Thrombosis Research 132 (2013) 531–536

Contents lists available at ScienceDirect

Thrombosis Research

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

Regular Article

Who are at risk for thromboembolism after arthroplasty? A systematic review and meta-analysis

Xindie Zhou, Wenkang Qian, Jin Li, Pengli Zhang, Zhigao Yang, Weiping Chen, Lidong Wu *

Department of Orthopedics Surgery, The Second Affiliated Hospital of Medical College, Zhejiang University, Hangzhou, China

ARTICLE INFO

Article history:
Received 9 June 2013
Received in revised form 29 August 2013
Accepted 3 September 2013
Available online 13 September 2013

Keywords:
Gene
Thromboembolism
Arthroplasty
Genetic Susceptibility
Polymorphism
Meta-analysis

ABSTRACT

Background: Thromboembolism, including deep venous thrombosis and pulmonary embolism, is a grave threat to patients undergoing total joint replacement. Using a systematic review and meta-analysis we asked whether gene mutations or polymorphisms could be risk factors for thrombosis after arthroplasty.
Methods: We performed a comprehensive search of Medline, PubMed, Embase, Cochrane databases, China National Knowledge Infrastructure (CNKI), and Google Scholar, and identified 19 studies detailing genetic investigations of patients with thromboembolism following joint replacement.
Results: Our meta-analyses included 5149 patients who underwent arthroplasty surgery. Significant associations with venous thromboembolism were identified for factor G1691A (odds ratio (OR) 1.41, 95% confidence interval (CI) 1.03 - 1.94, $p = 0.03$), prothrombin G20210A (OR 2.16, 95% CI, 1.27- 3.69, $p = 0.005$), and MTHFR/C677T/TT (OR 2.36, 95% CI 1.03 - 5.42, $p = 0.04$) in Caucasian populations. No significant gene mutation was identified in Asian populations.
Conclusion: This study suggests a way to identify patients scheduled for arthroplasty who are at higher risk of thrombosis, enabling individualized treatment.

Introduction

Deep venous thrombosis (DVT), with or without pulmonary embolism (PE), is a serious, potentially life-threatening complication after major orthopedic surgery. Venographic studies in the absence of thrombophylaxis show that the incidence of DVT rates is 42-57% for total hip arthroplasty (THA) and 41-85% for total knee arthroplasty (TKA) [1]. Despite the routine use of prophylactic mechanical and chemical measures perioperatively, numerous patients still develop DVT after major orthopedic surgery. The residual risk of DVT after THA is 9-36% [2–4]. This risk is even higher after TKA, as great as 52% [3]. Indeed, in the absence of prophylaxis, the estimated incidence of asymptomatic deep vein thrombosis (DVT) is 40-80% [5].

Therefore, reasonable perioperative anticoagulant management is necessary. However, excessive anticoagulation is always associated with a higher risk of hematoma formation and bleeding. As a result, thromboembolism prophylaxis measures must be improved, and we could tailor thromboprophylaxis to the patient's risk ideally. Thrombophilia can be acquired following surgery, immobilization, or cancer, or inherited, such as with mutations in Factor V Leiden (FVL), activated protein C (APC) resistance, or prothrombin mutations, or result from an interaction between inheritance and environmental factors, such as estrogen use, obesity, infection, smoking, gestation or other lifestyle factors. In addition, to identify factors that induce thrombosis, new laboratory prediction methods are being developed. The increased knowledge of genetic factors in numerous common diseases has led to the integration of human genomics into the practice of medicine [6]. Identifying and characterizing associated genetic risk and protective factors should help to develop treatment strategies for several etiological aspects of disease [7]. There is growing pressure on clinicians to screen for genetic thrombophilia in a variety of settings; however, no meta-analysis has examined whether thrombophilia contributes to venous thrombus embolism (VTE) in joint replacement surgery. We believe that it is essential to develop an evidence base to guide patient management and future research priorities in this area.

The purposes of this meta-analysis were to examine the types and the frequency of specific genetic abnormalities in patients scheduled for arthroplasty surgery, and to determine: whether there is an association between genetic thrombophilia and postoperative thromboembolic events.

Abbreviations: CI, confidence interval; OR, odds ratio; DVT, deep venous thrombosis; PE, pulmonary embolism; THA, total hip arthroplasty; TKA, total knee arthroplasty; FLV, factor V Leiden; APC, activated protein C; VTE, venous thrombus embolism; STREGA, strengthening the Reporting of Genetic Association Studies; STROBE, strengthening the Reporting of Observational Studies in Epidemiology; MTHFR, methylenetetrahydrofolate Reductase; PAI-1, plasminogen-activator inhibitor 1; ACE, encoding angiotensin-converting enzyme; I/D, insertion/deletion.

* Corresponding author at: Department of Orthopedics Surgery, The Second Hospital of Medical College, Zhejiang University, Hangzhou, 310000, China. Tel./fax: +86 571 87783530.
E-mail address: ldwu@yahoo.com (L. Wu).

0049-3848/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.thromres.2013.09.005

Methods

We searched the databases of Medline, PubMed, Embase, Cochrane library, China National Knowledge Infrastructure (CNKI) and Google Scholar for the publications of English and Chinese (January 1966 to February 2013), while using the Medical Subject Headings and text words of "genetic", "gene", "polymorphism", "genotype" "thrombosis", "thrombus", "thromboembolism", "embolism", "embolization", "arthroplasty", "joint replacement", " prosthesis", and "orthopedic surgery", as well as their extended words. Full-texts were obtained if the abstracts did not allow us to include or exclude the studies. The reference lists of related reviews were also searched to identify articles not included at the electronic search.

The selection criteria were follows: case–control, cross-sectional cohort and prospective cohort studies were included in our study, where VTE (PE and/or DVT, including symptomatic and asymptomatic) was analyzed as a dichotomous trait. Studies in abstract form or meeting reports, which the full paper could not be acquired, were also included in our study. All included patients experienced arthroplasty surgery and were investigated for related gene mutations. Each study included in our meta-analysis required a group of unrelated patients who had ethnically and geographically representative of the population from which the patients were selected genetic assessment. Exclude strategies are followed: (1) Biomechanical reports, case reports, in vitro, studies on animals, cadavers, literature reviews, technical notes and instructional course were excluded. (2) Studies carried out on patients, who were pregnant, with cancer or other diseases, such as thrombophilic disorders, or antiphospholipid syndrome, which may result in thrombosis, were excluded; (3) Studies on patients who were not experienced joint replacement surgery were excluded; (4) Studies on patients had VTE in portal vein, lower limb vein or other parts of the body before surgery were excluded; (5) Studies that only reported allele frequencies, but without genotype frequency were excluded; (6) Studies on patients who had diseases with blood coagulation system were excluded. Any publications with questionable inclusion/exclusion criteria were discussed and disagreements were resolved by consensus. The computer search yielded 19838 citations, and following application and refinement of the literature search strategy, 19 independent randomized controlled trials [8–26], containing 5149 patients, were eligible for data extraction and meta-analysis, and the flowchart of reviews which showed the detailed process of selection could be found in Fig. 1.

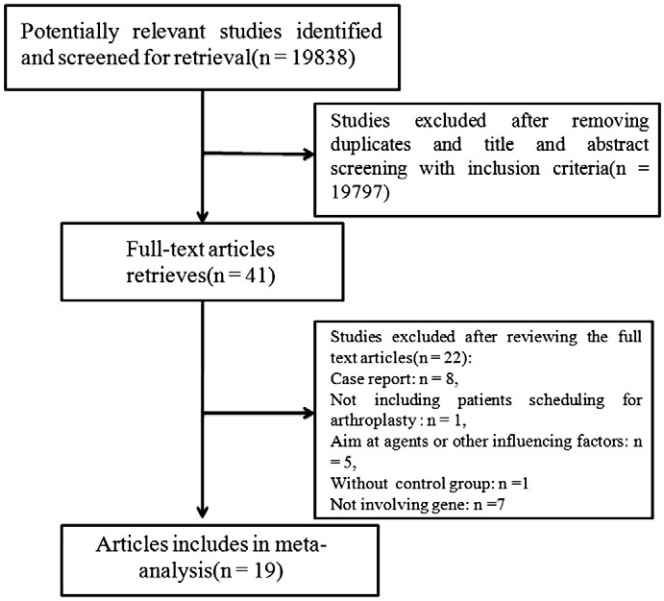

Fig. 1. A flowchart shows the results of the literature search and selection for this systematic review.

Two reviewers independently evaluated the methodological quality of the included studies by applying an 11-item quality checklist, derived from the STREGA [27] (Strengthening the Reporting of Genetic Association Studies) and STROBE [28] (Strengthening the Reporting of Observational Studies in Epidemiology) checklists. Specifically, the quality criteria were: (1) clear statement of objectives and hypothesis, (2) clear eligibility criteria for study participants, (3) clear definition of all variables, (4) clear diagnostic criteria, (5) replicability of statistical methods, (6) credible genetic testing method, (7) assessment of Hardy-Weinberg equilibrium, (8) assessment of ethnicity, and addressing the problem of mixed ethnicities statistically (if applicable), (9) sufficient descriptive data (age, sex, ethnicity), (10) statement of genotype frequencies, (11) consideration of population stratification. Information of each selected study was extracted on the name of first author, year of publication, study design, ethnicity and country of study population, size of the study, genetic testing method, prevention and diagnosis method of thrombosis, time of follow-up and genotype frequency for venous thromboembolic disease in cases and controls. The characteristics of the 19 trials included in the meta-analysis were summarized in Table 1. Most were relatively well-designed and the quality assessment score of most was high, with a mode of 11, the highest possible score, a median value of 9, and a range of 7–11. The principal diagnosis was osteoarthritis and femoral head necrosis. Fifteen of them identified in investigation Caucasian origin, while other four reported the gene mutation of the yellow race in Asia. Six genes, including seven polymorphisms, were investigated. And the summary of meta-analysis could be found in Table 2.

Data were checked independently and analyzed using Review Manager 5.0 by different reviewers. To determine the strength of genetic association a pooled odds ratio (OR) was calculated for each gene variant and a 95% confidence intervals (CI) established. If the results of heterozygous and homozygous patients were combined as positive mutations, the dominant model was analyzed, and if they were reported separately, both of the dominant and recessive models were analyzed. For each meta-analysis, tests for heterogeneity were performed with significance set at $p \leq 0.1$, and the degree of heterogeneity was measured using the I^2 value. Fixed effects analysis was used for comparing trials without showing heterogeneity, whereas random effects analysis was used for comparing trials showing heterogeneity. We also performed sensitivity analyses by excluding each study individually to determine the effect on the test of heterogeneity and the overall pooled estimates. For assessment of publication bias, funnel plots and the Egger regression asymmetry test were conducted for each gene with five or more publications by Stata 12. *P*-values less than 0.05 were considered to indicate significance.

Results

Based on our study, three gene mutations are significant association with the posterative VTE.

Factor V Leiden (FVL) mutation was most investigated followed with 18 studies [8–24,26], concentrating on the dominant inheritance of G1691A polymorphism. Fifteen studies [8–17,19,20,24,26] were identified in Caucasian populations. The pooled OR for FVL mutation, and the risk of VTE after arthroplasty in Caucasian populations was 1.41 (95% CI, 1.03–1.94, $p = 0.03$) (Fig. 2). The Egger regression intercept *p*-value (two-tailed) was 0.696 suggesting a low probability of publication bias (Fig. 3). There was no evidence of significant heterogeneity ($P_{Het} = 0.37$, I2 = 8%). No mutations of FVL were observed in Asian groups [21–23].

A total of seven studies [14–17,19,24,26] were identified that characterized the Prothrombin gene/G20210A mutation in Caucasian populations. The pooled OR for Prothrombin gene/G20210A was 2.16 (95% CI, 1.27–3.69, $p = 0.005$, Fig. 4) in Caucasian populations. The Egger regression intercept *p*-value (two-tailed) was 0.226, which suggested a low probability of publication bias (Fig. 5), and there was no evidence of significant heterogeneity ($P_{Het} = 0.11$,