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Hospital-Acquired Venous Thromboembolism or Bleeding Following Total Joint Arthroplasty: A Systematic Review and meta-analysis for the Association of the Gene Polymorphism.

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Hospital-Acquired Venous Thromboembolism or Bleeding Following Total Joint Arthroplasty: A Systematic Review and meta-analysis for the Association of the Gene Polymorphism.

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Abstract

This review seeks to understand the current existing literature on genetic polymorphisms to VTE following orthopedic surgery. Using PRISMA guidelines, 234 studies were retrieved from PubMed and Cochrane. The eligibility assessment yielded 16 studies including a systematic review. A STREGA and STROBE quality assessment found these studies to have high methodological quality. A significant association was found between the PAI-1 4G/4G genotype and resistance to anticoagulation therapy (OR = 2.692; 95% CI = 1.302 - 4.702). Moreover, the MTHFR C677T and A1298C polymorphisms significantly increased the incidence of VTE in patients that are compound heterozygotes (OR = 2.89; 95% CI = 1.40 – 5.96; p = .006). A significant association was also found for the Factor XI C25264C polymorphism (OR = 2.42; 95% CI 1.16 – 5.03). Finally, SNP rs710446 of the KNG1 gene (OR = 1.27; p = .00016), and SNP rs2069588 in the 3' UTR of the BDK4B2 (OR = 1.29; p = .00056) were also significantly associated with VTE following orthopedic surgery.

Introduction

The estimated rates of total hip arthroplasties (THA) and total knee arthroplasties (TKA) are projected to increase in the United States. Data obtained from the U.S. Census Bureau and US National Inpatient Sample projects the rate of THA to increase by 34%, 75%, 129%, and 284% by the years 2020, 2025, 2030, and 2040, respectively(1). Moreover, the rate of TKA is projected to increase by 56%, 110%, 182%, and 401%, respectively(1). Data from the National Input Sample determines that 1.3% of the patients who received THA or TKA between 2009 and 2011 develop a hospital acquired condition (HAC)(2). Thromboembolic events, including pulmonary embolism (PE) and deep vein thrombosis (DVT) are common, life-threatening but preventable HCAs that occur following TJA(3). Thromboembolism has multifactorial etiology and so contributing risk factors are environmental and genetic. Some environmental risk factors are provoking e.g. cancer, surgery, trauma, immobilization, pregnancy, long distance travel, hospitalization, catheterization, and acute infection(4). Other environmental risk factors are intrinsic to the patient e.g. age, sex, ethnicity, body mass index, oral contraceptive use, corticosteroid use, statin use, diet, physical activity, and air pollution(4). There are many risk factors that specifically contribute to VTE following TJA. A metanalysis of 14 case-control or prospective cohort studies found a significant relationship between VTE following TJA and prior history of VTE (RR > 10.6), varicose vein (RR > 2.7), and congestive cardiac failure (RR = 2) (5). There was a VTE risk ranging from 8-30% for other factors which are listed in order of increasing risk: female gender, age > 80, hypertension, active cancer, BMI > 30, black race(5). Many genetic risk factors have also been identified, including factor V Leiden mutation and prothrombin gene polymorphisms(4). Moreover, Wang et al. applied genetic risk scoring to known genetic polymorphisms associated with hemostatic disease provided 70.8% precision in identifying patients with VTE(6), which further supports a genetic role in VTE development.

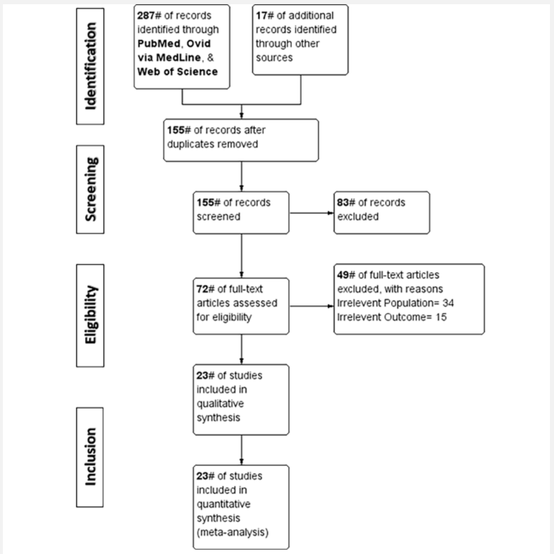
Methods

This systematic review and meta-analysis were conducted according to the preferred
reporting items for systematic review and meta-analysis (PRISMA) guidelines (11) and the Cochrane Handbook.(12)

Data Collection & Analysis

A total of 23 publications were identified from the literature search specific to Hospital-Acquired Venous Thromboembolism or Bleeding Following Total Joint Arthroplasty.

Table 1: Literature Search



Using the previously mentioned keywords, 304 relevant articles were obtained from the 3 online databases (PubMed, MEDLINE via Ovid, and Web of Science) as well as through manual retrieving. After screening and assessing eligibility, 23 clinical studies that investigated the association of genetic polymorphism and the incidence of venous thromboembolism following hip and knee arthroplasties were included. Only one of these 23 studies were randomized controlled trial. However, the remaining studies were prospective cohort (5 trials), retrospective cohort (2 trials) and case-control trials (15 trials). A flow chart demonstrating the study selection,
inclusion, and exclusion process is shown in (Figure 1). Study Characteristics. One Randomized Controlled triol (RCT), two retrospective cohort, five prospective cohort, and 17 case-control studies of the study period between 1997 and 2018 have examined the genetic association with the incidence of VTE. 8098 patients were enrolled in the 23 studies. A total of 69.5% (16/23) trials have studies these association in Caucasian population. However, Asian population were the subjects in 7 trials. The mean age of the VTE group across all studies was 66.3, while that in the non-VTE group was 65.1. A total of 36.3% (8/23) trials have been conducted in the United States, three trials in China, two trials in Italy (2/23) and Korea (2/23) While the other six trials came from Japan (1/23), Sweden (1/23), Hungary(1/23), Germany (1/23), India (1/23), and Australia (1/23).

Results

Meta-analysis:

1. **Factor V Leiden (FVL) G1691A** polymorphism Seventeen clinical trials (15-30) investigated the association of FVL (G1691A polymorphism) in Caucasian (14 trials) and Asian (3 trials) populations with VTE following TJA. The pooled results showed that FVL- G1691A polymorphism, in Caucasian populations, is statistically significant associated with the incidence of VTE following TJA. **[OR= 1.39(95% CI, 1.03-1.88; p value = 0.03)** [figure.3.] Asian population showed no association between FVL polymorphism and the incidence of VTE.

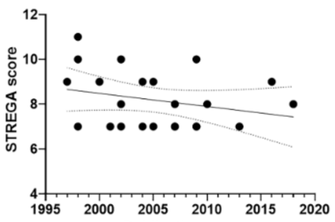
2. **Angiotensin Converting Enzyme (ACE) deletion/ deletion (D/D)** genotype Three trials (18, 19) investigated the association of Angiotensin Converting Enzyme (ACE) (D/D) genotype in Caucasian populations with VTE following TJA. The pooled results showed that there is no statistically significant association between ACE-D/D polymorphism-regardless, the population- and the incidence of VTE. **[OR= 1.40 (95% CI, 0.90-2.19; p value = 0.13]** [figure.3.]

3. **Prothrombin gene (G20210A)** Twelve clinical trials(16, 17, 20-24, 27-29, 31, 32) investigated the association of PG (G20210A polymorphism) in Caucasian (7 trials) and Asian (5 trials) populations with VTE following TJA. The pooled results showed that PG-G20210A polymorphism, in Caucasian populations, is statistically significant associated with the incidence of VTE following TJA. [**OR= 2.24 (95% CI, 1.37-3.66; p value = 0.001**] [figure.4.] Asian population showed no association between FVL polymorphism and the incidence of VTE.

4. **Methylenetetrahydrofolate Reductase (C677T/TT)** genotype Eight trials (16, 20-22, 24, 29, 32, 33) investigated the association of Methylenetetrahydrofolate Reductase (C677T/TT) in Caucasian (5 trials) and Asian (3 trials) with VTE following TJA . The pooled results showed that there is no statistically significant association between MTFR polymorphism-regardless the population- and the incidence of VTE. [**OR= 0.97 (95% CI, 0.69-1.38; p value = 0.88**] [figure.4.]

5. **Plasminogen activator inhibitor-1 (PAI-1) 4G/4G** genotype Four trials (16, 24, 29, 34) investigated the association of PAI-1 4G/4G polymorphism in Caucasian populations with VTE following TJA. The pooled results showed that PAI-1 4G/4G polymorphism, in Caucasian populations, is statistically significant associated with the incidence of VTE following TJA. [**OR= 1.72 (95% CI, 1.01-2.93; p value = 0.05)** [figure.4.]

Figure 1: Strengthening the Reporting of Genetic Association Studies (STREGA)



The studies included in this meta-analysis contained an average STREGA score of 7.9 with a median of 7, mode of 7, and range of 7-11. Many of the studies stated the objectives and hypothesis, provided clear eligibility criteria, defined all variables, contained replicable statistical methods, provided sufficient descriptive data (e.g. age, gender), and stated genotype frequencies. However, many of the studies omitted an assessment of Hardy Weinberg equilibrium and ethnicity. The descriptive statistics for each criterion of the STREGA methodology score are described in table (Table 2). The methodological quality the total STREGA methodology score was plotted against year of publication to estimate the trend of methodological quality (Figure 3). There is a negative correlation (r2 = 0.06969, slope- - 0.05852).

Conclusion

In conclusion, we do recommend that physicians screen TJA patients peri-operatively for **Factor V Leiden** mutation, **G20210A prothrombin** mutation, and **PAI-1 4G/4G genotype**. Detecting these genetic polymorphisms could be a good step to prevent the incidence of postoperative venous thromboembolism following TJA. However, the, ACE deletion/ deletion genotype are similarly unlikely to be associated with VTE. Moreover, patients that develop DVT might benefit from perioperative screening for PAI-1 4G/4G to determine if they are likely to be resistant to anticoagulation therapy. Patients would benefit from a screen for MTHFR polymorphisms; however, orthopedic surgeons should be aware that only compound heterozygotes for the C677T or A1298C polymorphisms have shown to be resistant to anticoagulation. Moreover, patients may also benefit from screening for **SNP rs710446** of the **KNG1** gene and **SNP rs20069588** for the **BDK482** gene, as well as the **Factor XI C25265C** polymorphism. These patients would benefit from more aggressive anticoagulation protocols.

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