Critical Reviews in Oncology / Hematology 125 (2018) 12–18

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Effect of anticoagulants on admission rates and length of hospital stay for acute venous thromboembolism: A systematic review of randomized control trials

Yongzhe Hong[a,b,1], Sola Mansour[a,1], Ghazi Alotaibi[a,c], Cynthia Wu[a], Michael Sean McMurtry[a,*]

[a] Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[b] The Second Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China
[c] Department of Medicine, King Saud University, Riyadh, Saudi Arabia

ARTICLE INFO

Keywords:
Anticoagulants
Admission rates
Length of stay
Venous thromboembolism
Systematic review
Deep vein thrombosis
Pulmonary embolism

ABSTRACT

Background: There is a paucity of data available on hospitalization and length of stay (LOS) for different anticoagulant therapies. We sought to compare and summarize admission rates and LOS, and describe the frequency of reporting these two outcomes in randomized control trials (RCTs) comparing different anticoagulant therapies for venous thromboembolism (VTE).

Methods: A literature search was conducted from inception to August 15, 2016 on RCTs of anticoagulant therapy for patients with VTE. Study selection, data extraction and risk of bias analysis were done by two reviewers independently. Meta-analyses were conducted for admission rates and LOS.

Results: A total of 4064 articles were identified. There were 74 articles of 70 studies included in the analysis. Hospitalization rates and LOS were reported in 13 (18.6%) and 12 (17.1%) of the 70 included studies, respectively. Low-molecular-weight heparin (LMWH)-treated patients were 33.0% less likely to be admitted to hospitals compared to unfractionated heparin (UFH) (RR = 0.67, 95% CI [0.58, 0.78]). The mean difference in LOS between LMWH and UFH was 2.54 days in favor of LMWH (95% CI [−4.94, −0.14]). Compared to parenteral therapy, using rivaroxaban was associated with a lower admission rate for a difference of 1.4–5.1% in VTE, 2.5% in DVT and 0.2% in PE. The LOS of patients receiving rivaroxaban was significant shorter than the LOS in parenteral therapy group for a difference of 1–5 days in VTE, 3 days in DVT and 1 day in PE.

Conclusion: Admission rates were lower and LOS was shorter using LMWH compared to UFH and oral therapy compared to parenteral therapy for acute VTE treatment in RCTs, based on limited eligible RCTs. These crucial clinically relevant outcomes are underreported in the existing VTE clinical trials.

1. Introduction

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cause of cardiovascular death after myocardial infarction and stroke (Goldhaber and Bounameaux, 2012). VTE places significant clinical and economic burden on the health care system. The estimated annual incidence of VTE is approximately 5 persons per 10,000 (Fowkes et al., 2003), and the economic burden of VTE is considerable, costing more than $1.5 billion/year in the United States (Dobesh, 2009). Anticoagulant therapy is the mainstay of treatment for VTE (Kearon, 1999). Historically, conventional therapy involved parenteral anticoagulants for at least 5 days and vitamin K antagonists (VKAs) started concurrently and continued for at least 3 months (Kearon et al., 2012).

Over the last few decades, there has been evolution in antithrombotic therapy with a transition from parenteral to newer anticoagulants. While unfractionated heparin (UFH) was widely used, low-molecular-weight heparin (LMWH) safely replaced it due to convenience and possibility of outpatient administration. Longer term treatment was delivered through VKAs (Garcia et al., 2012). However, these agents were limited by the need of frequent monitoring and dose adjustment. Direct oral anticoagulants (DOAC) are now available and address some of these limitations (Ageno et al., 2012).

While recurrent VTE and major bleeding have been traditional primary efficacy and safety outcomes in VTE trials, rate of hospitalization and length of stay (LOS) are also important. The latter two are

* Corresponding author at: 2C2 Walter Mackenzie HSC, 8440 112th Street, Edmonton, AB, Canada, T6G 2B7.
E-mail address: mcmurtry@ualberta.ca (M.S. McMurtry).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.critrevonc.2018.02.010
Received 14 September 2017; Received in revised form 5 January 2018; Accepted 21 February 2018

frequently overlooked outcomes. Hospital admissions are associated with potential complications such as hospital-acquired infections, neurological complications and other life-threatening diagnoses. These complications result in a delay of recovery and return to normal activities. They also prolong hospital stay and add higher costs to the healthcare system (Lagoe and Westert, 2010; Hoogervorst-Schilp et al., 2015). In-hospital complications occur in 5.7%–7.5% of admitted patients (Baker et al., 2004; Zegers et al., 2009), and result in an increase in the LOS by an average of 8 days (Sari et al., 2007). LOS has been treated as a great marker for measuring patient quality of care. Within the context of shrinking healthcare budgets and the ageing populations with complex healthcare needs (Busby et al., 2015), a better understanding of the effect of different anticoagulants therapy on VTE is urgently needed to reduce unnecessary inpatient treatment.

There is no prior review summarizing the impact of different anticoagulants on hospitalization rates and LOS for VTE. We sought to compare and summarize admission rates and hospital LOS and describe the frequency of reporting these two outcomes in randomized control trials (RCTs) comparing different anticoagulant therapies for VTE.

2. Methods

The following study was done in accordance with a review protocol established a priori, which is available on request from authors. This study was registered in PROSPERO. This review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

2.1. Selection criteria

We included all RCTs comparing two different anticoagulant therapy regimens for acute VTE. The primary outcomes of our study are LOS and admission rates. The secondary outcome is reporting rate of these two outcomes in the existing RCTs.

To improve the homogeneity of selected trials, studies were excluded if: 1. comparing different doses of the same anticoagulants; 2. evaluating thrombolysis; 3. evaluating inferior vena cava filters; 4. evaluating surgical thrombectomy; 5. focused on specific group of patients such as renal diseases, pregnant women, critical ill patients, extended therapy, or cardiac diseases; 5. pharmacokinetic studies; 6. evaluating DVT prophylaxis.

2.2. Search methods

A literature search was conducted on MEDLINE and EMBASE via Ovid platform from inception to August 15, 2016. A librarian was consulted during the developing of the search strategy. A full list of the search strategy was provided in Additional file 1 in the Supplementary material. The search was limited to studies of human adult participants. No language or date restriction was applied. We also checked the reference lists of eligible studies for additional relevant articles.

2.3. Study selection and data extraction

Two reviewers independently screened for eligible articles by titles and abstracts using the selection criteria. The full-texts of eligible studies were retrieved and reviewed by two reviewers afterwards. We solved disagreement by consensus. A senior author was consulted if the disagreement was unresolved. All eligible articles in accordance with the selection criteria were considered for data extraction.

After an agreement on studies included for data extraction was made, two reviewers independently extracted the data using the same pilot tested data extraction form. The main data items collected were patient characteristics, anticoagulants used, and all of the outcomes reported in the trials. Primary authors were contacted if additional information needed.

2.4. Data analyses

Two reviewers independently evaluated included studies which reported admission rate or LOS using the recommended risk of bias tool described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011). High, low, or unclear risk would be assign to seven domains including random sequence generation, allocation concealment, blinding of participants, personnel and outcome adjudicators, incomplete outcome assessment, selective reporting, and other sources of bias. Because it is recommended that funnel plot and test for asymmetry should not be used in meta-analysis that includes fewer than ten studies (Song et al., 2013), we would not use funnel plot if less than ten studies were included in meta-analysis stage.

We examined heterogeneity using I-square and Chi-squared tests. Heterogeneity was considered low or high if I-square $< 25\%$ or $> 75\%$, respectively. If the outcomes and interventions were similar between studies, we conducted meta-analyses using RevMan 5.3 software. Risk ratio (RR) and mean difference were employed to pool summary estimates. We performed meta-analyses on admission rate and LOS and used the random effects model if high heterogeneity presented. No sensitivity or subgroup analyses were pre-specified.

3. Results

A total of 4062 articles were identified through database searching. Two additional articles were identified, one from the reference list of included studies and another from the recommendation of content expert (Fig. 1). There are 81 articles eligible for obtaining full-texts and one RCT was available in abstract form only. In the end, 74 articles (70 studies) were included in the analyses, of which, 71 articles were original randomized controlled trials comparing different types of anticoagulant therapy. The remaining three articles are post-hoc analysis of two individual included trials (Matsuo et al., 2015; Bookhart et al., 2014; van Bellen et al., 2014). The characteristics of included studies were shown in Additional file 2 in the Supplementary material .

3.1. Risk of bias analyses

In the risk of bias analyses for individual studies reporting admission rate or LOS, most RCTs did not provide information on random sequence generation (Figs. 2 and 3). More than half of the trials had low risk with respect to detection bias, attrition bias and reporting bias. The major drawback of the trials were blinding of participants and personnel. Since the comparison of anticoagulants often involve distinctive way of administrations (subcutaneous, intravenous or oral), it is relatively difficult to blind the patients. Only the trials comparing fondaparinux to LMWH had low performance bias, since they were all subcutaneously administrated.

3.2. Reporting rate of hospitalization rates and LOS

Hospitalization rates and LOS were reported in 13 (18.6%) and 12 (17.1%) of the 70 included studies, respectively (Matsuo et al., 2015; Bookhart et al., 2014; Levine et al., 1996; Ramacciotti et al., 2004; Chong et al., 2005; de Lissovoy et al., 2000; Beckman et al., 2003; Belcaro et al., 1999; Naz et al., 2005; Häfeli et al., 2001; The Columbus Investigators, 1997; The Matisse Investigators, 2003; Koopman et al., 1996). There were 14.3% of RCTs comparing DOAC to other anticoagulants stated admission rates or LOS. And only 19.2% of RCTs comparing LMWH to anticoagulants other than DOAC reported these two outcomes.

Table 1 showed the LOS and admission rates of 14 articles of 13 studies. Ten trials compared LMWH to UFH (Levine et al., 1996; Ramacciotti et al., 2004; Chong et al., 2005; de Lissovoy et al., 2000; Beckman et al., 2003; Belcaro et al., 1999; Naz et al., 2005; Häfeli et al., 2001; The Columbus Investigators, 1997; Koopman et al., 1996), and