REVIEW ARTICLE

Efficacy and safety of pharmacological venous thromboembolism prophylaxis following liver resection: a systematic review and meta-analysis

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Abstract

Background: Current guidelines recommend pharmacological prophylaxis for patients undergoing abdominal surgery for malignancy. Liver resection exposes patients to risk factors for venous thromboembolism, but there is a risk of bleeding. The aim of this study is to evaluate the evidence base supporting the use of pharmacological thromboprophylaxis in liver surgery.

Methods: An electronic search was carried out for studies reporting the incidence of VTE following liver resection comparing patients receiving pharmacological prophylaxis with those who did not. The search resulted in 990 unique citations. Following the application of strict eligibility criteria 5 studies comprise the final study population.

Results: Included studies report on 3675 patients undergoing liver resection between 1999 and 2013. 2256 patients received chemical thromboprophylaxis, 1412 had mechanical prophylaxis only and 7 received no prophylaxis. Meta-analysis revealed lower VTE rates in patients receiving chemical thromboprophylaxis (2.6%) compared to without prophylaxis (4.6%) (Dichotomous correlation test, odds ratio: 0.631 [95% CI: 0.416–0.959], Fixed model, p = 0.030). Data regarding bleeding could not be pooled for meta-analysis, but chemical thromboprophylaxis was reported as safe in four studies.

Conclusion: This systematic review and meta-analysis of retrospective studies indicates that the use of perioperative chemical thromboprophylaxis reduces VTE incidence following liver surgery without an apparent increased risk of bleeding.

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Introduction

Venous thromboembolism (VTE) is a significant cause of morbidity, prolonged in-hospital stay and mortality following major abdominal surgery.[1] Patients undergoing liver resection often have a number of risk factors for VTE including older age, a diagnosis of malignant disease, prolonged operation times, intraoperative blood transfusion and immobility during post-operative recovery. There was a previously held notion that despite these risk factors patients undergoing liver resection were thought to be at lower risk of VTE during the post-operative period. The theoretical basis for this hypothesis was in part related to the reduced synthetic function of the remnant liver reflected clinically by a prolonged post-operative prothrombin time (PT).[2] However, an accumulating body of evidence suggests that there is an increased risk of VTE after hepatectomy with the risk being proportionate to the extent of resection. The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) reported that 2.9% of patients from a cohort of 5706 patients undergoing liver surgery suffered a symptomatic post-operative VTE.[3] The highest incidence of reported VTE events was in patients undergoing major liver resection.[3,4]

The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines recommend 4 weeks of post-operative chemical thromboprophylaxis in high risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications.[5] There is controversy as to whether these guidelines are applicable to

liver surgery. The core of this controversy is whether the benefit of reducing VTE outweighs the risk of bleeding after hepatectomy. A recent Clinical Guidelines Symposium at the America's Hepato-Pancreato-Biliary Association (AHPBA) Annual Meeting on VTE in Liver Surgery concluded that postoperative chemical thromboprophylaxis should be initiated immediately after hepatectomy in hemodynamically stable patients without evidence of bleeding.[6]

The aim of this study is to conduct a systematic review of the available data addressing the role of chemical thromboprophylaxis for patients undergoing liver resection. The principal focus of this study is to assess whether perioperative chemical thromboprophylaxis decreases the incidence of VTE without compromising safety and without causing an increase in bleeding complications. This study focuses on reports comparing patients undergoing liver resection with chemical thromboprophylaxis to those without.

Methods

Protocol and registration

The study protocol was registered with PROSPERO, the International Prospective Register of Systematic Reviews (registration number CRD42016045245).

Eligibility criteria

This is a systematic review and meta-analysis of published articles assessing the potential benefits and risks of chemical thromboprophylaxis given after hepatectomy. The principle focus of the review is on reports with individual patient-level data comparing rates of VTE and haemorrhagic complications between patients who received and those who did not receive chemical thromboprophylaxis after liver resection. Cohort studies and randomised controlled trials were included if they met the inclusion criteria.

Papers were excluded if they were not in English, were reviews without original data, were case reports or did not provide outcome data on patients receiving chemical thromboprophylaxis after liver surgery.

Information sources

A computerized literature search was performed using the Web of Science database (Thomson Reuters, UK) from January 1992 to August 2016. This database includes Medline, the data citation index and the BIOSIS citation index. The keywords and MESH headings hepatectomy/liver resection, thrombosis, venous thromboembolism, anticoagulation resulted in 948 unique citations after excluding duplications. Of these, 21 full text articles including data on patients receiving postoperative chemical thromboprophylaxis after liver resection were assessed for eligibility. Studies providing original data on VTE incidence after hepatectomy both in the presence and absence of chemical thromboprophylaxis were eligible for inclusion. Using these criteria five studies were identified, one of which evaluated the outcome of perioperative chemical thromboprophylaxis[7] and four the outcome of postoperative prophylaxis.[8–11] These five studies comprise the final study group. The search strategy is summarized in a PRISMA flowchart (Fig. 1).

Data extraction

Data were extracted independently by two co-authors (MB and RL). Data extraction was cross checked by the senior author (SJ). Data were extracted on the following: year of publication, study period, size of study population, patient age and gender, indication for surgery, specific details of thromboprophylaxis strategy; pharmacological agent administered, time of commencement, duration and use of mechanical thromboprophylaxis. Data were also collected on type of liver resection, duration of surgery, blood transfusion requirements, postoperative haemorrhagic complications, thromboembolic events and mortality.

Ethics review

The Central Manchester University Hospitals NHS Foundation Trust, Research and Development department reviewed the study and advised that no formal external ethical review was required as the study has no clinical contact and utilizes secondary sources of data.

Assessment of risk of bias

The risk of bias was determined using the guidelines published by the Cochrane Collaboration.[12] The Cochrane Collaboration's tool for evaluating the risk of bias examines seven domains including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. All the above domains were evaluated by two co-authors and categorized as low risk of bias, high risk of bias, or unclear risk of bias for each study.

Statistical analyses

Meta-analysis of VTE incidence was conducted with Comprehensive Meta-analysis software (version 3). Odds ratios with 95% confidence intervals (CIs) were calculated for dichotomous outcomes. Statistical heterogeneity across studies was analysed using Cochran's Q test and the I^2 statistic. The fixed-effect model was utilized as sampling error was regarded as the source of variation among effect sizes. A p value <0.05 was considered to indicate significance.

Results

Risk of bias in study population

The risk of bias calculated using the Cochrane Collaboration's tool was high for all five studies with both attrition and reporting bias present.