

Surveillance or no surveillance for deep venous thrombosis and outcomes of critically ill patients

A study protocol and statistical analysis plan

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Abstract

Objective: Surveillance ultrasounds in critically ill patients detect many deep venous thrombi (DVTs) that would otherwise go unnoticed. However, the impact of surveillance for DVT on mortality among critically ill patients remains unclear.

Design: We are conducting a multicenter, multinational randomized controlled trial that examines the effectiveness of adjunct intermittent pneumatic compression use with pharmacologic thromboprophylaxis compared to pharmacologic thromboprophylaxis alone on the incidence of proximal lower extremity DVT in critically ill patients (the PREVENT trial). Enrolled patients undergo twice weekly surveillance ultrasounds of the lower extremities as part of the study procedures. We plan to compare enrolled patients who have surveillance ultrasounds to patients who meet the eligibility criteria but are not enrolled (eligible non-enrolled patients) and only who will have ultrasounds performed at the clinical team's discretion. We hypothesize that twice-weekly ultrasound surveillance for DVT in critically ill patients who are receiving thromboprophylaxis will have more DVTs detected, and consequently, fewer pulmonary emboli and lower all-cause 90-day mortality.

Discussion: We developed a detailed a priori plan to guide the analysis of the proposed study and enhance the validity of its results.

Supplementary data, <http://links.lww.com/MD/C463> and the PREVENT trial Group

Trial registration: The PREVENT trial is registered at ClinicalTrials.gov, ID: NCT02040103. Registered on November 3, 2013; Current controlled trials, ID: ISRCTN44653506. Registered on October 30, 2013.

Ethics approval: The study protocol has been approved by the Institutional Review Board of King Abdullah International Medical Research Center, King Abdulaziz Medical City, Riyadh and the respective Institutional Review Boards of all the other participating centers.

The study is funded by King Abdulaziz City for Science and Technology, Riyadh, Kingdom of Saudi Arabia and King Abdullah International Medical Research Center, Riyadh, Kingdom of Saudi Arabia. The study sponsors do not have any role in the study design, collection, management, analysis and interpretation of data or in writing the report.

The authors report no conflicts interest.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:36(e12258)

Received: 12 August 2018 / Accepted: 14 August 2018

<http://dx.doi.org/10.1097/MD.00000000000012258>

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation, CI = confidence interval, DVT = deep vein thrombosis, GCS = graduated compression stocking, ICU = intensive care unit, IPC = intermittent pneumatic compression, IQR = interquartile range, LMWH = low-molecular-weight heparin, LOS = length of stay, PE = pulmonary embolism, RCT = randomized controlled trial, UFH = unfractionated heparin, VTE = venous thromboembolism.

Keywords: critical care, deep vein thrombosis, eligible nonenrolled, intensive care, intermittent pneumatic compression, pulmonary embolism, surveillance, thromboprophylaxis, ultrasound

1. Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with substantial morbidity and mortality among patients admitted to the intensive care unit (ICU) even with adequate prophylaxis.^[1] DVT is often silent and may result in fatal PE. A systematic review of autopsy-confirmed diagnostic errors in ICU patients demonstrated that 28% of autopsies reported at least one misdiagnosis, with PE being among the leading causes of potentially fatal misdiagnoses.^[2] A case-control study demonstrated that DVT risk stratification and history and physical examination performed poorly in discriminating among patients who did and who did not have DVT, indicating that history and physical examination for DVT are not useful in detecting lower limb DVT in the ICU.^[3] A retrospective study in hospitalized trauma patients who underwent once weekly surveillance ultrasounds found that 86% of identified DVTs were not clinically suspected.^[4]

As such, surveillance for DVT has been proposed to detect silent DVT. Several studies have showed that surveillance detects many DVT that would otherwise go unnoticed.^[3] Data from recent RCTs in critically ill patients that conducted surveillance for DVT reported much higher DVT incidence that what has been traditionally reported in nonsurveillance studies. For example, the EPO-TBI (Erythropoietin in Traumatic Brain Injury) trial documented a 17% incidence of DVT among patients with traumatic brain injury with once weekly ultrasound.^[5] The PROTECT trial (PROphylaxis for ThromboEmbolism in Critical Care Trial) documented 10% incidence of DVT among nontrauma ICU patients with twice-weekly ultrasounds.^[6] Similarly, a review of studies that examined DVT in postoperative hospitalized patients showed that surveillance studies reported much higher incidence of DVT than studies that reported symptomatic DVT only.^[7]

By earlier identification of silent DVTs, surveillance may reduce the incidence of PE and consequently reduce morbidity and mortality in critically ill patients. However, the supportive evidence for this premise in ICU patients is limited. In a pre-post study of implementing a twice-weekly surveillance for DVT in 4234 trauma ICU patients (pre 1422 and post 2812), the rate of DVT diagnosis increased by more than double (odds ratio [OR] 2.53; 95% CI 1.46–4.38) and the rate of PE decreased by about half (OR: 0.49; 95% CI: 0.26–0.90), but there was no change in mortality.^[8] As a result of the pre-post design of the study, differences were noted in baseline characteristics including the type and severity of trauma between the 2 time periods. Because of the limited evidence, it remains unclear whether the clinical benefit of DVT surveillance in detecting (and treating) silent DVTs compared to a clinician-directed approach outweighs the risks of anticoagulation and confers benefit on mortality in critically ill patients.

In the Pneumatic CompREssion for Preventing VENous Thromboembolism (PREVENT) trial, we will examine the effectiveness of adjunct intermittent pneumatic compression (IPC) use with pharmacologic thromboprophylaxis compared to pharmacologic thromboprophylaxis alone on the incidence of

proximal lower extremity DVT in critically ill patients. Enrolled patients undergo twice weekly surveillance ultrasounds as part of the study procedures. In the proposed analysis, we will compare enrolled patients who will have surveillance ultrasounds to patients who meet the eligibility criteria but are not enrolled (eligible non-enrolled patients or ENE) and who will have ultrasounds performed at the clinical team's discretion. We hypothesize that twice-weekly ultrasound surveillance for DVT in critically ill patients who were receiving thromboprophylaxis will have more DVTs detected, and consequently, fewer pulmonary emboli (PE) and lower all cause 90-day mortality.

2. Methods

2.1. Setting

The PREVENT trial is a concealed, stratified, unblinded, multicenter, multinational randomized controlled trial that examines the effectiveness of adjunct IPC use with pharmacologic thromboprophylaxis compared to pharmacologic thromboprophylaxis (with unfractionated heparin or low-molecular-weight heparin alone on the incidence of proximal lower extremity DVT in critically ill patients). The trial protocol and statistical analysis plan have been published previously.^[9,10] The trial is registered at Clinicaltrials.gov: NCT02040103 and Current controlled trials: ISRCTN44653506. The PREVENT trial is being conducted in 19 sites in Saudi Arabia, Canada, Australia, and India.

2.2. Study population

In this analysis, we will include data from participating sites in the PREVENT trial, which have ethics approval to collect minimal dataset on ENE patients and have reported at least 5 ENE cases. The surveillance group includes patients who were enrolled in the PREVENT trial. The nonsurveillance group will include ENE patients except those who decline informed consent and do not give permission for data collection. Patients who are not enrolled for other reasons will be included in the nonsurveillance group including patients who are unable to give consent and no substitute decision-maker is available, patients in whom informed consent is declined but with agreement to collect of minimal observational data, patients who are unable to provide consent within the randomization window of 48 hours from ICU admission, patients who are not enrolled because either the ICU physician or another treating clinician refused enrollment, and patients who were co-enrolled in trials with biologic interaction.

2.3. Data collection

We will collate and compare baseline data including: demographics (age, sex), body mass index, location immediately before ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, admission categories, and chronic illnesses defined by the APACHE II system between groups.^[11] We will also compare predefined pre-ICU VTE risk factors between

groups including personal history of VTE, family history of VTE, known thrombophilic states (protein C, protein S, or antithrombin deficiency, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, activated protein C resistance, factor V Leiden thrombophilia, prothrombin gene mutation, antiphospholipid antibody, hyperhomocysteinemia), post-partum status (within 3 months), estrogen therapy (oral contraceptive or hormone replacement), active malignancy (treatment within the past 6 months or palliation), history of malignancy (within the past 5 years, other than non-melanoma skin cancer), paralysis or immobilization of a lower or upper extremity related to stroke or injury before this hospital admission, hospitalization in the past 3 months for any reason (excluding this hospital admission), trauma (including acute spinal cord injury, hip fracture, pelvic fracture, femoral fracture and tibial, fibular, knee or other fractures below knee), recent surgery (in the last 48 h), and acute stroke (in this index hospital admission). We will compare baseline platelet count, international normalized ratio, partial thromboplastin time, and serum creatinine.

We will note the type of pharmacologic prophylaxis received by the 2 groups at the time of admission and the presence of femoral central venous catheter at the time of screening. We will also record and compare data on DVT prophylaxis including IPC use (for at least 1 day), graduated compression stockings (GCS) application (for at least 1 day) and therapeutic anticoagulation during ICU stay. The number of all radiologic tests performed for VTE detection during ICU stay will be recorded including lower extremity ultrasound, upper extremity and neck ultrasound, spiral computed tomography (CT) (CT angiogram or helical CT scan) to evaluate for PE, ventilation-perfusion (V/Q) scan of the lungs, CT scan of the abdomen to evaluate thrombosis, transthoracic echocardiogram and trans-esophageal echocardiogram. We will record outcomes including lower extremities DVT, PE, the duration of mechanical ventilation, ICU and hospital length of stay (LOS), and mortality. The primary outcome of the PREVENT trial will be all cause 90-day mortality.

2.4. Statistical analysis plan

Categorical variables will be reported as numbers and frequencies, and will be compared using the χ^2 test. Continuous variables will be reported as mean and standard deviation or median and interquartile ranges (IQR, Q1–Q3). Continuous variables will be tested using the Student *t* test or the Wilcoxon-Mann-Whitney test, as judged appropriate by normality testing. Because the assignment to surveillance and nonsurveillance group is not random, we will assess the association of the exposure (surveillance) and time to hospital mortality using multivariate logistic regression and Cox proportional hazards models analysis adjusting for Acute Physiology and Chronic Health Evaluation (APACHE) II score, type of pharmacologic prophylaxis received, presence of femoral central venous catheter, and use of IPC and GCS. We will include also other variables that are significantly different between the 2 groups ($P < 0.1$). Stratified analysis will be performed based on type of admission (medical versus others), type of pharmacologic prophylaxis (UFH vs. LMWH), and IPC use. Interaction terms will be included to assess effect modification of the subgroups on the association between the exposure and outcome. Assuming that we enroll 6 of each 7 eligible patients (6 enrolled patient: 1 eligible non-enrolled patient) and recognizing that the majority of participating centers have approval to collect data on ENE patients, we expect that 90% of the 2000 patients who will be enrolled in the PREVENT trial will

be included in the proposed analysis (projected enrollment of 1800 with 300 ENE patients). Anticipating that the mortality of enrolled patients is 20%, our study will have 80% power at 0.05 alpha to detect 7.5% higher mortality in the nonsurveillance group. All statistical analyses will be conducted using the SAS software version 9.1.3 or higher (SAS Institute, Cary, NC).

3. Discussion

The proposed substudy addresses the question of whether surveillance ultrasound in critically ill patients by facilitating DVT detection reduces the incidence of PE and lowers all cause 90-day mortality.

Our study has several strengths. The multicenter and multinational nature of the trial enhances the generalizability of its findings. The prospective nature of data collection improves data validity. As per the study protocol, ultrasounds are being performed by certified ultrasound technicians and interpreted by radiologists, which increases the accuracy of the results. Although the present study is not randomized, the 2 groups are run in parallel in the context of a large randomized trial, which reduces the risk of bias related to the use of historical controls that have been used in pre-post studies previously. We will adjust for relevant covariates, if noted, that differ between groups.

However, our study also has limitations. First, as it is not randomized, the presence of unmeasured confounders cannot be entirely excluded. Second, we will plan to conduct a cost-effective analysis based on the findings. To this end, one study showed that implementing surveillance for DVT in trauma ICU patients was associated with incremental costs that compare well with other life-saving interventions that have been accepted by the critical care community.^[8] A decision analytic model that compared DVT surveillance to a case finding approach demonstrated increased DVT detection and a reduction in subsequent VTE events. However, surveillance for DVT was associated with more bleeding events caused by a greater frequency of anticoagulation and a higher number of false-positive DVTs detected. This study found that the quality-adjusted survival was improved minimally and could not justify the additional costs of DVT surveillance compared with other commonly used interventions in critically ill patients.^[12] Finally, because we use ultrasounds performed by certified technicians and radiologists, the proposed study cannot clarify whether the same results could be achieved with point of care ultrasound performed by intensivists at the bedside.

In conclusion, this article outlines a priori plans for study protocol and analysis plan for surveillance or no surveillance for DVT and outcomes of critically ill patients.

Acknowledgments

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