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The Incidence and Location of Deep Vein Thrombosis in Lower Extremity Fracture Patients Receiving Sequential Chemical Prophylaxis

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Abstract

To investigate the incidence and location of deep vein thrombosis (DVT) in patients with lower extremity fractures receiving pharmacological thromboprophylaxis with LMWH followed by rivaroxaban. All patients aged $\geq$18 years with lower extremity fractures were included in the study. Duplex ultrasonography (DUS) was performed in the lower extremities before and after surgery for DVT evaluation. According to the location, the DVT was divided into proximal, distal, and mixed thromboses. According to fracture location, patients were classified as having fractures proximal, around, and distal to the knee. All patients received sequential chemical prophylaxis. A total of 404 patients with a mean age of 44.2 $\pm$ 13.8 years were included. The incidence of DVT postoperatively was higher than that preoperatively and at 1 month postoperatively. Patients with fractures proximal and around the knee had higher DVT incidences detected on DUS postoperatively and at 1 month postoperatively. Most DVTs were located in the distal vein. DVT incidence and severity were the highest immediately after surgery. DVT incidence in fractures around and proximal to the knee increased after surgery and at 1 month postoperatively. Although with chemical thromboprophylaxis, distal DVT was the most variable during the early stage.

Keywords

deep vein thrombosis, lower extremity fracture, anticoagulation, low-molecular-weight heparin, rivaroxaban

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Introduction

Deep vein thrombosis (DVT) of the lower extremity is a common complication in traumatic patients. The prevalence of post-traumatic DVT is reported as approximately 9.1%–11.1%.[1,2] Meanwhile, the prevalence of DVT increases after surgery. DVT should be prevented and treated in a timely manner; otherwise, it can lead to chronic pain, secondary varicose veins, or ulcers, which seriously affect the patients' quality of life. Even fatal pulmonary embolism (PE) can occur in some cases.[3] In recent years, orthopedists have paid increasing attention to the prophylaxis and treatment of DVT.

At present, chemical thromboprophylaxis is considered among the most effective methods to avoid lower extremity DVT.[4] Traditionally, low-molecular-weight heparin (LMWH) is a popular choice.[5] However, the dose of LMWH for the prevention of DVT and the treatment duration are controversial.[6,7] In addition, LMWH can lead to local pain and even subcutaneous induration, while some patients develop heparin-induced thrombocytopenia leading to bleeding and other adverse events.

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Selective factor Xa inhibitors (rivaroxaban[8] and apixaban[9]), which are new oral anticoagulants, are making postoperative anticoagulant therapy more convenient. Rivaroxaban provides a short-term and sustained treatment strategy for venous thrombosis.[10] Rivaroxaban decreases the risk of bleeding compared to LMWH without statistical significance.[8]

For patients at a high risk of thrombosis, perioperative prevention is needed in addition to continued anticoagulant therapy after discharge to prevent fatal PE, which is caused by DVT. However, there was no study on sequential chemical prophylaxis to prevent the DVT after patients discharged from the hospital. Therefore, this study aimed to investigate the incidence and severity of DVT in patients with lower extremity fractures who were receiving LMWH and rivaroxaban after surgery.

Materials and Methods

This study was approved by the institutional review board. The informed consent was obtained from the patients prior to study participation. This retrospective, single-center study was conducted at our level 1 trauma center from June 1, 2016 to March 31, 2017. The inclusion criteria were as follows: (1) patients with lower extremity fractures and (2) age $\geq$18 years. The exclusion criteria were (1) pathological fractures, (2) anticoagulant use before injury, and (3) fractures associated with an open injury that required an emergency surgical intervention.

After admission, all patients were placed on mechanical thromboprophylaxis using an intermittent pneumatic compression device. Chemical prophylaxis was administered with LMWH while in the hospital (4100 U once a day, GlaxoSmithKline Co, UK). After discharge, patients were prescribed rivaroxaban (10 mg/day) for 2 weeks postoperatively for fractures around and distal to the knee. Patients were prescribed rivaroxaban (10 mg/day) for 5 weeks postoperatively for fractures proximal to the knee. DVT screening of the lower extremities was performed with DUS before and after the operation. Patients diagnosed with DVT were administered LMWH at a therapeutic dose (4100 U, twice a day), and mechanical thromboprophylaxis was discontinued immediately. Patients diagnosed with proximal DVT (popliteal vein or more proximal) underwent preoperative placement of a retrievable inferior vena cava filter. CT arteriography was conducted in patients with suspected PE. Blood samples were collected on admission (2 h after admission), at 1 day preoperatively, and at 1, 3, and 5 days postoperatively. The blood samples were tested using an automatic blood coagulation analyzer (CA1500, Sysmex Corporation, Japan). We also evaluated the patients' D-dimer level and performed routine blood tests. The positive threshold of the D-dimer level was >1.4 mg/L.[11]

Screening for DVT with DUS is routinely performed at our institution for all trauma patients. One senior sonographer performed DUS of the bilateral lower extremities before and after surgery with Philips IU 22 duplex scanners (Royal Phillips Electronics, Amsterdam, The Netherlands). The criteria of positivity for VTE included non-compressibility, presence of intraluminal defect, absent or non-phasic Doppler signal, lack of respiratory variation above the knee segments, and inadequate flow augmentation to the calf and foot compression maneuvers.[11,12]

According to the location, the DVT cases were divided into proximal, distal, and mixed thromboses. The DVT located in the distal vein was classified as a distal thrombosis (calf muscle vein, fibular vein, and anterior/posterior tibial vein), whereas the DVT located in the proximal vein was referred to as a proximal thrombosis (iliac vein, femoral vein, and popliteal vein). The presence of both proximal and distal thromboses was considered as a mixed thrombosis.

According to the DUS results, the patients were divided into 2 groups: DVT group and no DVT group. For the no DVT group, LMWH (GlaxoSmithKline, 4100 IU, once per day) was continuously injected subcutaneously to prevent DVT. For the DVT group, LMWH (GlaxoSmithKline, 4100 IU, twice per day) was subcutaneously injected to treat DVT. When DUS detected a proximal or a mixed thrombosis preoperatively, an inferior vena cava filter was used to prevent fatal PE. Anticoagulant therapy was discontinued at 12 h preoperatively and restarted at 24 h postoperatively.

Statistical Analysis

Statistical analysis was performed using IBM SPSS 19.0 (SPSS Inc., USA). The Shapiro-Wilk test was used to determine whether the measurement data were normally distributed. The Chi-square and Fisher's exact tests were performed to compare the categorical variables between the DVT and no DVT groups. Moreover, Student's t-test was performed for continuous variables. Repeated measures analysis of variance (ANOVA) or data conversion was used for repeated measures data. Differences were statistically significant at a P-value < 0.05.

Results

Patients' Demographic and Clinical Characteristics

During the study period, 843 patients with lower extremity fractures were admitted to our department via the emergency department. A total of 404 patients who met the inclusion and exclusion criteria were enrolled. Patients' demographic and clinical characteristics are shown in Table 1. There were 208 women and 196 men with a mean age of 58.57 $\pm$ 19.06 years (18–88 years). In total, 193 patients had left lower extremity fractures, 185 had right lower extremity fractures, 5 patients had bilateral lower extremity fractures, and 21 patients had pelvic and acetabular fractures. There were 263 fractures proximal to the knee, 69 fractures around the knee, and 72 fractures distal to the knee. Fifty cases were diagnosed as associated multiple injuries. The numbers of patients with specific comorbidities were as follows: 68 with hypertension, 76 with coronary heart disease, 12 with diabetes, and 14 with delayed cerebral infarction. Eight patients had $\geq$2 comorbidities.

Table 1. Patients' Demographic and Clinical Characteristics.

No. of patients	404
Age(years)	58.57 ± 19.06
Sex(n)	
Female	208
Male	196
Unilateral / bilateral(n)	
Left lower extremity fractures	193
Right lower extremity fractures	185
Bilateral lower extremity fractures	5
Pelvic and acetabular fractures	21
Types of fracture	
fractures proximal to the knee (n)	
Intertrochanteric fracture	114
Femoral neck fracture	113
Femoral head fracture	2
Pelvic fracture	10
Acetabular fractures	11
Femoral shaft fracture	13
Fractures around the knee(n)	
Distal femoral fracture	7
Patellar fracture	18
Tibial plateau fracture	41
Anterior/posterior cruciate ligament avulsion fractures	3
fractures distal to the knee (n)	
Tibial and fibular shaft fracture	29
Ankle fracture	17
Calcaneus fracture	11
Pilon fracture	15
Comorbidity(n)	
Hypertension	68
Diabetes	12
Coronary heart disease	76
Arrhythmia	23
Stroke	14
Previous VTE	3
Tumor	7
Mean Charlson comorbidity index	2.62 ± 0.11
Multiple injuries	50
BMI	22.81 ± 4.24
Days between injury and admission (days)	1.48 ± 3.61
Days between injury and operation (days)	6.29 ± 4.44
operation time (mins)	123.35 ± 70.62
Days to mobilization(days)	7.61 ± 1.83
Length of hospital(days)	9.94 ± 3.72
Serum markers	
HGB at admission (g/L)	122.21 ± 18.61
HCT at admission (%)	36.57 ± 5.40
HGB at preoperative 1 day (g/L)	117.57 ± 18.11
HCT at preoperative 1 day (%)	35.04 ± 5.70
HGB at postoperative 1 day (g/L)	111.75 ± 57.89
HCT at postoperative 1 day (%)	32.96 ± 14.42
HGB at postoperative 3 day (g/L)	104.44 ± 15.90
HCT at postoperative 3 day (%)	31.16 ± 4.66
HGB at postoperative 5 day (g/L)	104.10 ± 16.50
HCT at postoperative 5 day (%)	30.94 ± 4.73
D-Dimer at admission (mg/L)	11.81 ± 13.84
D-Dimer at preoperative 1 day (mg/L)	4.86 ± 4.97
D-Dimer at postoperative 1 day (mg/L)	7.56 ± 9.02
D-Dimer at postoperative 3 day (mg/L)	5.69 ± 4.93
D-Dimer at postoperative 5 day (mg/L)	7.31 ± 5.91
CRP on admission (mg/L)	21.23 ± 31.47
CRP on discharged (mg/L)	28.45 ± 38.03
Creatinine Clearance (Cockcroft-Gault formula)	
Male	119.31 ± 45.21 (ml/min 1.73m^2)
Female	91.74 ± 38.72 (ml/min 1.73m^2)

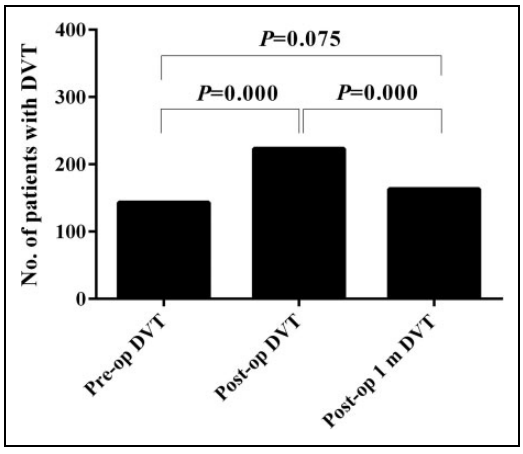

Figure 1. DVT cases preoperatively, postoperatively, and at 1 month post-operatively. Compared to that preoperatively, the incidence of DVT increased immediately postoperatively. Compared to that postoperatively, the incidence of DVT decreased at 1 month post-operatively. DVT = deep vein thrombosis.

Incidence and Location of DVT

The incidence of DVT in fractures proximal and around the knee immediately postoperatively was 58.93% (155/263) and 59.42% (41/69), respectively, whereas the incidence at 1 month postoperatively was 44.48% (117/263) and 39.13% (27/69), respectively. For fractures distal to the knee, the incidences immediately postoperatively and at 1 month postoperatively

were 33.33% (24/72) and 23.61% (17/72), respectively. The results showed that the incidence of DVT postoperatively was higher than that preoperatively (t = 7.905, $P = 0.000$). Furthermore, the incidence of DVT at 1 month after surgery was lower than that immediately after surgery (t = −5.686, $P = 0.000$). There was no significant difference between the incidence of DVT at 1 month postoperatively and that preoperatively (t = 1.787, $P = 0.075$) (Figure 1). From the preoperative to postoperative period, new DVT developed in 99 (24.50%) and DVT disappeared in 19 patients. From the immediate postoperative to the 1-month postoperative period, new DVT occurred in 30 (7.43%) patients, and DVT disappeared in 90 patients (22.28%).

We divided DVT cases into distal, proximal, or mixed thrombosis to describe the severity of DVT. Distal DVT occurred in 31.18% (126/404), 48.51% (196/404), and 36.13% (146/404) of patients preoperatively, immediately postoperatively, and at 1 month postoperatively, respectively. Distal DVT accounted for 88.11% (126/143), 87.89% (196/223), and 90.12% (146/163) of the overall DVT cases preoperatively, immediately postoperatively, and at 1 month postoperatively, respectively.

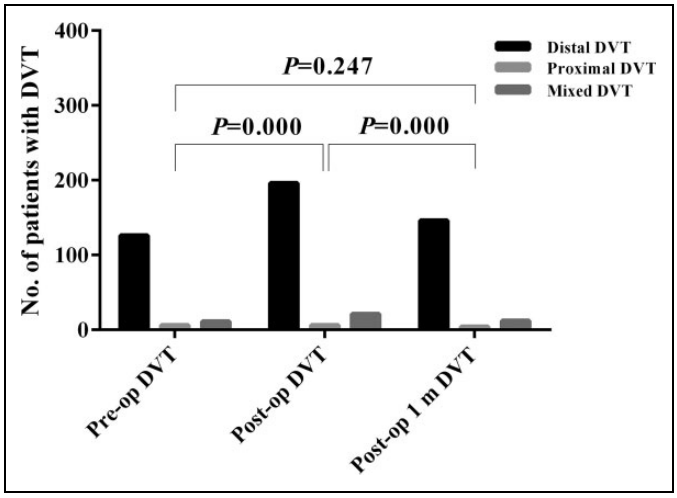

Figure 2. Location of DVT preoperatively, postoperatively, and at 1 month post-operatively. Compared to that preoperatively, the severity of DVT increased immediately postoperatively. Compared to that immediately postoperatively, the severity of DVT decreased at 1 month postoperatively. DVT = deep vein thrombosis.

The results indicated that DVT occurring immediately postoperatively was more serious than DVT occurring preoperatively (t = 6.404, $P = 0.000$), whereas DVT occurring at 1 month postoperatively was less severe than that occurring immediately postoperatively (t = −5.150, $P = 0.000$). The severity of DVT was not significantly different between the 1-month postoperative and preoperative periods (t = 1.159, $P = 0.247$) (Figure 2). These results were similar to the above-mentioned outcomes.

We analyzed DVT in patients with proximal knee fractures, fractures around the knee, and distal knee fractures. Preoperative DUS showed that the occurrence of DVT in the different fracture sites had no significant difference ($\chi^2 = 5.95$, $P = 0.051$). DUS performed immediately postoperatively and at 1 month postoperatively showed that the occurrence of DVT at different fracture sites had significant differences ($\chi^2 = 16.95$, $P = 0.0002$; $\chi^2 = 9.88$, $P = 0.007$; respectively) (Table 2). We used an α-value of 0.0167 (0.05/3) to explore the difference among the different fractures. We found that fractures proximal to the knee and fractures around the knee had greater incidences of DVT on postoperative DUS (compared to the fractures distal to the knee, $\chi^2 = 16.29$, $P = 0.00005$; $\chi^2 = 9.65$, $P = 0.002$; respectively) and on 1-month postoperative DUS (compared to knee distal fractures, $\chi^2 = 9.82$, $P = 0.002$; $\chi^2 = 5.19$, $P = 0.023$; respectively).

Serum D-Dimer Levels

Repeated measures ANOVA was used to detect the differences among the 3 time points. The results showed that there were statistically significant differences in the D-dimer levels preoperatively, postoperatively, and at 1 month postoperatively (F = 463.536, $P = 0.000$) (Figure 3).

The serum D-dimer levels were compared among the different fractures, and we found that D-dimer levels were higher in the DVT group than in the No DVT group, except for the patients with fractures proximal to the knee immediately postoperatively and at 1 month postoperatively (Table 3).

Table 2. DVT in Different Fractures and Stages.

	Fractures proximal to the knee	Fractures around the knee	Fractures distal to the knee	Total	χ^2	*P*
Preoperative DUS						
DVT	96	29	17	143	5.95	0.051
No DVT	166	40	55	261		
Postoperative DUS						
DVT	158	41	24	223	16.95	0.0002
No DVT	105	28	48	181		
1 month postoperative DUS						
DVT	117	29	17	163	9.88	0.007
No DVT	146	40	55	241		

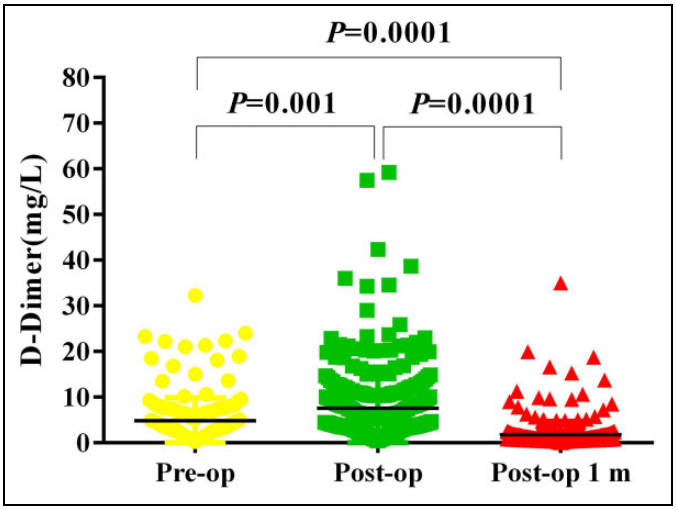

Figure 3. Differences in Serum D-dimer Level among pre-operation, post-operation, and 1-month post-operation.

Table 3. Serum D-Dimer in Different Fractures.

	DVT	No DVT	t	*P*
Preoperation				
Fractures proximal to the knee	6.33 ± 5.68	4.96 ± 5.70	1.33	0.185
Fractures around the knee	5.16 ± 3.61	2.84 ± 1.84	2.49	0.018
Fractures distal to the knee	5.70 ± 3.01	2.75 ± 1.99	2.96	0.006
Postoperation				
Fractures proximal to the knee	11.26 ± 12.32	5.18 ± 4.11	5.55	0.000
Fractures around the knee	6.63 ± 5.05	3.66 ± 3.88	2.42	0.018
Fractures distal to the knee	7.17 ± 5.73	3.39 ± 3.26	3.51	0.001
1 month postoperation				
Fractures proximal to the knee	3.00 ± 4.60	1.57 ± 2.08	3.07	0.003
Fractures around the knee	1.26 ± 0.92	0.90 ± 0.56	1.93	0.570
Fractures distal to the knee	1.31 ± 1.08	0.67 ± 0.47	2.19	0.046

Discussion

We retrospectively investigated the effects of LMWH followed by rivaroxaban in the prevention of DVT in patients with lower extremity fractures. Our main findings were as follows: (a) the incidence and severity of DVT postoperatively are the highest in the early postoperative period; (b) the incidence of DVT fractures around and proximal to the knee is markedly increased immediately postoperatively and at 1 month postoperatively; (c), most of the DVTs occurring immediately postoperatively were located in the distal vein; (d) similar to DVT, the serum D-dimer level was at its peak immediately post-operatively; (e) serum D-dimer level in the DVT group was higher than that in the no DVT group in most fractures.

Many factors contribute to the formation of DVT after trauma,[13,14,15] including age, tourniquet use, hypertension, diabetes, cerebral infarction, myocardial infarction, and so on. Patients with these factors are at risks for DVT, especially in those with fractures and those who had undergone surgeries.[16,17] In this study, we found that the incidence and severity of DVT were the highest immediately following surgery. Compared to that preoperatively, the incidence of DVT increased postoperatively. The severity also increased in 89 patients with new distal DVT and 7 patients with new mixed DVT, including 3 new proximal DVT. In 10 patients, the location of the DVT changed from distal to mixed veins, and in one patient, it changed from distal to proximal vein. Immobility due to severe pain after a fracture and operation may cause venous stasis in the lower extremities, thereby increasing the risk of DVT in these patients.[18]

The incidence at 1 month postoperatively showed a decreasing tendency compared to that immediately operatively. It should be noted that the increased risk of DVT is maintained with the 1-month postoperative period. Selby et al. measured several markers of in vivo coagulation and fibrinolysis and their regulation serially for 2 weeks after multi-system trauma in a prospective cohort of patients who received no anticoagulant prophylaxis. Asymptomatic DVT was assessed by routine bilateral venography. They noted a significant hypercoagulability within the first 24 h following trauma, a state that was maintained for 5–14 days.[19] Meissner et al. conducted a prospective study with 101 patients enrolled. They suggested that this hypercoagulation state persists for at least 1 month postoperatively in 80% of the patients.[20] This may explain why 40.44% of our patients had DVT at 1 month postoperatively despite the use of rivaroxaban for prophylaxis or therapy. We found that the incidence of preoperative thrombosis was similar among fractures proximal to the knee, fractures around the knee, and fractures distal to the knee. This is the first DVT study to analyze patients according to the fracture site. We found that fractures proximal to the knee and around the knee had high incidences of DVT. The rates of DVT were low for fractures distal to the knee. Basques et al. conducted a retrospective national-cohort study with 4412 patients and reported that the incidence of DVT in ankle factures was 0.8%,[21] and Pelet et al. conducted a retrospective study with 1540 patients were enrolled,they reported that the incidence was 2.66%.[22] Shin et al. retrospectively investigated 208 patients and reported that the prevalence of hip preoperative DVT was 11.1%.[1] These findings suggest that patients with fractures proximal and around the knee are more likely to develop DVT than those with fractures in the other regions of the lower extremity.

Most of the DVTs were located in the distal vein including the calf muscle veins, fibular vein, and anterior/posterior tibial vein. Palareti et al. reported that the proportion of distal DVTs varied from 23.4% to 59.7%.[23] The calf muscle veins are among the most frequent areas for DVT.[24] This is why distal

DVT is variable and changeable. Galanaud et al. reported that the mortality rate is significantly lower in patients with isolated distal DVT than in those with proximal DVT.[25] Thus, distal DVT is relatively safe compared to proximal DVT. Distal DVT must be prevented from transitioning to proximal DVT or mixed DVT. In clinical practice, the LMWH and rivaroxaban were the most effective chemical prophylactic agents. Compared with the LMWH, rivaroxaban, a new oral anticoagulant, was more convenient to use than LMWH. Performing blood tests to check for the patients' coagulation status in not required for rivaroxaban. However, rivaroxaban is much costly compared to LMWH, which limited its use.

The D-dimer assay is a useful and sensitive test for detecting post-traumatic DVT.[26-28] The serum D-dimer level was at the highest immediately postoperatively, reflecting DVT incidence. D-dimer levels were higher in the DVT group than in the no DVT group in most fracture types. However, the D-dimer level could not predict DVT. Novel mediators and biomarkers of thrombosis are needed in the future.[29]

There are some limitations to this study. First, the DUS is not the "gold standard" method for the diagnosis of DVT. However, it is very convenient and non-invasive compared to radiography, and orthopedists have accepted DUS for the diagnosis of DVT. Second, we did not analyze symptomatic DVT, because in a recent study, asymptomatic DVT accounted for the vast majority of overall DVT cases.[23] In this study, we only focused on the incidence and severity of DVT; thus, we only analyzed the overall DVT cases, not the symptomatic DVTs in particular.

Conclusions

The incidence and severity of DVT were the highest immediately postoperatively in patients with lower extremity fractures. The incidence of DVT in fractures around and proximal to the knee increased immediately postoperatively and at 1 month postoperatively. Although with chemical thromboprophylaxis, distal DVT was the most variable during the early stage.

Authors' Note

Ping Liu and Kun Zhang contributed equally to this study. Ping Liu and Kun Zhang conceived and designed the study. Yan Zhuang, Zhong Li, Yangjun Zhu, Hanzhong Xue followed the patients collected the data. Ping Liu analyzed the data, Peng-Fei Wang and Bin-Fei Zhang wrote the manuscript. All authors have read and approved the final manuscript.

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Declaration of Conflicting Interests

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