Thrombosis Research 134 (2014) 599–603

Contents lists available at ScienceDirect

Thrombosis Research

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

Regular Article

A systematic review on the effect of aspirin in the prevention of post-operative arterial thrombosis in patients undergoing total hip and total knee arthroplasty ☆

Federico Lussana [a,b], Alessandro Squizzato [c], Eleonora Tamborini Permunian [c], Marco Cattaneo [b,*]

[a] Haematology and Bone Marrow Transplant Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
[b] Medicina III, Azienda Ospedaliera San Paolo, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milano, Italy
[c] Medicina 1, Ospedale di Circolo Varese, Varese, Italy

ARTICLE INFO

Article history:
Received 13 April 2014
Received in revised form 31 May 2014
Accepted 17 June 2014
Available online 5 July 2014

Keywords:
Antiplatelet agents
Arterial thrombosis
Orthopedics
Venous thrombosis

ABSTRACT

Introduction: Major surgery is associated with increased risk of venous thromboembolism (VTE), which is decreased by anticoagulant drugs. Evidence is growing that major surgery is associated with increased risk of arterial thrombosis (AT). With the aim of testing aspirin ability in reducing the risk of post-operative AT, we performed a systematic review of studies in which acetylsalicylic acid (ASA) was compared to anticoagulant drugs in VTE prophylaxis of patients undergoing total hip replacement (THR) or total knee replacement (TKR).
Materials and Methods: Studies were identified by reviewing the reference of the ACCP guidelines and by electronic search of MEDLINE database from January 2012 to December 2013 and of the web database www.trialresultscenter.org.
Results: We analyzed 5 of the 78 studies that were identified by our search strategy; they included 5179 patients; the median follow-up was 90 days. The incidence of post-operative AT tended to be lower in ASA-treated patients, compared to anticoagulant-treated patients, although the difference did not reach statistical significance (OR 0.56, 95%CI 0.23-1.35). In contrast, the incidence of post-operative VTE tended to be higher in ASA-treated patients, compared to anticoagulant-treated patients (1.48, 95% CI 0.93-2.36).
Conclusions: Due to the heterogeneity and low quality of the studies, which do not allow firm conclusions, it is uncertain whether aspirin is effective in reducing the incidence of postoperative AT. Our results do emphasize the need for developing specifically designed studies to test the safety and efficacy of ASA in the prevention of post-operative AT.

Introduction

Patients undergoing major surgery are exposed to increased risk of venous thromboembolism (VTE), which is effectively reduced by anticoagulant drugs, and, albeit perhaps less effectively, other forms of thromboprophylaxis [1]. Evidence is growing that major non-cardiac surgery is also associated with increased risk of arterial thrombosis (AT), including acute myocardial infarction (AMI) and stroke [2,3]. Recently, 2 epidemiological controlled studies showed that the incidence of peri-operative AMI and stroke in patients undergoing total hip replacement (THR) or total knee replacement (TKR), relative to that of matched controls not undergoing THR or TKR, is high [4,5]. In THR patients, the adjusted hazard ratios (HR) were 25.5 for AMI and 4.7 for stroke in the first 2 weeks after surgery, remained elevated (5.05 for AMI and 2.1 for stroke) until the 6th post-operative week, and then declined to baseline values [4,5]. In TKR patients, the HR for AMI was 30.9 in the first 2 post-operative weeks and declined to baseline values thereafter; no data on the HR for stroke were reported [4]. Moreover, troponin levels, marker of myocardial injury, increase after non-cardiac surgery and predict the 30-day mortality [6].

Despite the very high HR, the absolute incidence of post-operative AT is much lower than that of post-operative VTE [4,5,7]. It is probably for this reason that studies that addressed the issue of preventing post-operative AT are scanty, in contrast with the large proliferation of randomized clinical trials that documented the efficacy of anticoagulants in the prevention of post-operative VTE. However, considering the high number of surgical interventions that are performed, it is expected that up to about 1 million patients suffer post-surgical cardiovascular

Abbreviations: VTE, venous thromboembolism; AT, arterial thrombosis; AMI, acute myocardial infarction; ASA, acetylsalicylic acid; THR, total hip replacement; TKR, total knee replacement; OR, Odds Ratios; HR, hazard ratios; CI, confidence intervals; RCTs, randomized controlled trials; ACCP, American College of Chest Physicians; LMWH, low molecular weight heparins.

☆ **Financial support:** none.

* Corresponding author at: Medicina III, Ospedale San Paolo, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Via di Rudinì 8, 20142 Milano, Italy. Tel.: +39 02 50323095; fax: +39 02 50323089.
E-mail address: marco.cattaneo@unimi.it (M. Cattaneo).

http://dx.doi.org/10.1016/j.thromres.2014.06.027
0049-3848/

complications worldwide every year [7]. Thus, prevention of post-surgical AT may be relevant in terms of reduction of morbidity and mortality worldwide. Peri-operative administration of beta-blockers has been tested in some studies, which showed that these drugs may be protective in some patients, but ineffective and even harmful in others [8,9].

It is well established that the coagulation system plays an important role in the pathogenesis of VTE, and that the risk for VTE in patients undergoing THR or TKR is effectively decreased by anticoagulant drugs [1]. However, some studies suggested that the antiplatelet agent acetylsalicylic acid (ASA) can also be effective [1]. Considering the major role played by platelets in the pathogenesis of AT and the efficacy of ASA in reducing the incidence of major adverse cardiovascular and cerebrovascular events both in secondary and, albeit to a lower extent, primary prevention [10], ASA can be expected to be particularly effective in reducing the risk of post-operative AT.

Based on this background, we performed a systematic review of studies in which ASA was compared to anticoagulant drugs in VTE prophylaxis of patients undergoing THR or TKR, with the aim of comparing its efficacy in preventing post-operative AT and VTE with that of anticoagulant drugs.

Material and Methods

Studies were identified by reviewing the reference of the last edition of the Evidence-Based Clinical Practice Guidelines American College of Chest Physicians (ACCP) on prevention of VTE in orthopedic surgery that are updated using comprehensive literature searches [1] and by electronic search of the PubMed database from January 2012 to December 2013. The search strategy was developed without any language restriction, using the following keywords: 'aspirin' AND (('hip' OR 'knee') AND 'arthroplasty'). The search was supplemented by manually reviewing the references of included studies and the references of the main published systematic reviews on thromboprophylaxis in THR and TKR patients and on thromboprophylaxis with ASA in surgical patients [11–15]. Electronic search of the web database www.trialresultscenter.org completed the search strategy.

The following data were extracted: study characteristics (year of publication, design, study centre), patients' characteristics (number, mean age, variation in age and gender), treatments and number of arterial and venous thrombotic complications.

Study identification by ACCP guidelines was performed by one reviewer (ETP). Study selection and data extraction were performed by a second reviewer (FL) and was checked by a third reviewer (AS). Studies were considered potentially eligible for this systematic review if they met the following criteria: they were randomized controlled trials (RCTs) or cohorts of patients undergoing elective TKR or THR; ASA was compared with anticoagulant drugs; arterial and venous thrombotic events were assessed in both groups.

Review Manager (RevMan. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used to determine pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) for all-cause mortality, all cardiovascular events (fatal and not fatal stroke and AMI), symptomatic VTE and any bleeding in patients undergoing THR or TKR who received ASA or anticoagulants (warfarin or heparin). OR and 95% CI were calculated using a fixed-effects and a random-effects model (DerSimonian and Laird method) [16]. Statistical heterogeneity was evaluated using the I^2 statistic, which assesses the appropriateness of pooling the individual study results [17]. The I^2 value provides an estimate of the amount of variance across the studies as a result of heterogeneity rather than chance. $I^2 < 30\%$ indicates mild heterogeneity, 30–50% moderate and >50% severe heterogeneity [17]. We were unable to assess publication bias by using funnel plots, due to the insufficient number of studies that we could analyze.

Results

The process of study selection is outlined in Fig. 1. We identified a total of 78 citations (39 by manually reviewing the reference lists of all retrieved articles and 39 retrieved from Medline), 56 of which were excluded upon reading their titles and abstracts, according to predefined inclusion and exclusion criteria. Twenty-two publications were retrieved in full for detailed evaluation. Seventeen studies were further excluded because they did not contain data about arterial thrombotic events (references available upon request). Four manuscripts [18–21] and 1 abstract [22], which included a total of 5179 subjects, were analyzed in our systematic review (Table 1). Two of them were RCTs [20,22], one was a prospective cohort [18] and 2 retrospective cohorts [19,21]. Four studies included patients undergoing elective THR or TKR [18,19,21,22] and the remaining one included patients undergoing elective THR [20]. The follow-up was 90 days in four studies [18–21] and 10-14 days in one study [22]. The comparator was low molecular weight heparins (LMWH) in 2 studies [20,22], vitamin K antagonists in 1 study [19] and LMWH or warfarin in 1 study [21]. In the remaining study [18], the comparator was "one of the drugs recommended by the 8th edition of the ACCP guidelines" [23]. The main characteristics of the 5 studies are summarized in Table 1. Globally, only 1 study reported AT as a pre-defined outcome, 2 studies were RCTs, but without adequate information about the randomization and no study clearly reported information on how the diagnosis of AT had been made. Therefore, the overall quality of studies was poor. This condition and the small number of included studies did not allow us to perform the analysis of the effects of ASA including only high quality level studies or studies with the same design, so we tried to make this estimation by pooling the results of all included studies.

The incidence of AT during the median follow-up of 90 days was 0.4% (AMI = 0.2%; stroke = 0.1%, excluding one study [22] in which coronary and cerebrovascular events were reported together), which is slightly lower than that reported by 2 recent large epidemiological studies (AMI: 0.51% in THR and 0.21% in TKR at 6 weeks post-surgery; stroke; 0.22% at 2 weeks post-surgery) [4,5]. The risk of AT tended to be lower in ASA-treated patients, compared to anticoagulant-treated patients, but the difference did not reach statistical significance (OR 0.56, 95%CI 0.23-1.35); there was no significant heterogeneity among studies ($I^2 = 0\%$) (Fig. 2). In contrast, the incidence of VTE tended to be higher in ASA-treated patients, compared to anticoagulant-treated patients, but also in this case the difference did not reach statistical significance (OR 1.48, 95% CI 0.93-2.36); we observed heterogeneity across the studies ($I^2 = 73\%$) (Fig. 2). The incidence of abnormal bleeding tended to be lower in ASA-treated patients (0.2%) than in anticoagulant-treated patients (0.4%) (OR 0.54, 95%CI 0.15-1.91; $I^2 = 0\%$). Finally, there was no reported death among ASA-treated patients, while 0.2% of anticoagulant-treated patients died.

Discussion

The risk of AT, including AMI and ischemic stroke, temporarily increases in patients undergoing major surgery. However, the common perception among physicians of the burden of this severe complication is less strong than that of VTE, probably as a consequence of its relatively low incidence. As a consequence, studies that addressed the issue of how to reduce the risk of AT after surgery are scanty especially when compared with the great proliferation of RCTs of post-surgical VTE prophylaxis in the last 4 decades. The protective effect of beta-blockers is uncertain and probably limited to high-risk patients [9]. ASA, an antiplatelet agent that reduces the risk of AMI and ischemic stroke in patients at risk [10], has been tested in studies of VTE prophylaxis, especially after orthopedic surgery, and found to be effective, albeit perhaps less so than anticoagulant drugs [1]. Because ASA has been directly compared with anticoagulant drugs in studies of VTE prophylaxis after major orthopedic surgery, we set out to evaluate whether