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Reviewer A

This is an interesting study.

Comment: Does this study include emergency surgery or cases requiring intestinal resection? Is outpatient, ambulatory inguinal hernia surgery excluded?

Response:

We thank the reviewer for the meaningful question. As mentioned in the Table 1, the patients that will be involved in this study need to be admitted in the general surgery department, therefore, the emergency surgery will be excluded in this study. As to cases requiring intestinal resection and the ambulatory inguinal hernia surgery, they will be involved if the cases fit the eligibility criteria of CHAT-3 in Table 1. Since the cases requiring intestinal resection are relatively complicated and may have an operation duration ≥ 45min, these patients could be at moderate or high risk for VTE, when they combine with one or two risk factors. Besides, ambulatory inguinal hernia surgery can also be included as it can be relatively simple, and have a shorter operation duration. The patients undergoing ambulatory inguinal hernia surgery may have a greater probability of low risk for VTE.

Reviewer B

The protocol for this randomized trial is overall well written and properly designed.

Comment 1: I suggest to define "risk of bleeding" in the text.

Response:

We thank the reviewer for the constructive suggestion. The risk of bleeding will be assessed according to the CHEST guideline on antithrombotic therapy for VTE, in which patients with ≥ 2 risk factors are considered as high risk of bleeding. We have added the related content in the manuscript, which has been highlighted. The risk factors reported on the CHEST guideline is presented on supplementary appendix Table S1.

(Editor's note: Due to permission issue, the authors decided to remove Table S1 and keep the reference in the text only.)

Comment 2: I do not really understand the value of preoperative D-dimers, could you discuss?

Response:

We thank the reviewer for the constructive suggestion. It is known that VTE cannot be diagnosed on positive D-dimer alone. However, 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 (JAMA. 201;320(15):1583-1594). Therefore, checking the level of d-dimer will help to exclude VTE before the inguinal hernia surgery and have a baseline information of patients' d-dimer. Moreover, the trend of d-dimer during the follow-up period will also help to evaluate the risk for VTE and exclude the occurrence of VTE among patients after inguinal hernia surgery. We have added the related content considering the reasons detecting the level of d-dimer in the manuscript, which has been highlighted.

Reviewer C

Comment 1: Line 40: low molecular heparin (LMWH) should put low molecular weight heparin (LMWH).

Response:

We thank the reviewer for the constructive suggestion. We are sorry about the carelessness. We have corrected the expression and the revision has been made in the manuscript which has been highlighted.

Comment 2: Line 99: If it is a prospective study, its period should not have started in June 2020, rather I think the authors refer to June 2021.

Response:

We thank the reviewer for pointing out our carelessness. We have corrected the study period as "from July 2021 to December 2022", which has been highlighted in the manuscript.

I think that the approach of the study is very interesting, although I think some considerations would be interesting, as long as the authors consider them appropriate:

Comment 3: On the one hand, the type of surgery (laparoscopic or laparotomic) to which the patient will be subjected is not described and that could make a difference

since laparoscopic surgery usually requires a longer surgical time together with the need for pneumoperitoneum than could favor ETV.

Response:

We thank the reviewer for the constructive suggestion. Admittedly, differences exist between laparoscopic surgery and open inguinal hernia surgery. Although the pain after laparoscopic surgery is less and the recovery is faster, the length of the surgery can be longer when compared with open surgery, because of the need for pneumoperitoneum. Patients with laparoscopic hernia repair may experience a transient increased intra-abdominal pressure caused by pneumoperitoneum, which may increase the risk of VTE. Based on the reviewer's suggestion, we will add the subgroup analysis considering the difference effects of the intervention between laparoscopic surgery and open inguinal hernia surgery. We have added the relative content in method part on the manuscript, which has been highlighted.

Comment 4: We do not know the intervention regimen (inpatient or outpatient surgery) and in the case of inpatient it would be interesting to know the length of stay, since during the same the mobility of the patient is usually more limited.

Response:

We thank the reviewer for the constructive suggestion. The patients involved in this study will be admitted in the general surgery department. They will discharge from the hospital several days after the surgery if they are well recovered. However, no matter in or out of the hospital, the intervention regimen will be done according to which arm they will be in. The intervention regimen is as follows: patients in the intervention arm will receive pharmacological prophylaxis using LMWH with the duration of 7 to 14 days, and will receive intensive education on VTE, as well as intensive follow-up at one week and 4 weeks after the surgery; patients in the control arm will not receive pharmacological prophylaxis and will be treated with current routine assessment and practice, and receive follow-up at 4 weeks after the surgery.

Moreover, as the reviewer mentioned, the length of stay can reflect the mobility of patients, and the patients with similar length of stay are more comparable. However, this is a prospective study, and the patients will be involved before the surgery. It is difficult to know the exact length of stay before the surgery. Nevertheless, we believe the length of stay will be an important index when doing the subgroup analysis. Accordingly, we have added the relative content in method part on

the manuscript, which has been highlighted.

Comment 5: When proposing a comparison with the Caprini method to establish the need to apply antithrombotic prophylaxis, I think it would be very interesting to compare the results of applying both methods of staging the risk of thrombosis in order to give greater validity to the one proposed by the authors, recognizing that it takes more work.

Response:

We thank the reviewer for the constructive suggestion. The CHAT-3 study has been designed to identify patients at moderate or high risk for VTE after inguinal hernia surgery using the simple three-factor model established by our study group before, and to use LMWH for VTE prevention, in comparison to the current routine assessment and practice used in those patients. The prediction performance of this three-factor model has been proved in our previous study, in which a logistic model-based decision tree model was used to analyze the data of CHAT-1 trial. This established model, including three important predictors of age > 60, VTE-related history, and operation duration ≥ 45 min, was found inferior to the Caprini model in prediction performance, with AUC (0.870) significantly higher than that of the Caprini model (0.73). Moreover, this model was found simpler and easier to use to identify patients with high VTE risk after inguinal hernia surgery. Therefore, in this study we focus on the effectiveness and safety of VTE prevention using LMWH in patients at moderate or high risk for VTE after inguinal hernia surgery, who are identified with this simple three-factor model established and well-demonstrated before.

Comment 6: If we take into account the low incidence of venous thrombosis in patients undergoing inguinal hernioplasty, I have doubts about the total number of necessary patients included in the study, given that if we expect an incidence of 0.2% in patients with high risk, as the authors collect in their work published in 2020, the probability of having this event in the control group would be only 10 cases and if it consisted exclusively of high-risk patients. With this I want to highlight the difficulty that can be found in obtaining significant differences between both groups in the incidence of the disease that allows them to validate their method to indicate or not antithrombotic prophylaxis

Response:

We thank the reviewer for the constructive suggestion. The calculation of sample size is determined according to the outcome of the study. As we know, the primary outcomes are the accordance of perioperative VTE prophylaxis according to current guidelines and the rate of pharmacological prophylaxis for VTE. Therefore, the sample size is calculated based on the risk assessment rate of perioperative VTE for patients underwent inguinal hernia surgery and the rate of appropriate prophylactic measures.

The reviewer mentioned that the sample size needed to be calculated based on the incidence of 0.2% in patients with high risk. It should be done when the primary outcome being the occurrences of perioperative VTE. Besides, the VTE risk of patients are not equal between the intervention arm and the control arm, as patients with moderate to high risk for VTE will be involved in the intervention arm, while patients with low risk for VTE will be involved in the control arm. Therefore, the occurrences of perioperative VTE in both arms are incomparable in our study.