Study Protocol

Rationale and design of a prospective, multicenter, randomized controlled trial of postoperative venous thromboembolism prophylaxis in Chinese adult patients with inguinal hernia (CHAT-3 trial)

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Background: Venous thromboembolism (VTE) is one of the most common causes of preventable harm for patients in hospitals. Nearly half of all VTE events was estimated to occur after surgical procedure. The Caprini risk score is the most extensively used risk assessment tool in predicting postoperative VTE, which is too complicate for surgeons to use properly in their clinical practice.

Methods: The CHAT-3 trial will be a prospective, multicenter, randomized, parallel-group trial, which is designed to identify patients at moderate or high risk of VTE after inguinal hernia surgery using the previously established three-factor model, and to use low molecular weight heparin (LMWH) for VTE prevention, in comparison to the current routine assessment and practice used in those patients. Totally, 1,008 patients planned to undergo inguinal hernia surgery will be enrolled, with cluster randomization at 1:1 ratio into intervention arm and control arm. The primary outcomes are the accordance of perioperative VTE prophylaxis based on current guidelines and the rate of pharmacological prophylaxis for VTE. The secondary outcomes are the occurrences of perioperative VTE, major bleeding, mortality of patients after inguinal hernia surgery, and trend of D-dimer during the follow-up period.

Discussion: This study will create evidence that whether the administration based on a simple model is of efficacy and safety for VTE prophylaxis among Chinese patients underwent inguinal hernia surgery.

Trial Registration: The CHAT-3 trial (Trial registration number: ChiCTR2000033769).

Keywords: Venous thromboembolism (VTE); inguinal hernia; surgery; low molecular weight heparin (LMWH); randomized controlled trial; management

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Introduction

Venous thromboembolism (VTE) is the potentially devastating complication that might occur following surgical procedures, being a common cause of morbidity and mortality post-surgery (1). Even with the use of prophylaxis, surgery still accounts for up to 25% of VTEs (1). Inguinal hernia repair is one of the most commonly performed surgeries, with approximately 20 million inguinal hernioplasties worldwide each year (2,3). It was reported by retrospective studies that a 91-day rate of VTE was 0.4% in patients following inguinal hernia surgery (4), and 30-day incidence of VTE was as high as 3.5% in patients with complex hernia surgery (5). In China, our previous study (CHAT-1) involving 14,322 patients with inguinal hernia in 58 hospitals in China reported that the incidence of VTE was 0.2% (6), and the incidence increased to 11.5% in patients over 60 years old (7). Therefore, prophylaxis of perioperative VTE in patients with inguinal hernia could not be neglected.

The Caprini risk score is the most extensively used risk assessment tool in predicting postoperative VTE. However, the Caprini risk score involved 39 factors and a box for additional risk factors, which makes it complicated for surgeons to use in their clinical practice (8). Moreover, surgeons appeared lack of awareness in postoperative VTE prophylaxis (9,10), especially surgeons in China (6). CHAT-1 trial reported that only 23.4% of patients with inguinal hernia underwent perioperative Caprini risk assessment, and a substantial number of patients had incorrect data on VTE assessment (6). Without correct evaluation, the risk for perioperative VTE risk would not be well understood, resulting in the low rate of appropriate prophylactic measures. Therefore, it is necessary to find ways that could easily identify high-risk patients who need intensified prophylaxis using anticoagulants. It is recognized that many factors, such as age, obesity, history of VTE, cancer, stroke, inflammatory bowel disease, are risk factors associated with the development of VTE (8). We used a logistic model-based decision tree model to analyze the data of CHAT-1 trial, and found that age >60 years, VTE-related history, and operation duration ≥45 min were three important predictors of perioperative VTE in patients after inguinal hernia surgery, with the area under the receiver operating characteristic curves (AUC: 0.870) significantly higher than that of the Caprini model (AUC: 0.73) (11). Apparently, this model is simpler and easier to use to identify patients with high VTE risk after inguinal hernia surgery.

Pharmacological prophylaxis is recommended for patients at moderate or high risk for VTE (12). Low molecular weight heparin (LMWH) is currently recommended as a pharmacological prophylaxis for VTE in patients undergoing general surgery (1), and short-term prophylaxis (7 to 14 days) is commonly accepted (1,12). Therefore, the CHAT-3 study has been designed to identify patients at moderate or high risk for VTE after inguinal hernia surgery using a simple three-factor model, and to use LMWH for VTE prevention, in comparison to the current routine assessment and practice used in those patients.

Methods

Study design and setting

The CHAT-3 trial will be a prospective, multicenter, randomized, parallel-group trial. From July 2021 to December 2022, patients who will undergo inguinal hernia surgery will be enrolled consecutively from 26 sites in China, using a competitive inclusion method. Patients will be randomly assigned to the intervention group and the control group (*Figure 1*). In the intervention group, patients' perioperative VTE risk will be evaluated by previously established three-factor model, and LMWH prophylaxis will be conducted in high-risk patients. In the control group, patients will be managed using current routine assessment and practice. The correctness rate of VTE prophylaxis in accordance with current guidelines (1,12) on prevention of perioperative VTE will be assessed. The occurrence of perioperative VTE, major bleeding, minor bleeding, and mortality will be recorded to evaluate the efficacy and safety of prophylaxis measures.

Population

Adult patients aged 18–80 years who will undergo inguinal hernia surgery will be consecutively enrolled. The complete eligibility criteria are listed in *Table 1*.

Randomization

Cluster randomization is chosen in this trial, as intervention to patients is clustered by prescribing physicians within one hospital, and individual randomization would have higher contamination risk between the intervention and control arms. Cluster randomization will be done using computer-generated randomization at an allocation sequence of

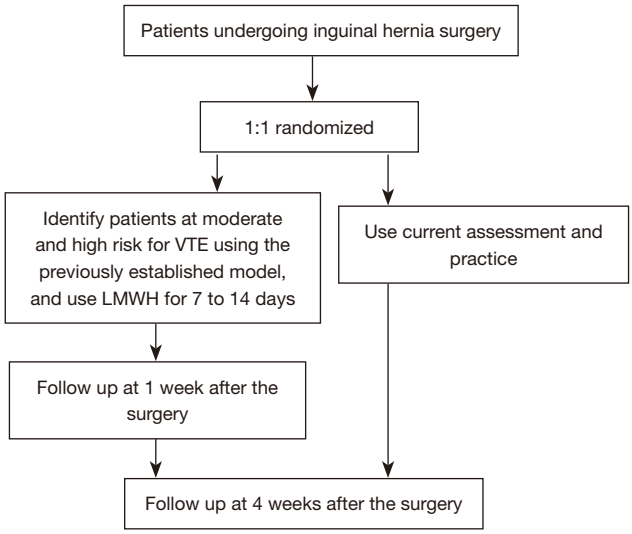

Figure 1 Study flowchart. VTE, venous thromboembolism; LMWH, low molecular weight heparin.

Table 1 Eligibility criteria of CHAT-3

Inclusion criteria
Age 18–80 years
Patients admitted in the general surgery department who will undergo inguinal hernia surgery
Exclusion criteria
Diagnosed VTE or receiving anticoagulation treatment
Undergo other operation within 3 months
History of hematological disease or blood coagulation dysfunction
Impaired liver function, defined as ALT ≥3 times the upper limit of normal
Impaired renal function, defined as an estimated glomerular filtration rate <30 mL/min/1.73 m^2
Combined with heart failure, respiratory failure, or refractory hypertension
Contraindicated to anticoagulation, or known allergy to heparin, or history of heparin-induced thrombocytopenia
Active malignant tumor
Pregnancy or lactation
Contraindicated to inguinal hernia surgery

VTE, venous thromboembolism; ALT, alanine aminotransferase.

1:1 between intervention arm and control arm after the confirmation of inguinal hernia surgery.

Study procedure and treatment

Patients assigned to the intervention group will be evaluated and treated according to the flow chart (*Figure 2*). The level of D-dimer will firstly be checked in patients involved. Afterwards, risk factors (>60 years; the presence of VTE history/VTE family history/thrombophilia; operation duration ≥45 min) of perioperative VTE will be evaluated. Meanwhile, the risk factors, including age >75 years, previous bleeding, cancer, renal or liver failure, etc., will also be assessed according to the CHEST guideline on antithrombotic therapy for VTE (13), in which patients with ≥2 risk factors are considered as high risk of bleeding. Patients with two or three risk factors are considered as moderate to high risk for VTE, who will receive pharmacological prophylaxis using LMWH with the duration of 7 to 14 days if they do not have high risk of bleeding. Patients with less than two risk factors, or with high risk of bleeding, will not receive pharmacological prophylaxis. Patients in the intervention group will receive intensive education on VTE, as well as intensive follow-up at 1 week and 4 weeks after the surgery. Patients assigned to the control group will be treated with current routine assessment and practice, and will receive follow-up at 4 weeks after the surgery.

Study outcomes

The primary outcomes are the accordance of perioperative VTE prophylaxis according to current guidelines (1,12) and the rate of pharmacological prophylaxis for VTE. The secondary outcomes are occurrences of perioperative VTE, major bleeding, minor bleeding, mortality of patients after inguinal hernia surgery, and trend of D-dimer during the follow-up period. A major bleeding is defined as any of the following situations according to the International Society on Thrombosis and Hemostasis (ISTH) criteria (14): (I) a ≥20 g/L fall in hemoglobin; (II) a transfusion of ≥2 units of red blood cells or whole blood; (III) bleeding at critical sites including intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome

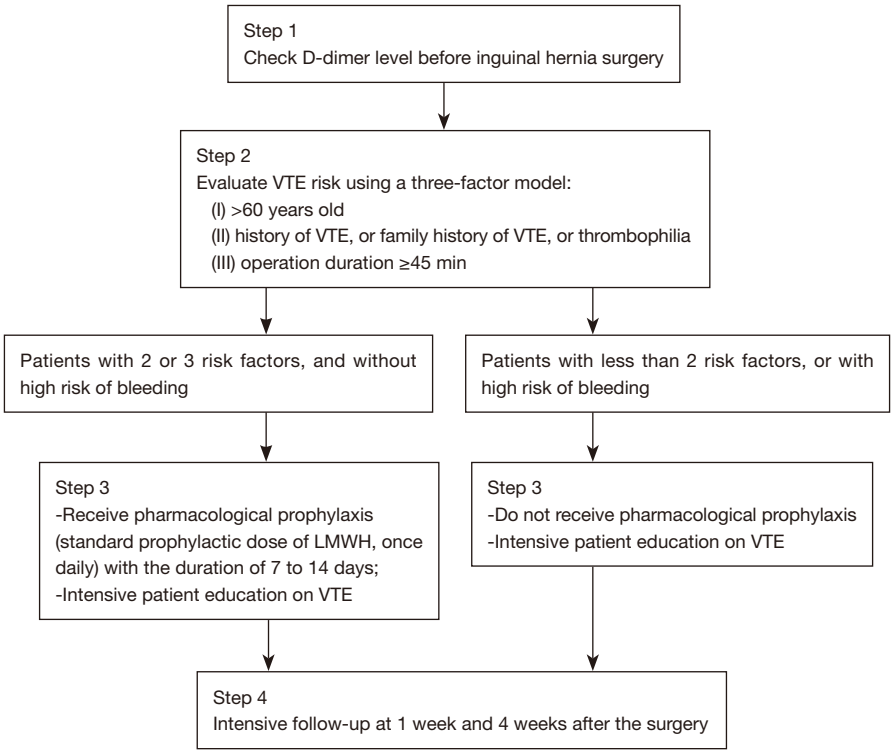

Figure 2 Detailed flowchart in the intervention group. VTE, venous thromboembolism; LMWH, low molecular weight heparin.

and retroperitoneal; (IV) bleeding with a fatal outcome. The incidence of minor bleeding events will also be recorded (15).

Sample size calculation

This study is designed as a multicenter, two-arm cluster randomized clinical trial. The total number of enrolled patients will be 1,008, with 503 in each arm. According to our previous study, the risk assessment rate of perioperative VTE for patients underwent inguinal hernia surgery was 23.4% in China, and only 1.2% of them received appropriate prophylactic measures (6). We assume that the risk assessment rate of perioperative VTE will achieve 50% and the appropriate prophylactic measures will cover 20% of the patients in the intervention arm. With the assumption of superiority, the sample size is estimated to be 105 and 168 with the risk assessment rate and prevention rate as the target, respectively. Taking the clustering into account, we inflate the sample size by a design effect to reach the required level of statistical power under cluster randomization. With a design effect of 6, the sample size is estimated to be 1,008 using the prevention rate as the calculating target. The sample size was calculated using PASS software version 15.

Subgroup analysis

An inguinal hernia repair may be done as an open surgery or as a laparoscopic surgery. Compared with open surgery, the pain after laparoscopic surgery is less and the recovery is faster. Nevertheless, the length of the laparoscopic surgery can be longer, because of the need for pneumoperitoneum (16). Patients with laparoscopic hernia repair may experience a transient increased intra-abdominal pressure caused by pneumoperitoneum, which may increase the risk of VTE (17). Moreover, the length of hospital stay can reflect the mobility of patients, and the patients with similar length of stay are more comparable. Therefore, subgroup analysis will be done according the type of surgery (open or laparoscopic) as well as the length of hospital stay (2 days or more than 2 days).

Statistical analyses

Statistical analyses will be performed with the SPSS software, version 22.0 (SPSS Inc., Chicago, Illinois, USA). Categorical data will be presented as numbers and percentages, and will be compared using the chi-square

test. Continuous variables will be presented as the means ± standard deviations. P values will be two-sided, with the statistical significance being set at 5% level. The proportion and 95% confidence interval (CI) will be calculated.

Ethics and dissemination

This study will be conducted according to the Declaration of Helsinki, ethical principles of medical research involving human subjects (revision Fortaleza, Brazil, October 2013). All of the participants will sign written informed consent before randomization. The protocol has been approved by Ethics Committee of Beijing Chao-Yang Hospital (No. 2020-6-9-1) and other participating institutions. The results of this study will be disseminated through publication in peer-reviewed journals. The access to study data will be made available by providing anonymized datasets after the agreement of committee of CHAT-3.

Discussion

VTE is one of the most common causes of preventable harm for patients in hospitals (18). Surgery is an important factor in the development of VTE. Nearly half of all VTE events was estimated to occur after hospitalization for surgical procedure (4). However, surgeons do not have full awareness of VTE risk for patients after surgery, and only a small proportion of surgical patients receive appreciate prophylactic measures. The CHAT-3 study aims to identify patients at moderate or high risk for VTE after inguinal hernia surgery, and LMWH will be used in those patients for VTE prevention, in comparison to the current routine assessment and practice. The hypothesis is that the intervention will help to identify high risk patient, increase the prophylaxis rate of perioperative VTE, and subsequently to decrease the occurrence of VTE in postsurgical period.

Our previous study has reported that only 23.4% of patients after inguinal hernia surgery underwent risk assessment for VTE in China, and as low as 1.2% of patients received appropriate prophylactic measures (6). Even worse, with the day case surgery becoming increasingly common in inguinal hernia repair in China, patients' length of hospital stay decreases to 24 to 48 h, which makes it difficult to make the comprehensive evaluation on patients' risk for postsurgical VTE. Moreover, studies have found that the peak risk of VTE following inguinal hernia repair occurred in the first 2 weeks (19). A significant number of patients are not protected with anticoagulants, and can develop VTE after discharge from the hospital (20). Therefore, early discharge from the hospital can result in undetectable VTE, especially asymptomatic events.

Currently, the most extensively used risk assessment tool is Caprini risk score, which is complicated for surgeons to use in their clinical practice. Therefore, VTE risk assessment tool should be easy to understand and convenient to use. The assessment model used in this trial is more simple with only three factors, including age >60 years, VTE-related history, and operation duration ≥45 min. Evidence showed that the incidence of VTE rose markedly with increasing age (21). The incidence of VTE was reported to be 20% in those aged 40 to 60 years, which increased to 36.4% in patients aged 61 to 70 years, and 62.5% in patients over age 71 (20). Even receiving prophylaxis, the VTE incidence doubled in the patients aged 61 to 70 and tripled in those aged 71 or greater (20). These are in accordance with the age factor in Caprini risk assessment model, in which age 41 to 60 years, age 61 to 74 years, and age 75 or over, count for 1 point, 2 points and 3 points, respectively (22). Notably, the most prominent risk factors for development of VTE are a history or family history of VTE, as well as thrombophilia (21,23), which counts for 3 points in Caprini risk assessment model (22). Patients with a VTE history were considered 8 times more likely to suffer a recurrent event than those without relevant history (8). The third risk factor in our assessment model is the operation duration ≥45 min, which counts for 2 points in Caprini score (22). Operations lasting from 1 to 2 hours were estimated to have an association with a 20% VTE incidence without prophylaxis, and the VTE incidence increased with the length of surgery (8). In this trial, patients with two or three risk factors are considered as moderate to high risk for VTE, with the corresponding Caprini score being 3 to 9. Those patients are recommended to receive pharmacological prophylaxis according to the current guidelines (1,24). Accordingly, the use of our model for VTE risk evaluation may simplify the assessment process for surgeons in the short hospitalization.

In the CHAT-3 study, postsurgical VTE risk in patients after inguinal hernia surgery will be evaluated using three-factor model. Patients at moderate or high risk for VTE will receive LMWH for pharmacological prophylaxis. This is the first study focusing on the risk assessment and pharmacological prophylaxis of postsurgical VTE among Chinese patients underwent inguinal hernia surgery. The trend of D-dimer level during the follow-up period will be evaluated in the study as an index reflecting blood clotting

disorders. Although VTE cannot be diagnosed on positive D-dimer alone, D-dimer is known as a sensitive marker for VTE and excludes VTE without need for further testing among patients with a low clinical probability of VTE (25). Meanwhile, we will also assess the perioperative VTE, bleeding events, mortality between intervention and control arms during the follow-up at one week and 4 weeks post-surgery. Overall, the results of this study will create evidence that whether the administration based on a simple model is of efficacy and safety for VTE prophylaxis among Chinese patients underwent inguinal hernia surgery.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1594). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study will be conducted according to the principles of the Declaration of Helsinki (as revised in 2013) and has been registered in Chinese Clinical Trial Register platform (Trial number: ChiCTR2000033769). All of the participants will sign written informed consent before randomization. The protocol has been approved by Ethics Committee of Beijing Chao-Yang Hospital (No. 2020-6-9-1) and other participating institutions.

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