years (range 21–59 years), 73% were male, and 96% were recorded as white British. Those receiving treatment for drug use and registered at the practice (n = 734) were similar to those receiving treatment who were registered elsewhere (n = 627) in age (34 years versus 33 years) and sex (male: 73% versus 70%), and ethnicity (white British 98% versus 97%).

Illicit heroin was used by 89.0% of the cohort (injected by 46.6%, smoked by 37.1%) and crack cocaine was used by 24.5% (Table 1). Other drugs used by less than 10% of the cohort included illicit methadone (8%), buprenorphine (6%), benzodiazapines (6%), and cannabis (5%). Analysed by sex, proportionally more females smoked heroin rather than injecting it, and more females used crack cocaine than males (Table 1).

Workforce participation was limited with 12% of the sample in regular employment, 71% unemployed, and 12% undisclosed. A total of 2.3% of the sample identified themselves as sex workers (three males and 14 females). Acute housing problems were reported by 8% and risk of eviction by 4% of the sample.

Descriptive data for the patients with DVTs

A history of ≥1 DVT was present in 102 people in the sample, giving a prevalence of 13.9% (95% CI = 11.5 to 16.6). In these people, the mean age of self-reported first use of heroin was 22 years (range 9–46 years) and the mean age for when the first DVT occurred was at 30 years (range 20–50 years), some 8 years later. Most people had at least one DVT confirmed by a Doppler ultrasound (82.4%), and half (50%) had the site of the first DVT recorded. All except two cases (one with distal leg DVT and one with DVT in the arm) were proximal.

DVTs reported annually over 5 years, from March 2004 until February 2009, were combined to estimate the annual incidence of DVT (Table 2). The annual incidence of DVT was 3.2% (95% CI = 2.6 to 3.7), although this increased with age and sex. The annual incidence of DVT was higher in crack cocaine users (4.8%, 95% CI = 3.3% to 6.2%) than non-users (2.7%, 95% CI = 2.1% to 3.3%).

Compliance with heparin use

For completed episodes of treatment for DVT, the mean length of treatment was 20 weeks (range 0–67 weeks). Data were available for 85/102 (83.3%) patients with past DVT who had either completed treatment with anticoagulants or who were currently receiving treatment; their compliance was 74%.

Complications

Leg ulcers had occurred in 15.7% (95% CI = 9.2 to 24.2) of patients with past DVT. Other complications occurred in 23.5% (95% CI = 15.7 to 33.0) of patients, the most common being oedema. Definite pulmonary emboli

Table 1. Commonly used drugs and delivery method

Drug	*n* (%)	Male, %[a]	Female, %[a]	*P*-value
Heroin (illicit)	653 (89.0)	88.2	93.3	0.041
Inject	342 (46.6)	49.0	41.2	0.055
Smoke	272 (37.1)	33.8	46.9	0.001
Sniff or oral	10 (1.4)	1.1	2.1	0.190
Other or don't know	29 (4.0)	4.3	3.1	0.410
Crack cocaine (freebase)	180 (24.5)	22.5	31.8	0.012

[a]*As a proportion of the total within sex.*

Table 2. Annual incidence of deep vein thrombosis by age band and sex

	Male	Female	All
Age band, years	**Mean, % (95% CI)**	**Mean, % (95% CI)**	**Mean, % (95% CI)**
20–29	1.8 (1.0 to 2.5)	3.6 (2.0 to 5.2)	2.4 (1.7 to 3.1)
30–39	3.1 (2.1 to 4.0)	6.5 (3.8 to 9.1)	3.8 (2.8 to 4.7)
40–49	3.3 (0.9 to 5.8)	5.6 (0.3 to 11.0)	3.9 (1.6 to 6.2)
50–59	8.0 (0.5 to 15.5)	None	6.9 (0.4 to 13.4)
Combined	2.6 (2.0 to 3.2)	4.7 (3.4 to 6.1)	3.2 (2.6 to 3.7)

Table 3. Current health and psychological functioning and previous deep vein thrombosis (DVT)

	DVT	No DVT	DVT — no DVT
Treatment Outcomes Profile field[a]	**Mean (SD), *n***	**Mean (SD), *n***	**Mean (95% CI)**
Physical health status	10.7 (4.3), 98	12.3 (4.3), 624	1.6 (0.6 to 2.5)
Psychological health status	10.7 (4.5), 98	11.9 (4.6), 625	1.1 (0.2 to 2.1)
Overall quality of life	11.6 (5.0), 98	12.5 (4.6), 625	0.9 (–0.1 to 1.9)

[a]Each measure scores 0 (poorest) to 20 (best).

Table 4. Risk factors associated with deep vein thrombosis (DVT)

Poisson (negative binomial) regression dependent variable: DVT 5-year count		
Parameter	**Exp β, (95% CI)[a]**	***P*-value[b]**
Intercept	0.006 (0.001 to 0.026)	<0.001
Age	1.05 (1.02 to 1.09)	0.002
Female	1.69 (1.03 to 2.76)	0.036
Current user of intravenous drugs	5.55 (2.57 to 12.0)	<0.001
Previous user of intravenous drugs	2.65 (1.17 to 6.04)	0.020
Sex worker	3.08 (1.30 to 7.29)	0.010

[a]Exponential of Wald coefficient and 95% CIs show the incident rate ratio. [b]P-value: hypothesis test for Wald χ^2.

were recorded in two patients (2%) and possible pulmonary emboli in a further four (3.9%) patients.

The subjective health status (physical health, mental health, and quality of life) available from the TOP data was compared between patients with and without a DVT; patients with DVT reported worse physical and mental health status (Table 3).

Predictors of DVT

An exploration of putative risk factors for the number of DVTs experienced during a 5-year period identified some associations; these are outlined in Table 4. DVT occurrence (expressed as an incident rate ratio) increased with age and female sex; females experienced a rate of DVT that was 1.69 times higher than that of males. Sex-worker status (of females, in the main) independently significantly increased the rate of DVT by 3.1 times. Compared with those who had never injected drugs, previous and current intravenous drug use demonstrated a stepwise increase in risk.

DISCUSSION

Summary

To the authors' knowledge, this is the first study to show accurately the risk of developing a DVT in patients who are undergoing treatment for opioid (principally heroin) addiction. The high prevalence and incidence of DVTs in this group was confirmed. The prevalence of DVT was 13.9% and the annual incidence of new DVTs was estimated to be 3%. This contrasts strongly with the annual incidence in the general population of 2–3 per 10 000 for the 30–49-year-old age group.[12]

Mean age of a first (or only) DVT was 30 years, occurring on average 8 years after heroin was used for the first time. Rising age, female sex, and being a sex worker were all associated with a greater risk of DVT, as was intravenous delivery of drugs. The chance of developing a pulmonary embolism appeared low (2–6%), but leg ulcers were recorded in 15.7% of the sample who had past DVT and further complications were recorded in others. Compliance with heparin use appeared relatively good in this group.

Patients with prior DVT who were receiving treatment for drug addiction reported both a lower subjective physical and mental health status than those who had not had a DVT and were receiving treatment.

Strengths and limitations

Doppler ultrasound may be inaccurate in diagnosing recurrent DVT[13] but, given both the reasonable rate of confirmation of suspected DVTs in the current study by imaging, and the evidence that a clinical diagnosis of DVT in this group is accurate,[3] the prevalence rate of 13.9% is likely to be robust.

There are some limitations in assessing the risk of pulmonary emboli. It was often difficult to determine precisely whether a pulmonary embolism had occurred as ventilation-perfusion scans were not carried out consistently within hospitals and the current study would not capture patients who were dying from massive pulmonary emboli.

When conducted in representative populations, retrospective and descriptive epidemiological studies are useful for quantifying problems if clinical records are accurate. However, they are not a strong design for attributing causes of problems, as was attempted with an exploration of potential risk factors for DVT in users of opioid drugs. The accuracy of analysis based on retrospectively reviewed data sources, linking clinical data with self-reported behaviours and their timings, limits the robustness of findings, however plausible. A carefully designed prospective cohort study would help address these limitations.

Comparison with existing literature

For patients admitted to hospital with a DVT, the risk of a pulmonary embolism is reported at 7%, rising to 10% for proximal

Funding

None.

Ethics committee

Not required.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors declare they have no competing interests.

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DVTs.[4] In this study a prevalence of 2–6% was found, although this was for a history of having had a pulmonary embolism at any time, rather than at the time of presentation of the DVT.

The poorer subjective health scores for patients with DVT receiving treatment for drug addiction mirrors evidence for long-term problems in the general population of patients with DVT. In general, DVT leads to poorer physical quality-of-life scores compared with those of the general population, with even poorer scores in those with post-thrombotic syndrome.[9,14] Within those who use drugs and have DVT, pain appears to be the mediating factor between the extent of post-thrombotic complications and impairment of functioning.[15,16]

Intravenous crack cocaine and heroin use are known to be particularly damaging to veins, possibly exacerbated by the citric acid used to dissolve the drugs and the local anaesthetic property of the cocaine.[17] This finding was supported by the association this study found between use of injections and having a DVT. Use of crack cocaine is known to be high in sex workers, particularly in those who work on the street, compared with parlour workers.[18] Sex workers were found to be particularly at risk of DVT, they have a high use of stimulants including cocaine which is thought to be particularly damaging to veins.

Implications for practice

As there is no evidence from this study that patients are at greater risk of developing pulmonary embolism than the general population, there is also no evidence to support deviation from the 3-month treatment recommendation for a first DVT that is applied to other patients.[7] Currently, there are no recommendations about length of treatment in subsequent DVTs in this group.

The high prevalence of long-term leg complications and the lower health and wellbeing scores for patients with prior DVT is a matter for attention. Leg ulcers are likely to be relatively accurately reported as they would require treatment from a nurse, but the presence of other complications is likely to be less accurate and under-reported. Further work needs to be done to understand and intervene in order to prevent morbidity from DVT sequelae, such as leg complications; however, alleviating the chronic pain and encouraging exercise may be difficult in this group.

It is possible that the seemingly good compliance with heparin treatment (none of the patients had been treated with warfarin) may be partly due to the presence of continuing symptoms that act as something of 'a reminder' of the problem. Further study could investigate qualitatively the range of beliefs about DVTs and their treatment in this group, and better quantify continuing causes of disability. Currently, there are no known effective strategies — above and beyond clinical management of drug addiction — to reduce the risk of DVT in users of intravenous drugs. The findings from this study identify groups at high risk of developing DVTs — namely, sex workers and those injecting illicit drugs — with whom special vigilance may be appropriate.

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