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Review Article

Epidemiology and risk factors for deep vein thrombosis in patients with hip fractures

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Abstract: Elderly people are particularly vulnerable to hip fractures owing to osteoporosis, decreased mobility, and the tendency to land on the hips in the event of an accidental fall. Hip fractures are one of the most common types of fractures sustained in the elderly population. This review focuses on the epidemiology and risk factors for deep vein thrombosis (DVT) associated with hip fractures. Hip fracture is a strong risk factor for DVT, and DVT is a major contributor to the morbidity and mortality among patients with hip fractures. The review discussed the epidemiology of thrombotic events, risk factors for DVT and the clinical implications of DVT in patients with hip fractures.

Keywords: Deep vein thrombosis, epidemiology, hip fracture, venous thromboembolism

Introduction

Venous thromboembolism (VTE) was shown to be the most common adverse event in inpatient hospital settings in low-income and middle-income countries (incidence rate = 3.0%, 95% CI = 1.0%-4.8%) [1]. Morbidity and mortality attributable to venous thromboembolic events was shown to impose a considerable financial burden on health services [2]. It is also considered as a preventable major postoperative complication. Despite the widespread use of prophylaxis guidelines, no major change in the incidence of VTE has been observed over the past two decades. Currently employed clinical strategies for prevention of deep vein thrombosis (DVT) are largely inadequate. The pathophysiological basis of venous thrombosis has been gradually learnt in recent years. Anticoagulant therapy reduces the incidence of VTE, but it is associated with a risk of bleeding and infection [3]. However, preoperative anticoagulation therapy with low molecular weight heparin (LMWH) may not significantly reduce the risk of postoperative DVT, as compared to that achieved with postoperative initiation [4]. When thinking of VTE, one tends to relate it to thrombosis of veins in the lower extremities. A vast majority of hip fractures occur in elderly patients and are caused by falls; these typically cause a series of complications, which impair the quality of life, and lead to a poor prognosis. Amongst these, DVT is a serious complication which may lead to pulmonary embolism (PE) or even death. Older age, prolonged hospitalization, orthopedic surgery and prolonged immobility place these patients at a high risk of DVT.

The incidence of DVT in patients with hip fractures is very high, but not well-studied. Older patients [5] (chair-bound or dependent patients, and patients living in institutional settings) are at a significantly greater risk of DVT as compared to younger patients, and the underlying reasons are believed to be multifactorial.

Moreover, VTE is a potentially fatal postoperative complication that requires urgent attention. As most patients with hip fractures tend to be in the elderly age-group, a special group vulnerable to perioperative complications, the relative risk of VTE in patients with hip fractures is higher than that in patients with fractures at other sites. In current clinical practice, D-dimer and Doppler imaging are the mainstream investigations for diagnosis of VTE; however, the condition may not be recognized in older patients due to atypical presentation [5].

Risk of dvt in hip fracture patients

Baseline characteristics of the patients are shown in **Table 1**. In the published literature,

Table 1. Risk factors for DVT in hip fractures

Reference	Sample size/Femal	Sex (M/F)	Age	Region	Study period	Prevalence of DVT
Luksameearunothai et al. (2017)	92/68	24/68	78 ± 10	Thailan	2015.7-2016.6	16.3% (15)
Zahn et al. (1999)	21/19	2/19	79.5	UK		62% (13)[a]
Hefley et al. (1996)	122	97/36	71 ± 9	USA	1987.4-1989.10	6% (7)[b]
	11					55% (6)[a]
Cho et al. (2015)	152/100	52/100	78.2	Korea	2013.7-2013.12	2.6% (4)
Smith et al. (2011)	101		75.8	USA		9.9% (10)
Shin et al. (2016)	208			Korea	2010.12-2014.8	7.7% (16)
Song et al. (2016)	119/77	42/77	75.2 ± 9.7	China	2010.9-2014.6	29.4% (35)[c]
Liu et al. (2016)	222/141	81/141	75 ± 8	China	2009.1-2010.12	1.4% (3)
Chan et al. (2004)	95	32/63	80	Hong Kong	1996.1-1996.7	5.3% (5)
Lim et al. (2004)	104	26/78	78	Singapore	2001.4-2001.11	7.7% (8)
Cracowski et al. (1998)	100	75/25	84	France	1995.1-1995.6	44% (44)
Hong et al. (2016)	271/204	/204	76.6	Singapore	2011.1-2013.12	4.1% (11)[d]
Li et al. (2008)	75/42	33/42		China	2003.7-2006.5	48% (36)
Westrich et al. (2005)	200/158	42/158	81.3	USA	1998.5-2002.6	3.5% (7)

a, delay of more than 48 h from the time of injury to operation; b, within 48 h between the fracture and admission to the hospital; c, developed DVT in affected limbs before surgery; d, developed DVT in affected limbs after surgery.

the reported incidence of DVT in patients with hip fracture has tended to vary depending on the nature of studies, i.e., retrospective studies, prospective cohort studies or registry-based studies. At the same time, the reported incidence rates for preoperative and postoperative DVT have tended to vary in previous studies [6-9]. In a prospective study of 152 Korean patients with hip fractures, the incidence of preoperative DVT was 2.6%, while that of postoperative DVT occurring within and beyond 72 hours of surgery was 1.4% and 13.3%, respectively [10]. In a study, the incidence of VTE in patients undergoing hip fracture surgery (HFS) was 4.3% [11], which is comparable to the 2.2% [12] incidence rate reported by Kim, et al. In a study of elderly Chinese patients with hip fractures, the incidence of DVT during hospital stay was 5.3%; one of 73 patients was found to have developed DVT 3 months after operation [13]. DVT is a relatively common disease and it recurs frequently. It affects the quality of life of patients and is a major cause of death in patients with hip fractures. Therefore, identification of patients with hip fractures, who are at a high risk of DVT is a key imperative, and interventions aimed at minimizing recurrence should be given due attention.

Several environmental and genetic risk factors contribute to the occurrence of DVT in patients with hip fractures. The etiology of both DVT and hip fracture is multifactorial and risk factors for both conditions are intricately linked with each other. Therefore, understanding of the interaction between these risk factors can facilitate DVT research, and may help identify targeted prevention and treatment measures.

Provoking risk factors

Surgery as a risk factor for DVT in patients with hip fracture

Evaluation of the risk factors for DVT should be an integral part of preoperative assessment of patients with hip fractures. Surgical approach, duration of surgery and technique used for internal fixation affect the occurrence of DVT. Longer duration of surgery may lead to prolonged venous stasis. Intraoperative injury to soft tissues including the vessel wall and postoperative patient-immobilization are inevitable aspects of hip surgery, which increase the risk of DVT [14-16]. However, in a recent study, majority of patients with hip fractures who developed postoperative DVT already had thrombus before the surgery as shown by preoperative venography [7]. Furthermore, the incidence of preoperative DVT in patients who underwent surgery > 48 h after fracture was higher than that in patients who underwent surgery within 48 h of sustaining the fracture. Therefore, delayed operation may increase the risk of DVT in these patients [6, 17]. In the case of cemented total hip arthroplasty, the heat produced during polymerization of cement could injure neurovascular tissues, and in-

crease the risk of DVT [18]. In a prospective epidemiological study of patients with hip fractures in Asia, the incidence of DVT in the lower limbs was evaluated by bilateral venography performed 6-10 days after surgery. In this study, the incidence of postoperative DVT after total hip replacement (n = 175) and hip fracture surgery (n = 96) was 25.6% and 42%, respectively, and proximal DVT accounted for 5.8% and 7.2% of cases, respectively [19]. Hip arthroscopy-assisted surgery provides excellent visualization and is being increasingly adopted; however, there are still risk factors of DVT. Guidelines of the American Academy of Orthopedic Surgeons do not address thromboprophylaxis for hip arthroscopy surgery or post-arthroplasty DVT prophylaxis. Owing to the reported increase in complications, guidelines for the prevention of DVT after hip arthroscopy are needed [20, 21]. In addition, prolonged immobilization of the patient, the use of tourniquets, excessive traction or rotation of the lower limbs also greatly increases the chance of indirect injury to adjacent blood vessels [22].

Cancer as a risk factor for DVT in patients with hip fractures

Cancer associated thrombosis (CAT) is a known complication that increases morbidity and mortality among cancer patients [23, 24]. Compared with cancer patients who do not develop thrombosis, those who develop thrombosis have a sharply reduced life span. Patients undergoing open pelvic operations were shown to be at a higher risk of VTE [25]. Several instances of tumor thrombi that originated from bone sarcomas and other tumors have been reported [26-28]. Therefore, cancer patients who sustain fractures are at an increased risk of thrombosis. Close monitoring and active intervention is required in these patients to prevent venous thrombosis.

Inflammation as a risk factor for VET

VTE patients with infection tend to have immune dysfunction; patients who have postoperative complications of an infectious nature are at particularly high risk of immune dysfunction [29, 30]. Inflammatory pathways are intricately associated with the occurrence and development of venous thrombosis [31-33], as many of these are involved in the fibrinolytic and coagulation cascades [34]; the inflammatory pathways may be triggered in response to bacterial, viral, fungal or parasitic infection. VTE is a chronic disease, for which anti-inflammatory treatment is as important as prophylactic anticoagulation therapy [35]. In a study of 22,733 HCV-infected patients, incidence rate of 'any thromboembolic event' was 233.4 events per 10,000 person-years; the results showed that patients with HCV infection are at a higher risk of thromboembolic complications [36]. Infections of skin, respiratory system, urinary tract, and abdominal organs diagnosed in the community or in the hospital were shown to increase the risk of VTE by more than two-fold [33]. Moreover, acute cytomegalovirus (CMV) infection is a potential contributor to VTE. Yildiz et al. studied 1007 consecutive patients with VTE, and identified 10 patients with synchronous acute CMV infection that were younger and exhibited a female predominance [37].

Other environmental provoking risk factors for DVT in hip fractures

In a prospective study, patients living in their own home with hip fracture were found to be at a higher risk of DVT [38]. Furthermore, immobility is another central issue in patients with hip fractures that can cause a series of physiological and clinical effects. One of them is long-term bed rest after fracture [39]. The iliac vein compression syndrome (IVCS), also called May-Thurner syndrome or Cockett syndrome, was first described by Virchow in 1851 when he observed a left-sided predominance of iliofemoral DVT [40]. IVCS usually occurs in the second or third decade of life and is especially prevalent in women [41]. Studies have highlighted the need to improve awareness of IVCS as a risk factor for left-sided DVT in patients with hip fracture [42]. Other factors such as pregnancy and postpartal period, immobilization, hospitalization, and catheterization may also increase the risk of DVT in patients with hip fracture. However, further studies are needed to confirm their relationship with DVT.

Non-provoking risk factors

Age as a risk factor for DVT in hip fractures

In the general population, age is a well-known risk factor for DVT. Increasing age is associated with cardiovascular diseases, which also increases the risk of postoperative DVT after sur-

gery for hip fractures. In several studies, the age of patients who developed postoperative DVT was shown to be much higher than that of patients who did not develop DVT [43-46]. In a retrospective cohort study of 454 elderly Asian patients with hip fracture, 6.4% developed DVT [47]. In a study of 271 patients with hip fractures, the incidence of postoperative DVT was higher among female patients who were over 65 years of age [19]. Indeed, elderly patients with hip fracture are more likely to experience hospital-associated DVT and have a high risk of morbidity and mortality. Multi-system malfunction, increased blood viscosity caused by blood loss, prolonged immobilization and decreased physical activity after fracture all contribute to a relatively slow blood flow and hypercoagulable state. Moreover, the possibility of DVT is often disregarded in older patients, who tend to exhibit atypical signs and symptoms [5]. Identification of patients undergoing hip surgery who are at a high-risk of DVT can help improve perioperative thromboprophylaxis and ensure appropriate care of patients during hospital stay and even after discharge from hospital. Moreover, education of caregivers regarding prevention and early detection of signs of DVT is an important intervention to minimize the associated morbidity.

Time as a risk factor for DVT in hip fractures

Patients with hip fractures are at a substantial risk of venous thrombosis irrespective of the treatment strategy, and this risk increases with delay in treatment [17]. In a prospective study of 152 Korean geriatric patients with hip fractures, 2 of the 137 patients (1.4%) who were admitted to a hospital within 72 hours of injury developed DVT; out of the remaining 15 patients who did not receive treatment within 72 hours, two patients (13.3%) developed DVT [10]. In a study by Zahn et al., patients who underwent surgery after a delay of > 48 h from the time of injury were more likely to develop DVT regardless of the treatment and/or prophylaxis with heparin. Further, the incidence of DVT increased to 54.5-62% with further delay beyond 48 h [6]. Therefore, time elapsed since injury should be considered as a risk factor during preoperative evaluation of patients with hip fracture.

Other environmental nonprovoking risk factors for DVT in hip fractures

Recent studies have suggested that smokers with fracture are at a slightly higher risk of VET, and that current smokers have a higher risk of VET than former smokers [48]. In addition, chronic inhalation of tobacco smoke may lead to chronic pulmonary disease, which results in a hypercoagulable state [49, 50]. Moreover, the incidence of VTE in Asian patients with low body mass index (BMI) was considered to be lower than that in Western patients [51]. Despite the significant increase in the number of risk factors identified, a large number of thrombotic events still occur. It seems likely that this simply reflects the effect of factors that have not yet been discovered, or the effect of genetic factors. As nonprovoking risk factors, sex, age, obesity, race or ethnicity, oral contraceptive or hormone therapy, statin use, physical activity and sedentary life style may have an impact on the risk of DVT in patients with hip fracture; more clinical studies are needed to analyze these effects.

Fracture-related risk factors

A series of changes occur in the body in the aftermath of hip fracture. These include local hemorrhage and release of exogenous coagulation factors from injured soft tissues, which collectively activate the coagulation cascade. These chemical changes result in a hypercoagulable state. In a study of 127 elderly patients with hip fractures, both preoperative and postoperative fibrinogen levels were significantly higher than the normal reference levels, which may have a direct impact on the coagulation system [52]. Moreover, studies conducted on transgenic mice and murine infusion models suggest that fibrinogen can contribute to DVT via multiple mechanisms [53]. Together, these studies indicate that hyperfibrinogenemia plays a causal role in the pathogenesis of DVT, and is not merely a biomarker of DVT risk.

Exposure of subcutaneous tissues and local trauma to soft tissues and blood vessels caused by fracture activate blood extrinsic coagulation pathway, which results in a hypercoagulable state. Moreover, inflammatory mediators released by necrotic tissues can stimulate the coagulation system, which further activates the coagulation system.

Blood biomarkers predictive of dvt in fractures

D-dimer levels

D-dimer is a clinically relevant biomarker of activation of hemostasis and fibrinolysis. It is a

relatively sensitive marker of DVT for patients with fracture before and after surgical operation. D-dimer is frequently used as part of diagnostic workup for suspected DVT in patients with hip fractures [54]. However, high levels of D-dimer are frequently found in patients with cancer, infection, and other medical conditions such as heart failure and renal failure. Liu et al. assessed D-dimer levels in patients with various fractures and found that the D-dimer levels were significantly higher than those in the control group; patients with fractures of femur showed significantly higher D-dimer levels as compared to that in patients with fractures at other sites [55]. However, the low molecular weight of D-dimer is a problem, which renders it easily diffusible in the bloodstream.

Soluble fibrin

The final stage of blood coagulation is induced by the increase in plasma levels of soluble fibrin, which is accompanied by intensification of platelet-aggregation. As a biomarker, soluble fibrin was shown to enhance the functional activity of the platelet link in the hemostatic system, which is a prerequisite for thrombosis [55]. Soluble fibrin is a more sensitive marker of DVT than D-dimer. Previous studies have shown high plasma levels of soluble fibrin in the early stages of thrombotic diseases [56, 57]. In a pilot study, the values of soluble fibrin and D-dimer were compared in 119 outpatients with suspected venous thromboembolism; the results showed that the sensitivity of soluble fibrin for detection of DVT was comparable to that of D-dimer, whereas both the positive-predictive value and the specificity of soluble fibrin was higher than that of D-dimer [58].

Many types of diagnostic biomarkers of thrombosis have been reported in recent studies. These include, platelet count, hemoglobin, white cell count, fibrinogen, rotational thromboelastometry, factor VIIa, thrombin generation, tissue factor activity, P-selectin, procoagulant phospholipids, plasminogen activator inhibitor-1 (PAI-1), heparanase, prothrombin time, activated partial thromboplastin time (aPPT), albumin, sodium and interleukin-1. These may play a pivotal role as biomarkers of DVT, and the mechanisms are just now being elucidated [59, 60].

Recurrence of dvt

DVT tends to recur frequently, and reported rates of recurrent DVT were 4-13 per 100,000 person-years [61]. The risk of the first recurrence of DVT varies with time and is the highest during the first 12 months. Increase in BMI, increase in patient age, paralysis of the leg, and active cancer are considered to be independent predictors of recurrence. In a prospective cohort study, a nomogram was developed [DAMOVES score (D-dimer, Age, Mutation, Obesity, Varicose veins, Eight, Sex)] to predict recurrence risk and to guide the need for continuation of anticoagulant therapy after initial treatment for 3 months [62].

Future research should be directed towards identification of the optimal targets for prophylaxis of VTE. Groups currently considered to be at high risk of VTE, such as all patients undergoing hip or knee replacement surgery, include few individuals who would experience VTE in the absence of prophylaxis. Identification of individuals within these groups who are at a high risk of incident or recurrent VTE, and who would benefit most from primary or secondary prophylaxis, is a key imperative. Increasing awareness of patients and caregivers regarding prevention of thrombosis [63], and minimizing the risk of bleeding complications caused by treatment of those at low risk are other key areas of work.

Conclusion

In recent years, risk factor analysis and preventive research on DVT has been an active area of research. The three major causes of DVT are slow blood flow, venous wall injury and hypercoagulable state [64]. Although some independent risk factors and predictors have been identified, further research on prevention and treatment of DVT in patients with hip fractures is of much clinical relevance. In summary, several gaps exist in our understanding of the epidemiology and risk factors for DVT in patients with hip fracture. The present review summarizes the evidence from small single-center studies. Large multi-center, cross-national prospective studies are required to further characterize the epidemiology of DVT in patients with hip fracture.

Disclosure of conflict of interest

None.

Abbreviations

DVT, deep vein thrombosis; VTE, Venous thromboembolism; LMWH, low molecular weight hep-

arin; PE, pulmonary embolism; HFS, hip fracture surgery; CAT, Cancer associated thrombosis; CMV, cytomegalovirus; IVCS, iliac vein compression syndrome; BMI, body mass index; PAI-1, plasminogen activator inhibitor-1; aPPT, activated partial thromboplastin time.

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