

Features for deep vein thrombosis in the uninjured limbs of lower extremity fractures: a retrospective study 1454 patients

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Abstract

Objective: The purpose of this study was to investigate the incidence of and independent risk factors for deep venous thrombosis (DVT) in the uninjured limb, before and after operation, in patients with lower extremity fractures.

Methods: We collected the clinical data of patients with lower extremities fractures who presented at Xi'an Honghui Hospital between 1 July, 2015 and 31 October, 2017. Doppler ultrasonography was used to diagnose the DVT. Patients were examined pre- and postoperatively. The patients were then divided into a thrombosis group and a no thrombosis group according to the preoperative and postoperative ultrasonography results. The thrombosis group was defined as patients admitted to our hospital with DVT in the uninjured limb and the no thrombosis group was defined as patients without DVT in the uninjured limb.

Results: This study enrolled 1454 patients who met the inclusion criteria. The incidence of preoperative DVT in the uninjured limb was 9.63% whereas the postoperative incidence was 20.29%. Age (OR=0.965, 95 CI%: 0.954 - 0.977; $P=0.000$) and gender (OR=0.667, 95% CI: 0.451-0.986, $P=0.042$) were independent risk factors for preoperative DVT in the uninjured limb. Blood loss (OR=0.997, 95 CI%: 0.995-1.000; $P=0.020$), D-dimer levels at admission (OR=0.941, 95 CI%: 0.887-0.999; $P=0.045$), and postoperative day 5 D-dimer levels (OR=0.889, 95 CI%: 0.819-0.965; $P=0.005$), were independent risk factors for postoperative DVT in the uninjured limb.

Conclusion: In conclusion, the actual incidence of DVT in the uninjured lower extremity after fracture may currently be underestimated and should be pay more attention.

Introduction

Deep vein thrombosis (DVT) occurs frequently in orthopaedic patients. It can increase the length of the hospital stay and associated costs, affect the recovery process of patients, and potentially cause a fatal pulmonary embolism [1]. In recent years, orthopaedists have paid increasing attention to the prophylaxis and treatment of DVT. Currently, drug prevention is considered one of the most effective methods to decrease the risk of lower extremity DVT [2]. Traditional low-molecular-weight heparin (LMWH) [3] is used as the standard protocol.

There are only a few studies that directly identify the incidence and importance of DVT of the uninjured limb in patients with lower extremity fractures. Mok et al. reported that the incidence of DVT in uninjured limbs is 14.3% [4]. Song et al. reported that 29.4% of preoperative patients had DVT in either the uninjured or injured limb and that percentage has increased to 32.8% postoperatively [5]. In fact, there was a risk for DVT in the uninjured limb as well. Meissner et al suggested that the hypercoagulation state persists for at least one month after injury in 80% of patients [6]. Therefore, DVT in the uninjured limb is possible. Decker and Weaver et al. demonstrated that a DVT could occur in both the injured and uninjured leg with a trend for higher incidences in the injured leg [7].

On the basis of these factors, this study aimed to retrospectively analyse the data of patients with lower extremity fractures to investigate the incidence of DVT in the uninjured limb in in-patients with lower-extremity fractures.

Patients And Methods

Ethical statement

The study was approved by the Institutional Review Board (IRB) of Xi'an JiaoTong University.

Included and excluded criterion

Inclusion criteria: a) age \geq 16 years, b) recent lower extremity fractures requiring surgical treatment, c) hospital stay > 48 h, d) availability of results of preoperative and postoperative ultrasonography.

Exclusion criteria: a) delayed lower extremity fractures, defined as injuries without surgical treatment within 3 weeks of injury, b) open soft tissue fractures c) serious medical problems without tolerating surgery, d) poor compliance patients.

Methods

All patients admitted to the hospital were routinely assessed using the the risk assessment profile for thromboembolism score (RAPT) to determine the risk of thromboembolism. We also assessed patients for contraindications for anticoagulation therapy. For patients without anticoagulation contraindications, LMWH was injected subcutaneously once a day to prevent DVT. Mechanical thrombo-prophylaxis, administered for 20 min, twice a day, via a pressure pump was also utilized to prevent a DVT. Blood samples were collected within two hours after admission, one day preoperatively, one day postoperatively, and five days postoperatively.

We used Doppler ultrasonography to diagnose the DVT. The diagnostic criteria the presence of a constant intraluminal filling defect. Patients were examined pre-and postoperatively. All patients underwent ultrasonography of the double lower limbs on the day before the scheduled surgery and between the third and fifth day after surgery. DVTs were classified into three types: central (femoral and iliac veins), peripheral (calf muscle, fibular, and anterior/posterior tibial veins), and mixed thrombosis (both central and peripheral thromboses).

Based on the results of the ultrasonography, the patients were divided into two groups: thrombosis group and no thrombosis group. The thrombosis group was defined as patients admitted to our hospital suffering a DVT in the uninjured limb and the no thrombosis group was defined as patients without a DVT in the uninjured limb. For patients without thrombosis, LMWH was continuously injected subcutaneously to prevent DVT. Patients with thrombosis had LMWH injected subcutaneously, twice per day, to treat the DVT. When preoperative ultrasonography results showed a central or mixed thrombosis, an inferior vena cava filter was used to prevent the risk of pulmonary embolism. The anticoagulant

therapy was stopped 12 hours before surgery and restarted again 24 hours after surgery. When the patients were discharged, the protocol was changed to rivaroxaban for 35 days after operation.

Statistics analysis

Statistical analysis was performed using the SPSS Version 19.0 (SPSS Inc., Chicago, Illinois, USA). The measurement data was analyzed to determine if the data is normally distributed. The statistical analysis utilized the independent sample t-test. For the enumeration data, chi-square test was used. Multivariate analysis was used to detect the risk factors. The difference was statistically significant if $P < 0.05$.

Results

Patient characteristics

In total, 1454 patients suffering a lower extremity fracture were screened. After excluding, 334 patients suffering uninjured limb DVT. Of these patients, 269 fractures happen above the knee, 37 fractures happen around the knee, 28 fractures happen below the knee. All the patients underwent surgery. The procedures included: open reduction with internal fixation in 284 patients, hemiarthroplasty in 3 patients, total hip replacement in 1 patient, and closed reduction in 46 patients. All patients were treated with low-molecular-weight heparin at admission. On average, all the patients were aged 71.43 (standard deviation [SD] 13.86) years range from 17 to 95 years old. Of these patients, 218 (65.27%) were female and 116 (34.73%) were male. No fatal bleeding events or bleeding into a critical site was found in this study.

The incidence of uninjured limb DVT in preoperative ultrasound

The preoperative ultrasound data for patients with a lower extremity fracture with or without a thrombosis in the uninjured limb was compared in the patients' characteristics (**Table 1**). All the patients were diagnosed using ultrasound to identify the thrombosis in lower limbs. There were 140 patients with a thrombosis to the uninjured limb (9.63%) and 1314 patients without a thrombosis to the uninjured limb (90.37%). There were 9.01% peripheral DVT, 0.07% central DVT, and 0.55% mixed DVT. Peripheral DVT constituted 93.57% (131/140) of all DVTs.

Importantly, there were 50 patients with a left lower extremity fracture who suffered a DVT in both lower extremities (3.44%), 22 with a left lower extremity fracture who suffered a right lower extremity DVT (1.51%), 34 with a right lower extremity fracture who suffered a left lower extremity DVT (2.34%) and 34 with right lower extremity fractures who suffered a DVT in both lower extremities (2.34%).

Univariate analysis of preoperative uninjured limb DVT

There were no statistically significant differences between the two groups in: medical morbidity excluding hypertension and coronary heart disease, Body Mass Index, days between fracture and hospitalization, D-dimer at admission, preoperative D-dimer, or CRP at admission. However, in the thrombosis group, female patients, patients with a fracture located above the knee, and patients classified as stage \geq of American

Society of Anesthesiologists Physical Status Classification System (ASA) were statistically different than the no thrombosis group. In addition, more patients in the thrombosis group suffered hypertension and coronary heart disease than in the no thrombosis group. (32.86% vs. 21.91%, $P=0.003$; 32.86% vs. 21.76%, $P=0.003$), Age (72.42 ± 13.57 vs. 60.98 ± 19.38 , $P=0.000$) was found to be another vital factor contributing to thrombosis (**Table 1**).

Multivariate analysis of preoperative uninjured limb DVT

Multivariate analysis was used to detect the risk factors by entering age, sex, types of fracture, hypertension, coronary heart disease and ASA classification. The results showed that age (OR=0.965, 95 CI%: 0.954 - 0.977; $P=0.000$) and sex (OR=0.667, 95% CI: 0.451-0.986, $P=0.042$) were independent risk factors for preoperative DVT.

The incidence of uninjured limb DVT in postoperative ultrasound

All patients underwent ultrasonography postoperatively to identify the thrombosis in lower limbs. Thrombosis was found in the uninjured limb of 295 patients (20.29%) and 1159 patients did not have a thrombosis in the uninjured limb (79.71%). There were 19.33% peripheral DVT, 0.21% central DVT, 7.57% mixed DVT. Peripheral DVT constituted 95.25% (281/295) of all DVTs (**Table 2**).

Importantly, there were 127 patients with a left lower extremity fracture who suffered a DVT in both lower extremities (8.73%), 25 with a left lower extremity fracture who suffered a DVT in the right lower extremity (1.72%), 33 with a right lower extremity fracture who suffered a DVT in the left lower extremity (2.27%) and 110 with a right lower extremity fracture who suffered a DVT in both lower extremities (7.56%).

Univariate analysis of postoperative uninjured limb DVT

In two groups, there was no statistically significant difference in the medical morbidity excluding hypertension, coronary heart disease and stroke, Body Mass Index, length of hospital stay, days between fracture and hospitalization, days between fracture and operation, duration of operation, liquid transfusion, preoperative D-dimer values, C-reactive protein at admission and at postoperative day 5. However, in the thrombosis group, more patients were female ($P=0.000$), fracture above the knee ($P=0.000$), and ASA stage \geq ($P=0.000$) compared to the no thrombosis group. Similar to the preoperative ultrasound data, age is a contributing factor to postoperative thrombosis (71.76 ± 13.42 vs. 59.62 ± 19.66 , $P=0.000$). Coronary heart disease, stroke, and hypertension were also important factors contributing to postoperative thrombosis ($P=0.003$, $P=0.017$, $P=0.009$). In addition, blood loss was another factor that contributed to postoperative thrombosis ($P=0.000$). In the serum markers, D-dimer at admission, at postoperative day 1, at postoperative day 3, at postoperative day 5 were higher in the thrombosis group (**Table 2**).

Multivariate analysis of postoperative uninjured limb DVT

Multivariate analysis was used to detect the risk factors by entering age, gender, types of fracture, hypertension, coronary heart disease, stroke, ASA classification, blood loss, D-dimer at admission, D-dimer at postoperative day 1, D-dimer at postoperative day 3 and at D-dimer at postoperative day 5. The results show that D-dimer at admission (OR=0.941, 95 CI%: 0.887-0.999; $P=0.045$), D-dimer at postoperative 5 day (OR=0.889, 95 CI%: 0.819-0.965; $P=0.005$), and blood loss (OR=0.997, 95 CI%: 0.995-1.000; $P=0.020$) were independent risk factors for postoperative DVT.

The dynamic changes of uninjured limb DVT before and after operation

There were 334 patients suffering uninjured limb DVT in 1454 patients. There was a total of 53.60% (0.90%, 52.40%, 0.30%) patients without changes during the hospital stay. There were 5.39% of patients who went from having a preoperative peripheral DVT to no thrombosis postoperatively. Conversely, 34.73% (33.83%, 0.30%, 0.60%) of patients changed from having no preoperative thrombosis to developing a peripheral, central, or mixed DVT postoperatively (**Figure 1**).

Discussion

There are few studies that directly identify the incidence and importance of DVT in the uninjured limb in patients with lower extremity fractures. Most previous research analysed the distribution of DVT in the injured limb across the different fractures[3], or risk factors contributing to a DVT in the injured limb during the hospital stay[8]. Song et al [5] reported the changes in DVT in the injured limb in 119 patients and found a high incidence of preoperative DVT in patients[5]. They also found that the incidence of DVT in the uninjured limb is low. In addition, some studies reported symptomatic DVT but ignored asymptomatic DVT. Sun et al. reported that 11.2% of DVTs are asymptomatic[9]. Some studies reported that all patients suffering DVT were clinically asymptomatic [10, 11]. In the field of thrombosis after fracture, we should not only focus on symptomatic DVT but also pay attention to asymptomatic DVT. Asymptomatic DVT is a potentially important but easily ignored risk factor for thrombosis.

We retrospectively investigated the changes in preoperative, postoperative, symptomatic, and asymptomatic DVTs in the uninjured limb of patients with lower extremity fractures, We found: **a.** the incidence of preoperative DVT in the uninjured side is 9.63% and increases to 20.29% postoperatively, **b.** peripheral DVT constitutes 93.57% of all preoperative and 95.25% of postoperative uninjured limb DVTs.

The dynamic changes in preoperative and postoperative uninjured limb DVT are obvious. There were 116 new postoperative DVTs to the uninjured limb, primarily peripheral DVTs. Peripheral DVTs are likely to occur in calf muscle veins[12]. The DVTs in the uninjured limb of 298 patients were peripheral from before to after operation. The result is similar to DVT of the injured limb. The majority of patients diagnosed with a DVT in the uninjured limb postoperatively had already suffered a DVT in the uninjured limb before operation[5].

In this study, the incidence of DVT in the uninjured limb in lower extremity fractures is high, increasing from 9.63% preoperatively to 20.29% postoperatively. Previous studies report that the incidence is lower

than that in our study but the reasons vary[4]. First, some studies reported symptomatic DVT but ignored asymptomatic DVT. In fact, Sun and Chen et al. reported that 11.2% of DVTs are asymptomatic[9]. Second, the mean number of days between fracture and surgery is 6.95 days in our study. However, other studies have shown the preoperative incidence of injured limb DVT to be between 54% and 62% for patients with acute fracture whose surgery was delayed by >48 hours[13, 14]. Most of the patients in this study presented a few days after the fracture occurred. The delay may result from preoperative medical evaluation and optimization or transfer from community hospitals to tertiary-care facilities. Elderly patients tend to be sicker on admission and therefore more likely to require more time for preoperative preparation[8, 9]. The delays in surgical intervention may predispose patients to developing thromboembolic problems and may be related to the uninjured limb thromboembolic problems. Third, thrombosis could be detected by ultrasonography, venography, and multidetector computed tomographic venography[8, 15]. The diagnostic sensitivity and the specificity is different for each modality and thus, these factors may be contributing to the high incidence of DVT more than other factors[15].

There are many factors contributing to the formation of thrombosis after trauma, including the fracture and surgical intervention[5, 16-18]. In this study, we found that age and gender were independent risk factors for preoperative DVT in uninjured limb and that D-dimer at admission and at postoperative day 5 and blood loss were independent risk factors for postoperative DVT. Knudson and Gomez et al. found that age is an independent risk factor for thrombosis in adult patients with trauma[19]. One study showed that the incidence of DVT is higher in men than women but the reasons are still not clear.[20] However, some scholars hold the opposite view, believing that gender does not affect the incidence of DVT[21]. Furthermore, blood loss is another factor promoting the hypercoagulability states[22]. In the multivariate analysis of postoperative DVT, blood loss is an independent risk factor (OR=5.430, $P=0.020$). Blood loss in thrombosis group is higher than in the no thrombosis group (Table 2); however, there is no difference in liquid transfusion. The hypercoagulation states, one factor that increases the thrombosis risk, may be the main reason contributing to this phenomenon. Meissner, Chandler et al. and Selby, Geerts et al. proved that the hypercoagulability state persists for a long time[6, 23]. In addition, the surgical intervention itself is the introducing factor for hypercoagulability states[24, 25]. Thus, DVT in uninjured limb and the increased incidence of DVT are easy to comprehend.

In conclusion, the actual incidence of DVT in the uninjured lower extremity after fracture may currently be underestimated and should be pay more attention.

Abbreviations

DVT Deep vein thrombosis

LMWH Low-molecular-weight heparin

BMI Body mass index

ASA American Society of Anesthesiologists

OR Odds ratio

Declarations

Acknowledgments

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Availability of data and materials

The survey was implemented by Xi'an Honghui Hospital. According to relevant regulations, the data could not be shared.

Author Contributions

Conceptualization: ZY, ZK.

Data curation: FC, LZ, YK, SK, KC, and HH.

Formal analysis: ZBF and QSW.

Roles/Writing-original draft: QSW, CYX and ZBF.

Ethics approval and consent to participate

The study was approved by the ethical board of Xi'an JiaoTong University (No. 2014026).

Conflict of interest

The authors declare that they have no competing interests.

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Tables

Table 1. Patient characteristics according to preoperative ultrasound

	Thrombosis	No Thrombosis	Overall	<i>P</i>
Number	140	1314	1454	
Age	72.42±13.57	60.98±19.38	62.09±19.19	0.000
Gender				
Female	98	694	792	0.000
Male	42	620	662	
Unilateral or bilateral				
Left fracture right thrombus	22	-	22	0.000
Right fracture left thrombus	34	-	34	
Left fracture bilateral thrombosis	50	-	50	
Right fracture bilateral thrombosis	34	-	34	
Only affected limb thrombosis	-	333	333	
No lower extremities thrombosis	-	981	981	
Types of fracture				
Above the knee	109	812	921	0.001
Around the knee	14	264	278	
Below the knee	17	238	255	
Types of venous thrombosis				
central	1	8	9	0.000
peripheral	131	289	420	
mixed	8	36	44	
Medical morbidity				
Hypertension (%)	46 (32.86)	288 (21.91)	334	0.003
Diabetes (%)	18 (12.86)	106 (8.07)	124	0.054
Coronary heart disease (%)	46 (32.86)	286 (21.76)	332	0.003
Arrhythmia (%)	19 (13.57)	142 (10.81)	161	0.322
Stroke (%)	12 (8.57)	76 (5.78)	88	0.189
Associated trauma (%)	14 (10.00)	167 (12.71)	181	0.356
BMI	21.15±7.64	22.41±5.31	22.28±5.58	0.331
Days between fracture and hospitalization (days)	6.14±28.49	2.05±5.58	2.44±10.36	0.093
Days between fracture and operation (days)	8.01±42.35	6.84±12.77	6.95±17.86	0.744
ASA classification				

1	10	245	255	0.005
2	88	766	854	
3	41	299	340	
4	1	4	5	

Serum markers

D-Dimer at admission (mg/L)	13.93±13.91	12.58±20.33	12.71±19.80	0.453
D-Dimer at preoperation (mg/L)	5.96±6.27	5.05±6.32	5.15±6.31	0.289
CRP at admission (mg/L)	21.83±34.47	21.14±31.96	21.11±32.22	0.868

ASA, American Society of Anesthesiologists; CRP, C- reactive protein.

Table 2. Patient characteristics according to postoperative ultrasound

	Thrombosis	No Thrombosis	Overall	<i>P</i>
Number	295	1159	1454	
Age	71.76±13.42	59.62±19.66	62.09±19.19	0.000
Gender				
Female	191	601	792	0.000
Male	104	558	662	
Unilateral or bilateral				
Left fracture right thrombus	25	-	25	0.000
Right fracture left thrombus	33	-	33	
Left fracture bilateral thrombosis	127	-	127	
Right fracture bilateral thrombosis	110	-	110	
Only affected limb thrombosis	-	433	433	
No lower extremities thrombosis	-	726	726	
Types of fracture				
Above the knee	240	681	921	0.000
Around the knee	34	244	278	
Below the knee	21	234	255	
Types of venous thrombosis				
central	3	10	13	0.000
peripheral	281	377	658	
mixed	11	46	57	
Medical morbidity				
Hypertension (%)	85 (28.81)	249 (21.48)	334	0.009
Diabetes (%)	32 (10.85)	92 (7.94)	124	0.120
Coronary heart disease (%)	87 (29.49)	245 (21.14)	332	0.003
Arrhythmia (%)	41 (13.90)	120 (10.35)	161	0.091
Stroke (%)	27 (9.15)	61 (5.26)	88	0.017
Associated trauma (%)	34 (11.53)	147 (12.68)	181	0.588
BMI	21.90±6.58	22.38±5.30	22.28±5.58	0.516
Length of hospital	9.76±3.84	9.54±4.26	9.58±4.18	0.429
Days between fracture and hospitalization (days)	3.49±19.85	2.18±5.85	2.44±10.36	0.263
Days between fracture and	6.98±29.78	6.95±13.23	6.95±17.86	0.986

operation (days)

ASA classification

1	21	234	255	0.000
2	183	671	854	
3	89	251	340	
4	2	3	5	

Duration of operation (mins)	109.39±57.43	113.68±73.00	112.81±70.12	0.349
Blood loss (ml)	293.39±300.20	223.05±241.20	237.32±255.74	0.000
Liquid transfusion (ml)	1730.61±623.94	1739.41±557.11	1737.62±571.12	0.814

Serum markers

D-Dimer at admission (mg/L)	16.46±23.89	11.76±18.52	12.71±19.80	0.002
D-Dimer at preoperation (mg/L)	6.10±6.17	4.90±6.33	5.15±6.31	0.072
D-Dimer at postoperative 1 day (mg/L)	10.29±9.02	5.93±6.25	6.85±7.15	0.000
D-Dimer at postoperative 3 day (mg/L)	7.69±6.97	5.16±6.03	5.73±6.34	0.000
D-Dimer at postoperative 5 day (mg/L)	10.56±7.47	6.20±5.04	7.27±6.02	0.000
CRP at admission (mg/L)	22.14±33.96	21.00±31.80	21.22±32.22	0.731
CRP at postoperative 5 day (mg/L)	36.68±39.47	32.49±44.19	33.33±43.37	0.437

ASA, American Society of Anesthesiologists; CRP, C- reactive protein.

Figures

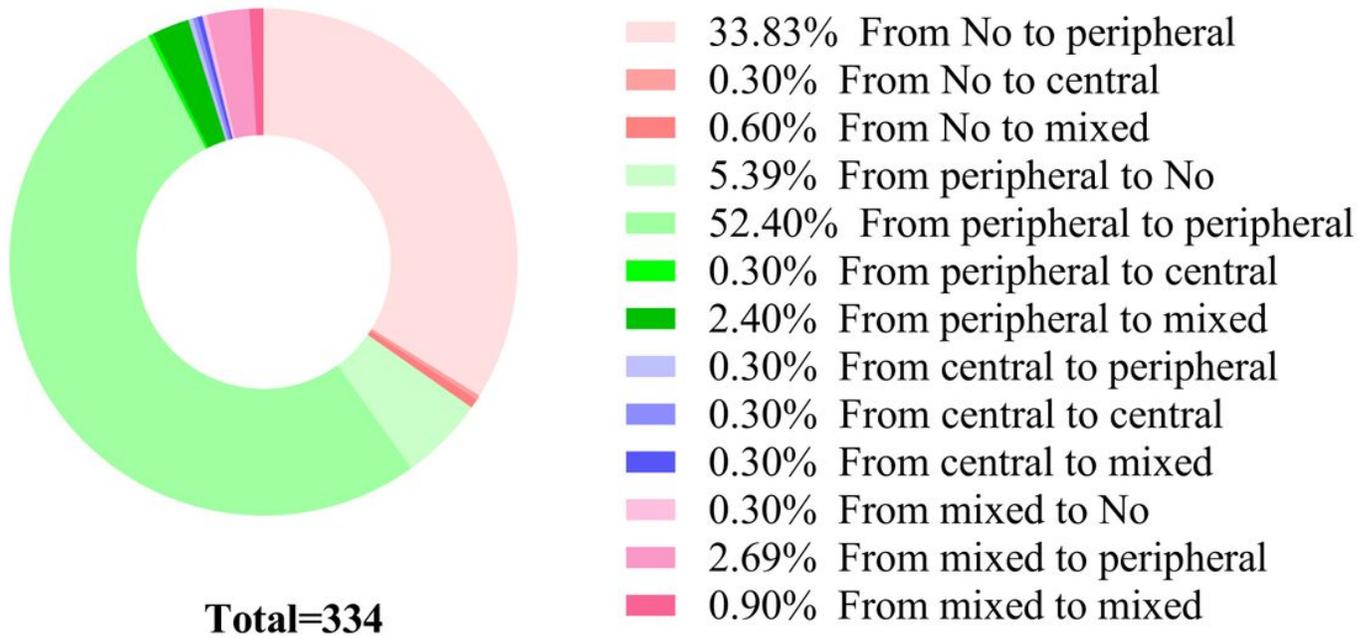


Figure 1

The dynamic changes of uninjured limb DVT before and after operation.