Appendix 1 (as supplied by the authors): Study protocol

BACKGROUND

Venous thromboembolism (VTE), comprised of deep venous thrombosis (DVT) and pulmonary embolism (PE), is the formation of blood clots in the large veins of the lower limbs, pelvis, or lungs obstructing blood flow (1). It is diagnosed clinically, blood d-dimer levels and confirmed with a Doppler ultrasound. If left untreated, thrombi can propagate and embolize to distant sites, with the highest risk posed on pulmonary arteries, a life-threatening complication. An estimated 900,000 Americans are affected by VTE annually (2), and 10-30% die within a month of diagnosis (2). In addition to many well-established modifiable and non-modifiable risk factors for thrombosis development, patients who are hospitalized are particularly known to be at a great risk of morbidity and mortality due to thrombosis (3,4).

A number of thrombosis prevention measures for hospitalized patients such anticoagulation and pneumatic calf compressors have been widely used due to evidence of effectiveness. Moreover, ambulation remains the first and most recommended step for thrombosis prevention, even in hospitalized patients and post-operative patients in particular. This is based on the association of VTE with long distance travel, first identified in the 1950's, that was attributed to venous stasis; a component of Virchow's classic triad in the pathogenesis of thrombus formation (5). For a traveler, who is otherwise healthy without any risk factors for thrombosis development, ambulation may be sufficient (6). However, this remains questionable for hospitalized patients who are likely to have multiple risk factors for thrombosis. Moreover, the hospitalized population is at a risk of falls with serious consequences during ambulation.

Therefore, weighting of risks and benefits of ambulation for thrombosis prevention in hospitalized patients is essential prior to recommending it.

In the era of evidence based medical practice, and given the high prevalence of thrombosis in hospitalized patients, the complexity of thrombosis pathogenesis and the variability of risk factors in different populations, it is imperative to identify and assess the level of evidence that supports ambulation as a preventive measure against thrombosis in hospitalized patients. Up to our knowledge, there are currently no published systematic reviews that assess this.

OBJECTIVES

The objective of this systematic review is to assess the comparative effectiveness of ambulation compared to other commonly used measures/ standards of care (namely; anticoagulation or calf compressors) as a preventive measure for thrombosis prevention in all hospitalized patients using evidence from both observational studies and randomized controlled clinical trials (RCTs).

METHODS

Ethical approval is not required and will not be obtained.

a. Criteria for considering studies for this review

Types of studies:

Both observational studies and RCTs published in English will be considered for review. Studies must compare ambulation to either no preventive measure or any other prevention modality such as anticoagulation or pneumatic calf compressors in an acute care setting. Case-

series reports, studies that do not specify ambulation, and those done in outpatient, intensive care unit or rehabilitation settings will be excluded. We will not limit our studies to any publication year.

Types of participants:

We will include studies that enrolled hospitalized patients of any age group. We will not limit our selection based on indication of hospital admission, disease process, or length of hospital stay. Both surgical and medical patients will be included. Patients with known risk factors such as obesity or thrombophilas will be included for subgroup analysis.

Types of intervention:

Any indicator of movement (ambulation, exercise, physiotherapy) with the intention of thrombosis prevention will be considered. Ambulation for any distance, duration, frequency, assisted or not, will be included. Further, for surgical patients, studies with both early and late ambulation will be included.

Types of outcome measures:

Primary outcomes: Reported in-hospital or post discharge venous thrombosis in any site will be included in the review. Any diagnostic criteria or diagnostic modality (clinical, d-dimer, Doppler, spiral CT) will be accepted if well described in the study.

Secondary outcomes: We will include mortality, and falls or any associated complication of ambulation as secondary outcomes.

b. Search methods for identification of studies

Electronic searches will be conducted in MEDLINE using PubMed, EMBASE, Cochrane, Web of Science, and Scopus. Additionally, hand searching for articles and reference

lists will be used. We will not search the gray literature. The concepts, "Ambulation," "Thrombosis," and "Prevention" will be used to build our search strategy with the help of an informationist.

c. Search strategies by database

See Appendix B.

d. Data collection and analysis

Selection, Data extraction and management

All yielded articles from all databases will be imported into DistillerSR, where 2 independent reviewers will complete title and abstract screening to identify relevant articles. Full text articles will be retrieved for agreed upon articles to assess for eligibility. DistillerSR forms will then be used for data abstraction.

Assessment of risk of bias in included studies

Selected observational studies will be assessed for risk of bias and confounding using the Newcastle-Ottawa instrument, and RCTs will be assessed using the tool provided in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1).(7)

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