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**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, How-Ran Guo, DSc, MD, MSc, Full Professor, Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, Tainan 70428, Taiwan. [hrguo@mail.ncku.edu.tw](mailto:hrguo@mail.ncku.edu.tw)

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Clinical Trials Study

# Effects of ulinastatin therapy in deep vein thrombosis prevention after brain tumor surgery: A single-center randomized controlled trial

Yun-Na Tao, Qian Han, Wei Jiao, Li-Kun Yang, Fang Wang, Shan Xue, Meng Shen, Yu-Hai Wang

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**Yun-Na Tao, Qian Han, Li-Kun Yang, Fang Wang, Shan Xue, Meng Shen, Yu-Hai Wang,** Department of Neurosurgery, The 904<sup>th</sup> Hospital of Joint Logistic Support Force, Wuxi 214044, Jiangsu Province, China

**Wei Jiao,** Nursing, The 904<sup>th</sup> Hospital of Joint Logistic Support Force, Wuxi 214044, Jiangsu Province, China

**Corresponding author:** Yu-Hai Wang, MD, PhD, Chief Physician, Doctor, Full Professor, Neurosurgeon, President, Department of Neurosurgery, The 904<sup>th</sup> Hospital of Joint Logistic Support Force, No. 101 Xing Yuan North Road, Wuxi 214044, Jiangsu Province, China.

[wangyuhai1516@163.com](mailto:wangyuhai1516@163.com)

## Abstract

### BACKGROUND

Venous thromboembolism (VTE) is a common neurosurgical complication after brain tumor resection, and its prophylaxis has been widely studied. There are no effective drugs in the clinical management of venous thromboembolism, and there is an absence of evidence-based medicine concerning the treatment of severe multiple traumas.

### AIM

To explore whether ulinastatin (UTI) can prevent VTE after brain tumor resection.

### METHODS

The present research included patients who underwent brain tumor resection. Patients received UTIs (400,000 IU) or placebos utilizing computer-based random sequencing (in a 1:1 ratio). The primary outcome measures were the incidence of VTE, coagulation function, pulmonary emboli, liver function, renal function, and drug-related adverse effects.

### RESULTS

A total of 405 patients were evaluated between January 2019 and December 2021, and 361 of these were initially enrolled in the study to form intention-to-treat, which was given UTI ( $n = 180$ ) or placebo ( $n = 181$ ) treatment in a random manner. There were no statistically significant differences in baseline clinical data between the two groups. The incidence of VTE in the UTI group was remarkably improved compared with that in the placebo group. UTI can improve coagulation dysfunction, pulmonary emboli, liver function, and renal function. No significant

difference was identified between the two groups in the side effects of UTI-induced diarrhea, vomiting, hospital stays, or hospitalization costs. The incidence of allergies was higher in the UTI group than in the placebo group.

## CONCLUSION

The findings from the present research indicated that UTI can decrease the incidence of VTE and clinical outcomes of patients after brain tumor resection and has fewer adverse reactions.

**Key Words:** Ulinastatin; Venous thromboembolism; Brain tumor resection; Randomized control trial; Outcome

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**Core Tip:** Venous thromboembolism (VTE) is a common neurosurgical complication after brain tumor resection and its prophylaxis has been widely studied, with high morbidity, mortality, increased hospitalizations and higher health care costs. The findings from the present research indicated that ulinastatin can decrease the incidence of VTE and clinical outcomes of patients after brain tumor resection and has fewer adverse reactions.

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## INTRODUCTION

Venous thromboembolism (VTE) is a frequently occurring complication following a neurosurgical procedure for the resection of brain tumors, and its prophylaxis has been widely studied[1], with high morbidity and mortality rates, increased medical expenses, and higher hospitalization numbers[2]. Previous reviews reported that patients with malignant glioma have a 3-to-60% risk of VTE[3]. Patients undergoing craniotomies had a 31% and 5% risk of developing deep vein thrombosis (DVT) and pulmonary embolism (PE), respectively, according to studies[4-6]. DVT following brain tumor removal may be caused by multiple variables, including prolonged postoperative bed stay, direct stimulation of the tissue injury-induced coagulation pathway, tumor-specific procoagulant impacts, prolonged coma, advanced age, a larger tumor size, and the use of steroids during surgery.

Among patients undergoing a craniotomy, VTE is prevented *via* mechanical and/or pharmaceutical prophylaxis. Patients with CNS tumors who are treated with anticoagulants, such as unfractionated heparin and low-molecular-weight heparin, have demonstrated positive outcomes in VTE prevention. However, anticoagulant medication may contribute to the risk of intracranial hemorrhage[7-9]. Furthermore, drugs that effectively prevent DVT without elevating the risk of intracranial hemorrhage are currently unavailable.

Ulinastatin (UTI) is a serine protease inhibitor with a molecular weight of 67000 and is extracted from human urine. The primary pharmacological characteristics of this compound include anti-inflammatory effects, modulation of the immune system, and protection of organs[10-12]. UTI plays an important role in ischemia-reperfusion injury (IRI) because of its antiapoptotic and anti-inflammatory responses[13]. By conducting a meta-analysis, He *et al*[14] found that patients who underwent cardiologic surgical procedures may benefit from UTI treatment by preventing postoperative inflammation and offering pulmonary protection. Our recent research using animal models illustrated that UTI may reduce the severity of brain damage by suppressing oxidative stress and apoptosis[11], alleviating early brain injury following intracerebral hemorrhage by suppressing neuronal inflammation through the related molecular signaling pathway[15] and alleviating cerebral IRI[16]. The good treatment effectiveness in animal experiments also promotes its wide use in clinical patients. In China, the therapy of patients suffering from inflammatory diseases, postsurgical organ protection, and shock often involves the administration of UTIs[17]. Lyu *et al*[18] reported that a high dosage of UTI may help alleviate postsurgical hemorrhage and enhance platelet recovery without adding a considerable extra financial burden to patients. In abdominal surgery, 6000 UI/kg UTIs can inhibit coagulation and fibrinolysis[19].

However, the effectiveness of UTI is uncertain due to the specific nature of brain tumor patients and the absence of large-scale, evidence-based medical research on the topic. This research set out to determine whether UTI may reduce VTE after brain tumor surgery.

## MATERIALS AND METHODS

### Study design

Between January 2019 and December 2021, we conducted a randomized experiment in Jiangsu Province, China. During



this period, 405 patients were subjected to the screening process, and of them, 361 were originally recruited in the trial to establish the intention-to-treat (ITT) group. The current study was carried out to discover whether the intervention is effective. The methodology that was used for this study was endorsed by the Clinical Research Ethics Committees of the Wuxi Taihu Hospital of PLA (2019-YXLL-091), and the research was implemented in strict conformity with the guidelines outlined in the Declaration of Helsinki. The registration number for the study was CWXH-IPR-2018004 (date: January 11, 2019). All collaborating institutions' Ethics Committees approved the study's protocol. Patients' comprehensive awareness of time, place, and personal, as well as their ability to understand the investigator's explanation, were used to determine whether or not they were competent to give written informed consent. Moreover, patients were randomized (1:1) to receive either an intravenous infusion of 400000 IU UTI or placebos prepared in 250 mL of 0.9% saline and administered over 1 h over every 12 h for 7 d. In addition, 100 mL of saline diluted to 0.9% might be given to individuals with fluid restriction[12]. If liver enzyme levels rose more than three times their baseline values after the procedure, the infusion could be delayed for one day (Figure 1). The last follow-up time was 30 d after the operation.

### Methods for enrolling participants and selecting a sample

The current study comprised participants from the emergency intensive care unit (ICU). The following conditions were set as inclusion criteria: (1) Patients ranging in age from 18 to 70 years; (2) diagnosis of brain tumor by computed tomography or magnetic resonance imaging; and (3) allocation at random to receive either UTI or a placebo. The exclusion criteria were as follows: (1) Patients who, at admission, had a very low probability of being salvaged; (2) allergy to UTI; (3) medications for preventing coagulation taken during the last 48 h before admission; (4) pregnant women and patients; (5) medications that suppress the immune system; (6) multiorgan failure; and (7) additional potential reasons identified by the investigators.

### Random sampling and concealment

SPSS software v.14.0 was applied to conduct permuted-block randomization centered on a computerized program that generated random numbers from an allocation list (in a one-to-one ratio). To preserve the validity and blinding of the study, this randomization was performed by an independent statistician. The final results of random sample procedures were placed in numbered envelopes at the research center until the study's completion. Following the predetermined order of randomization, a research nurse administered the study treatments. Patients and researchers alike were blinded to the treatment that was being administered. Treatment allocation may be unmasked, and study medication may be changed or withdrawn in the case of an emergency, such as acute liver failure, if two specialists agree that doing so is in the best interest of the patient. The events were meticulously documented. We obtained data regarding the patient's personal characteristics, past medical records, and relevant examination results.

### Outcome evaluation

An anonymous committee, specialized in diagnosis and assessment, evaluated all clinical, radiological, and therapy information without knowing the identities of the patients. In this committee, two researchers had received their training before the commencement of the current investigation and were not involved in the patient's treatment decisions and treatment. The incidence of VTE during hospitalization served as the primary endpoint of this trial. The secondary endpoints included: (1) coagulation function, including the levels of plasma prothrombin time, fibrinogen, and activated partial thromboplastin time, as determined by an automated coagulation analyzer; (2) The incidence of pulmonary embolism; (3) The indicators of liver function levels, including aspartate aminotransferase and alanine aminotransferase; and (4) Levels of kidney function, including the levels of urea nitrogen and creatinine.

### Analysis of safety and complications

We recorded ICU stays and found that abnormal liver enzymes and granulocytopenia were the most common negative outcomes of UTI. Intracranial hemorrhage, vomiting, diarrhea, and allergic reactions are all rare complications. Two physicians and nurses verified the presence of complications *via* a physical examination, whereas granulocytopenia was identified by routine blood level testing. The presence of abnormal liver enzymes was identified by testing liver function. During the first two weeks, we examined the associated index every 2 d.

### Hospital expenses and length of stay after surgery

It has been widely noted that patients who need intensive medical treatment due to several serious injuries or diseases tend to remain in the hospital for much longer and incur much greater costs. Therefore, the current study compared the two groups in terms of their average length of hospital stay and total healthcare expenditures.

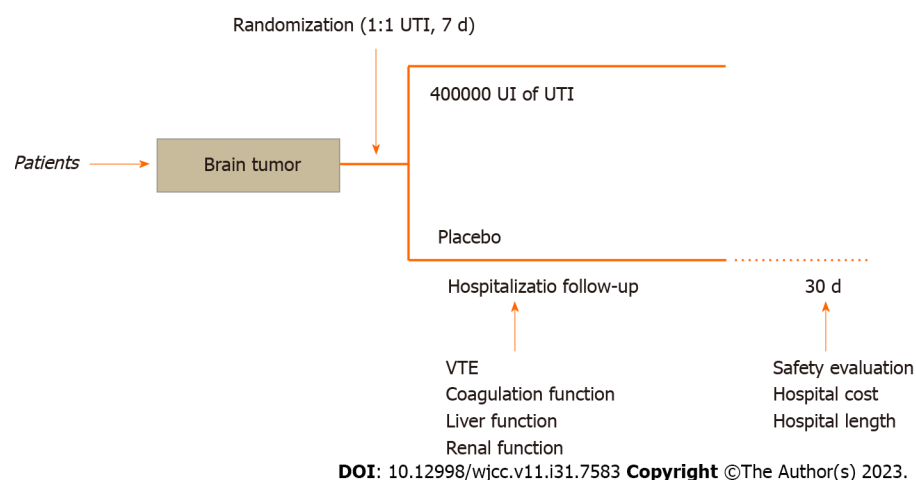
### Sample size estimates

In our preliminary experiment, the incidence of VTE was 7.2% in the group that received UTI treatment, whereas it was 17.3% in the group that received the placebo, as evidenced by the primary endpoint. We recruited 360 patients (180 in each group) as determined by 80% statistical power at an alpha of 0.05. In total, we included 180 participants in the UTI group and 181 in the control group. All baseline data were included in the study database, and a study nurse recorded all the study-related data.

### Statistical analysis

A study nurse input information from both the first evaluation and subsequent follow-up tests into the research's database. The data were recorded using handwritten forms and entered into a password-secured computer database. The





**Figure 1 Study design.** UTI: Ulinastatin; VTE: Venous thromboembolism.

data for all continuous variables are expressed as the mean  $\pm$  SD. The analyses of statistical data were conducted with the aid of SPSS 19.0 statistical software (SPSS, Inc., Chicago, United States). Nonnormally distributed measurements are indicated by M (Q1, Q3). To evaluate the quantitative data, we employed independent sample *t* tests. To assess the categorical data, both the chi-square test and Fisher's exact *t* test were employed. The threshold for statistically significant values was established at  $P < 0.05$ .

## RESULTS

Between January 2019 and December 2021, 405 individuals were examined, and 361 of these patients were originally recruited to establish the ITT group, which was randomized to receive either UTI ( $n = 180$ ) or placebo ( $n = 181$ ) treatment. During the investigation, researchers did not encounter any cases requiring opening blindness. In addition, we found no evidence of significant variation in the baseline data between the two groups (Table 1). No patients were lost to follow-up during the entire duration of the current study. Patients were included in the final analysis based on their treatment allocation (ITI analysis) (Figure 2). On June 31, 2022, the last randomly selected patient was enrolled.

### The primary endpoint

After treatment, the VTE incidence throughout the hospital stay was 11.91% (43/361), according to the findings. The incidence of VTE during hospitalization was 8.33% (15/180) in the UTI group and 15.47% (28/181) in the placebo group. A significant increase in the incidence of VTE in the placebo group was noted in contrast with the UTI group ( $P = 0.036$ , Figure 3). We also evaluated the differences in data between the two groups of patients with VTE and found no statistically significant variations in terms of their respective baseline data (revised Table 2).

### The secondary endpoints

Compared to the placebo group, the UTI treatment group produced substantial alleviation in coagulation function, liver function indices, and kidney function indices ( $P < 0.05$ , Table 3). Additionally, no significant variation in the incidence of pulmonary embolism was noted between the two groups ( $P > 0.05$ , Table 3).

### Safety assessment

Among the many potential complications of a UTI, granulocytopenia and impaired liver enzymes are among the most prevalent. We discovered that 17 (9.44%) participants in the UTI group and 14 (7.73%) participants in the placebo group suffered granulocytopenia, but the variation across the two groups was insignificant ( $P > 0.05$ , Table 4). In the UTI group, abnormal liver enzymes were found in 16 patients (8.88%), whereas in the control group, they were found in 11 patients (6.08%), with insignificant differences ( $P = 0.310$ , Table 4). Additionally, no significant variation was noted across the two groups in terms of the potential adverse complications of UTI-induced vomiting (18.88% vs 12.15%,  $P = 0.077$ , Table 3) and diarrhea (24.44% vs 17.12%,  $P = 0.087$ , Table 4). The UTI cohort experienced a higher incidence of allergic responses than the placebo cohort (17.50% vs 8.40%,  $P = 0.023$ , Table 4).

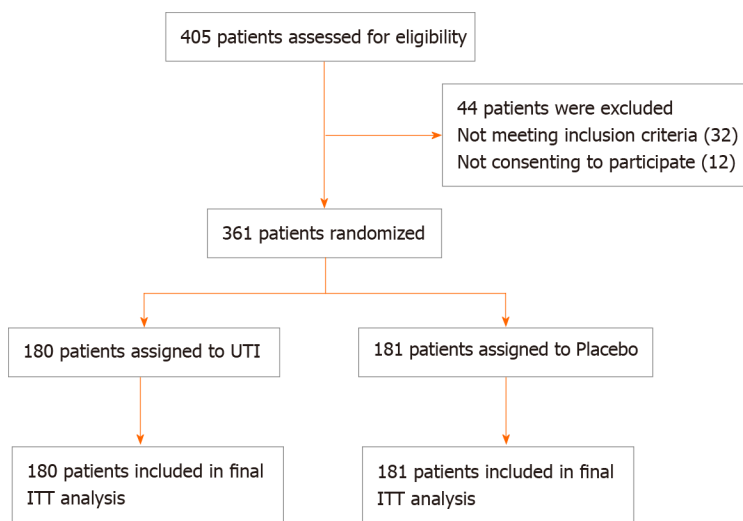
### Hospital expenses and length of stay after surgery

The average number of days that the patient stayed in the hospital was 13.46 d in the UTI group in contrast with 14.13 for those receiving a placebo, but the variation was insignificant ( $P = 0.174$ ). The mean hospitalization expenditure was similar between the two groups (52700 RMB vs 51200 RMB,  $P = 0.515$ , Table 4).

**Table 1 Comparison of baseline data, *n* (%)**

	UTI group ( <i>n</i> = 180)	Placebo group ( <i>n</i> = 181)	<i>P</i> value
Age (yr, mean ± SD)	58.7 ± 4.2	59.1 ± 4.3	0.372
Gender			0.881
Male	109 (60.56)	111 (61.33)	
Female	71 (39.44)	70 (38.67)	
BMI (kg/cm <sup>2</sup> , mean ± SD)	22.1 ± 2.1	22.5 ± 2.4	0.090
Smoking history			0.561
Yes	73 (40.56)	68 (37.57)	
No	107 (59.44)	113 (62.43)	
Living environment			0.393
Town	126 (70.00)	134 (74.03)	
Countryside	54 (30.00)	47 (25.97)	
Past medical history			
Hypertension	65 (36.11)	60 (33.15)	0.554
Hyperlipidemia	76 (42.22)	69 (38.12)	0.427
Diabetes	59 (32.78)	52 (28.73)	0.405
Cholelithiasis	31 (17.22)	35 (19.34)	0.603
Brain tumor type			0.355
Benign tumor	114 (63.33)	123 (67.96)	
Malignant tumor	66 (36.67)	58 (32.04)	
Surgery time (h, mean ± SD)	4.6 ± 1.5	4.4 ± 1.4	0.191

BMI: Body mass index; UTI: Ulinastatin.



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**Figure 2 Trial profile.** ITT: Intention-to-treat; UTI: Ulinastatin.

## DISCUSSION

The present study suggests that the risk of VTE is significantly reduced by UTI treatment among patients undergoing brain tumor surgery. We also discovered that UTI is associated with enhanced hepatic and kidney function as well as improved coagulation dysfunction. UTI use does not increase the risk of serious complications, and the increased risk of

**Table 2 Comparison of baseline data between two venous thromboembolism group patients, *n* (%)**

VTE Patients	UTI group ( <i>n</i> = 15)	Placebo group ( <i>n</i> = 28)	<i>P</i> value
Age (yr, mean ± SD)	59.9 ± 8.1	59.4 ± 8.5	0.853
Gender			0.782
Male	9 (60.00)	18 (64.29)	
Female	6 (40.00)	10 (35.71)	
BMI (kg/cm <sup>2</sup> , mean ± SD)	22.4 ± 2.5	22.1 ± 2.4	0.702
Smoking History			0.598
Yes	10 (66.67)	19 (67.86)	
No	5 (33.33)	9 (32.14)	
Living environment			0.702
Town	13 (72.22)	23 (82.14)	
Countryside	2 (27.78)	5 (17.86)	
Past medical history			
Hypertension	8 (53.33)	15 (53.57)	0.988
Hyperlipidemia	8 (53.33)	12 (42.86)	0.512
Diabetes	7 (46.67)	13 (46.43)	0.988
Cholelithiasis	6 (40.00)	10 (35.71)	0.782
Brain tumor type			0.484
Benign tumor	8 (53.33)	18 (64.29)	
Malignant tumor	7 (46.67)	10 (35.71)	
Surgery time (h, mean ± SD)	4.7 ± 1.7	4.6 ± 1.5	0.843

BMI: Body mass index; UTI: Ulinastatin; VTE: Venous thromboembolism.

**Table 3 Comparison of the secondary end-points**

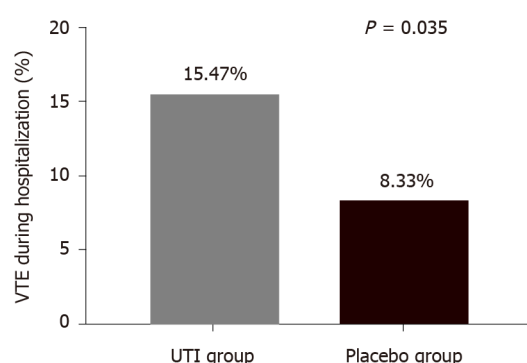
	UTI ( <i>n</i> = 180)	Placebo ( <i>n</i> = 181)	<i>P</i> value
Coagulation function, mean ± SD			
PT (s)	9.25 ± 2.27	15.36 ± 2.81	< 0.001
APTT (s)	21.13 ± 3.28	26.22 ± 3.29	< 0.001
D-D (mg/L)	1.84 ± 0.72	2.41 ± 0.92	< 0.001
FIB (g/L)	2.71 ± 0.49	2.89 ± 0.58	0.002
Pulmonary embolism	3 (1.67%)	1 (0.55%)	
Liver function index levels, mean ± SD			
ALT (U/L)	39.27 ± 4.16	41.29 ± 4.25	< 0.001
AST (U/L)	28.84 ± 3.26	29.48 ± 3.87	0.09
Renal function index levels, mean ± SD			
Scr	54.33 ± 8.21	56.08 ± 9.42	0.06
BUN	6.37 ± 2.95	8.11 ± 3.10	< 0.001

APTT: Activated partial thromboplastin time; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; D-D: D-Dimer; FIB: Fibrinogen; PT: Prothrombin time; Scr: Serum creatinine.

**Table 4 Comparison of safety evaluation, and postoperative hospital stays and costs, *n* (%)**

	UTI ( <i>n</i> = 180)	Placebo ( <i>n</i> = 181)	<i>P</i> value
Granulocytopenia	17 (9.44)	14 (7.73)	0.562
Abnormal liver enzymes	16 (8.88)	11 (6.08)	0.310
Diarrhea	44 (24.44)	31 (17.12)	0.087
Vomiting	34 (18.88)	22 (12.15)	0.077
Allergies	29 (16.11)	15 (8.29)	0.023
Hospitalization stays, day, mean $\pm$ SD	13.46 $\pm$ 4.56	14.13 $\pm$ 4.79	0.174
Hospitalization costs, CNY $\times 10^4$ , mean $\pm$ SD	5.27 $\pm$ 2.28	5.12 $\pm$ 2.09	0.515

UTI: Ulinastatin; CNY: ChinaYuan.



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**Figure 3 The primary endpoint.** UTI: Ulinastatin; VTE: Venous thromboembolism.

allergies may be related to the combination of drugs. All patients had mild symptoms and eventually recovered. Furthermore, hospitalization costs were not increased by UTI treatment.

The results illustrated that the incidence of VTE during hospitalization was 11.91% (43/361), which was consistent with earlier reports[20,21]. In a large sample single center over a 10-year period study, Smith *et al*[22] showed a 3.3% incidence of pulmonary emboli and 13.7 cases of DVT, with a history of VTE, patient sex, ethnicity, postoperative ICU duration, and tumor histology all being strong predictors of postoperative DVT. Elevated rates of VTE have also been documented in patients with high-grade gliomas, and this correlation has been described in several studies[23-25]. Patients with gliomas were prone to developing symptomatic VTEs, especially in the first two months after surgery. Moreover, the risk of death rose by 30% in the first two years after developing VTE[26]. To our knowledge and contrary to reports in the literature, patients who received medicinal prophylaxis did not show significantly different outcomes from those who did not[22, 23]. Traditional anticoagulant treatment is seldom used during surgery because of the potential for increased intracranial hemorrhage. Norden *et al*[27] reported that patients who were administered anticoagulants had a greater risk of intracerebral hemorrhage and a higher rate of severe bleeding. Additionally, patients with gliomas may experience hemorrhage during BVZ therapy, although anticoagulants are generally well tolerated. Despite this, studies have shown that patients who received chemoprophylaxis are at a greater risk of VTEs than those who do not[28]. Thus, there is a pressing need for novel medications that are both effective at preventing DVT and reducing the risk of intracranial hemorrhage.

UTI is a glycoprotein that is 67 kDa in weight and is purified from the urine of healthy individuals. It is used for the treatment of acute inflammatory diseases, hemorrhagic shock, toxic shock, and sepsis[12,29]. Basic research has reported that UTIs may affect a wide range of processes, including immunological and inflammatory processes, organ protection, apoptosis, and oxidative stress[10,30]. Through immunoregulation and attenuation of excessive inflammatory responses, UTI protects against lung damage in models of lipopolysaccharide-induced pulmonary injury[31]. Karnad *et al*[12] conducted a modified ITT analysis of a multicenter randomised controlled trial (RCT) and showed that intravenous injection of UTI reduced mortality in patients with severe sepsis. In the present study, the incidence of VTE during hospitalization was 8.33% (15/180) in the UTI group and 15.47% (28/181) in the placebo control group, suggesting that this intervention was successful in reducing the overall incidence rate of VTE. Nishiyama *et al*[19] reported that the use of UTIs during abdominal surgery may suppress coagulation and prevent fibrinolysis. Increasing studies have also demonstrated that UTI can reduce postoperative bleeding, promote platelet recovery, attenuate vascular endothelial cell damage, protect liver function, and improve clinical outcomes after surgery[18,32-34].

Additionally, TBI patients treated with UTI had a better chance of survival, less inflammatory response, and recovered immunological and liver function[35]. Almost all UTI research has focused on traumatic brain injury, while there are no evidence-based treatments for VTE after brain tumor resection. Some of the drawbacks of this research are as follows. Due to the research being a single-center RCT, the findings may not apply to a wider population. The present research only reported a single dose of UTI treatment. Clinical outcomes of VTE prophylaxis following brain tumor removal need to be investigated in future multicenter RCTs.

## CONCLUSION

According to the results of the current study, UTI treatment after brain tumor resection can lower the incidence of VTE, attenuate hyperinflammation, alleviate coagulation dysfunction, and improve liver and kidney functions. Additionally, it lowered the cost during hospital stays significantly. Additional research is needed with patients receiving varying doses of UTI to fully understand its potential applicability in patients with multiple traumas.

## ARTICLE HIGHLIGHTS

### Research background

Venous thromboembolism (VTE) is a frequently occurring complication following a neurosurgical procedure for the resection of brain tumors, and its prophylaxis has been widely studied, and deep vein thrombosis (DVT) following brain tumor removal may be caused by multiple variables. Furthermore, drugs that effectively prevent DVT without elevating the risk of intracranial hemorrhage are currently unavailable.

### Research motivation

There are no effective drugs in the clinical management of venous thromboembolism, and there is an absence of evidence-based medicine concerning the treatment of severe multiple traumas. Previous study showed that ulinastatin (UTI) may help alleviate postsurgical hemorrhage and enhance platelet recovery without adding a considerable extra financial burden to patients.

### Research objectives

To explore whether UTI can prevent VTE after brain tumor resection.

### Research methods

We conducted a randomized experiment, 405 patients were subjected to the screening process, and of them, 361 were originally recruited in the trial to establish the intention to treat group. Patients received UTIs (400000 IU) or placebos utilizing computer-based random sequencing (in a 1:1 ratio). Then to explore the incidence of VTE, coagulation function, pulmonary emboli, liver function, renal function, and drug-related adverse effects.

### Research results

The present study suggests that the risk of VTE is significantly reduced by UTI treatment among patients undergoing brain tumor surgery. We also discovered that UTI is associated with enhanced hepatic and kidney function as well as improved coagulation dysfunction. UTI use does not increase the risk of serious complications, and the increased risk of allergies may be related to the combination of drugs. All patients had mild symptoms and eventually recovered. Furthermore, hospitalization costs were not increased by UTI treatment.

### Research conclusions

UTI treatment after brain tumor resection can lower the incidence of VTE, attenuate hyperinflammation, alleviate coagulation dysfunction, and improve liver and kidney functions. Additionally, it lowered the cost during hospital stays significantly.

### Research perspectives

Additional research is needed with patients receiving varying doses of UTI to fully understand its potential applicability in patients with multiple traumas.

## FOOTNOTES

**Author contributions:** Tao YN, Han Q, Jiao W, and Wang YH were involved in the conception and design of the study; Tao YN, Han Q, Yang LK, Wang F, Xue S, and Shen M were involved in the data analysis; Tao YN, Han Q, Yang LK and Wang YH were involved in the acquisition of data; Tao YN and Shen M contributed substantially to drafting the manuscript and figures; All the authors have read and approved the final manuscript.

**Institutional review board statement:** The methodology that was used for this study was endorsed by the Clinical Research Ethics Committees of the Wuxi Taihu Hospital of PLA (2019-YXLL-091), and the research was implemented in strict conformity with the guidelines outlined in the Declaration of Helsinki.

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**Country/Territory of origin:** China

**ORCID number:** Yu-Hai Wang 0000-0002-6442-8677.

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