The effectiveness and safety of direct oral anticoagulants compared to conventional pharmacologic thromboprophylaxis in hip fracture patients: a systematic review and meta-analysis of randomized controlled trials

Background. Current guidelines recommend administration of direct oral anticoagulants (DOACs) to patients undergoing major elective orthopedic surgeries as a possible pharmacologic thromboprophylaxis postoperatively. However, they did not introduce recommendations for administration of DOACs as an option for pharmacologic thromboprophylaxis in patients undergoing hip fracture surgery (HFS). The aim of this study is **t**o compare the effectiveness and safety of DOACs administered for pharmacologic venous thromboembolism (VTE) prophylaxis in patients undergoing hip fracture surgery to conventional pharmacologic VTE prophylaxis, as well as mortality between these thromboprophylaxis medications.
Methods. We will perform a systematic review of multiple electronic databases, websites and scientific programmes of recent conferences for randomized controlled studies (RCTs) including patients who were subjected to HFS and prescribed either DOACs as pharmacologic VTE prophylaxis or a conventional VTE prophylaxis drug in order to conduct a meta-analysis comparing effectiveness, safety and mortality of these agents between the patient groups studied. Endpoints will be clinical manifestations of VTE regarding effectiveness, clinical presentation of bleeding regarding safety and mortality. We will generate forest plots to depict the relative risk of clinical manifestations of VTE, bleeding and mortality between the two studied patient groups and to investigate if there is statistical significance for each patient group to present any of the clinical manifestations studied. Additionally, we will calculate the inconsistency (I^2) statistic and assess the risk of bias of RCTs included in our meta-analysis by using the modified Cochrane collaboration tool.
Discussion. This review and meta-analysis will conclude if DOACs are more effective and safer to conventional thromboprophylaxis medications for postoperative thromboprophylaxis in patients subjected to HFS.

Background

Hip fractures (HFs) are seen globally and are a serious concern at the individual and population level. By 2050, it is estimated that there will be six million cases of HFs worldwide annually. The increase of age is related to the increase of the incidence of HF. [1] High rate of hip fracture in older people has two main causes: increased skeletal fragility and increased risk of fall-related trauma. About 90% of HFs is associated with a fall, with the vast majority of such falls being from a standing height or less. Other risks factors for HFs are the white race, hormonal and dietary factors, smoking, alcohol consumption, co morbidities such as visual and cognitive impairment and neuromuscular diseases, primary or metastatic neoplasms, polypharmacy, reduced physical activity.[2] However, HF incidence has decreased during the last decades in some countries. Actions to prevent and treat osteoporosis and other metabolic bone diseases and targeted interventions to reduce the risk of falling of elderly could partly explain the declining HF incidence.[3] Most HFs are treated surgically by implanting a prosthesis.

Patients with HF fulfill all three factors of Virchow's triad that contribute to the development of venous thrombosis. They present venous blood flow stasis due to use of lower extremity tourniquet, lower extremity immobilization and bed rest, vascular endothelial injury because of surgical manipulations and hypercoagulability due to operation stress and use of foreign bodies such as polymethylmethacrylate bone.[4] According to Caprini's thrombosis risk factor assessment score, patients with HF are assessed with a total risk factor score of 5, meaning that these patients, even if they do not suffer from other morbidities, present 40-80% incidence for deep vein thrombosis and 1-5% mortality if they do not receive any type of thromboprophylaxis.[5] Thromboprophylaxis reduces dramatically incidence of venous tromboembolism.[6]

Latest American college of chest physicians (ACCP) guidelines recommend pharmacologic VTE prophylaxis for at least 10 to 14 days, and up to 35 days, along with mechanical VTE prophylaxis (intermittent pneumatic compression device and venous foot pumps) during hospitalization for patients subjected to major orthopaedic surgery. In patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) recommended pharmacologic thromboprophylaxis includes one of the following: low-molecular-weight heparin, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (UH), adjusted-dose vitamin K antagonist (VKA), aspirin. In patients undergoing HFS recommended pharmacologic thromboprophylaxis includes one of the following: LMWH, fondaparinux, UH, adjusted-dose VKA, aspirin.[6]

DOACs have been emerged as an alternative therapy for VTE prophylaxis and treatment during the last decade.[7] Latest ACCP guidelines taking into account the results of randomized controlled trials regarding patients undergoing THA or TKA recommended the administration of DOACs as a possible pharmacologic VTE prophylaxis in these patient groups. On the contrary, they did not introduce recommendations for administration of DOACs as an option for pharmacologic VTE prophylaxis in patients undergoing HFS.[6]

The aim of this study is the systematic review of literature and meta-analysis of RCTs reporting the use of DOACs for pharmacologic VTE prophylaxis in patients undergoing HFS and comparing their effectiveness and safety to the administration of conventional pharmacologic VTE prophylaxis in respective patient group, as well as mortality between these patient groups.

Methods

Eligibility criteria

Inclusion criteria will be the following:

- RCTs in English language,
- study subjects of human species,
- male or female adults patients, subjected to HFS,
- patients administered exclusively either a DOAC or a conventional pharmacologic VTE prophylaxis drug postoperatively, and
- studies clearly reporting effectiveness and safety of administered agents along with mortality of each patient group.

Exclusion criteria will be the following:

- studies including drugs that did not take approval or were withdrawn,
- studies including patients taking antithrombotic medications preoperatively,
- studies not describing the exclusive use of one DOAC or conventional pharmacologic VTE prophylaxis agent in each patient, but mentioning combination of more than one antithrombotic drugs as postoperative thromboprophylaxis in each patient, and
- studies not clearly mentioning the number/percentage of patients who subjected to HFS, took each pharmacologic VTE prophylaxis drug, presented VTE or hemorrhagic complications or died during the period studies conducted.

Endpoints

The endpoint regarding effectiveness of DOACs compared to conventional pharmacologic VTE prophylaxis drugs in HFS patients will be the incidence of VTE up to 6 weeks postoperatively, as latest ACCP guidelines recommend pharmacologic VTE prophylaxis up to 35 days postoperatively.

The endpoint regarding safety of DOACs compared to conventional pharmacologic VTE prophylaxis drugs in HFS patients will be the incidence of any bleeding up to 6 weeks postoperatively, as latest ACCP guidelines recommend pharmacologic VTE prophylaxis up to 35 days postoperatively.

Mortality for each patient group of all selected studies will be an additional endpoint. We will conduct an analysis to compare mortality between patients administered a DOAC and patients received a conventional pharmacologic VTE prophylaxis medication after HFS up to 6 weeks postoperatively, regardless death was either of thromboembolic or of bleeding cause.

Search strategy

Two independent review authors will search the electronic databases of PubMed, MEDLINE, EMBASE, CNKI, Google Scholar and Cochrane for relevant studies published ur to 31st December 2020. Moreover, we will search World Health Organization (WHO), European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) and ClinicalTrials.gov websites and scientific programmes of recent haematology, thrombosis and orthopaedic conferences for relevant studies. The bibliographic lists of the relevant articles and reviews will be searched for further eligible studies, which might not have been found during the initial search based on the key words. The title and abstracts of articles identified from the literature search will be assessed and full-texts of relevant studies will be retrieved. Disagreements upon inclusion of studies will be solved by a third independent adjudicator. A re-run will be conducted prior to final statistical analysis and all authors will be contacted for any missed studies.

Data collection
Data will be extracted from the selected studies by two independent authors and will be recorded in spreadsheets. Disagreements upon data extraction will be solved by a third independent adjudicator. The software that will be used for data management will be Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020. Data will be presented on tables, containing information regarding first author's name, year and journal of publication of every study and patient age and gender, the number of patients presented the various endpoints will be studied.

Data synthesis and statistical analyses
Relative risk for individual studies will be combined using a fixed effects meta-analysis.We will generate forest plots to depict the relative risk (RR) of VTE, bleeding events and mortality between patients administered a DOAC and patients receiving a conventional pharmacologic VTE prophylaxis drug and to investigate if there is statistical significance between these patient groups to present any of the clinical manifestations studied. 95% confidence intervals will be calculated for each clinical manifestation and a p-value less than 0.05 ($p \leq 0.05$) will be considered as statistically significant. Additionally, we will calculate the inconsistency (I^2) statistic that describes the percentage of variation across studies that is due to heterogeneity rather than chance. The software will be used for this statistical analysis was Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020.

Subgroup analysis
We will use paired sample Student's t-test in order to calculate whether there is statistically significant difference or not in age between patients administered a DOAC and patients receiving a conventional pharmacologic VTE prophylaxis drug.

Risk of bias
We will use the modified Cochrane collaboration tool to assess the risk of bias of RCTs included in our meta-analysis. The five domains that will be assessed for risk of bias will be selection (random sequence generation, allocation concealment), performance (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition (incomplete outcome data) and reporting (selective reporting). Bias risk will be assessed as a judgment (high, low, or unclear) from above five domains for each RCT selected. Two independent review authors will assess the risk of bias independently and disagreements upon risk assessment will be solved by discussion.

Discussion
This review and meta-analysis will conclude if DOACs are more effective and safer to conventional thromboprophylaxis medications for postoperative thromboprophylaxis in patients subjected to HFS.

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