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The Role of Aspirin in Prophylaxis Management of Venous Thromboembolism

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I am considering submitting this professional writing to the Journal of Thrombosis and Thrombolysis. The journal's author guidelines include a maximum of 2500 words with 3 figures and 2 tables, a brief abstract followed by 4 to 5 key points captured in a bullet format. This project will be submitted under as "Review Article."

Abstract

Acetylsalicylic acid (ASA) or aspirin is a well-known anticoagulant that provides relatively inexpensive primary and secondary prevention of cardiovascular disease. The known standard of care involves preventing cardiovascular disease in the arterial vasculature. More recent studies suggest aspirin also prevents venous thromboembolism (VTE) recurrence, such as pulmonary embolism (PE) and deep venous thromboembolism (DVT). This review considers aspirin as an antiplatelet therapy in cardiovascular disease, mechanism of action, and summarizes the best available evidence-based medicine which investigates aspirin's role as an anticoagulation therapy in VTE.

Important points

The new mechanism of action of aspirin suggests benefits for VTE prevention.

Aspirin is a well-studied anti-platelet in cardiovascular disease.

VTE recurrence rates do not change if previous anticoagulation was given.

Limited and small studies suggest rivaroxaban as an effective extended anticoagulation therapy in VTE.

Current research is limited.

Introduction

Acetylsalicylic acid (ASA) or aspirin is the standard of care for primary and secondary prevention of cardiovascular disease. Recent studies also suggest its use in the prevention of venous thromboembolism (VTE) recurrence, which includes pulmonary embolism (PE) and deep venous thromboembolism (DVT). This review considers aspirin as an antiplatelet therapy in cardiovascular disease, mechanism of action, and summarizes the best available evidence-based medicine which investigates aspirin's role as an anticoagulation therapy in VTE.

Mechanism of Action

Investigation of aspirin's mechanism of action explains for its diverse benefits and provides insight into aspirin's role as an anti-thrombotic medication. Low dose aspirin, 75mg to 81 mg, irreversibly acetylates cyclooxygenase (COX-1) which inhibits platelet generation of thromboxane A2 and results in an antithrombotic effect. Moreover, aspirin prevents the generation of prostaglandin H2 which is a thromboxane A2 precursor, inhibits thrombin formation by increased secretion of tissue factor inhibitor and acetylation of prothrombin, and promotes fibrinolysis by acetylation of fibrinogen. Additionally, aspirin inhibits platelets which decreases platelet factors V and XIII, fibrinogen, platelet factors III and IV, thrombospondin, and von Willebrand factor which are involved in thrombosis development. Furthermore, high doses of aspirin may reduce the production of coagulation factors in the liver (Mekaj, et. al., 2015).

The Benefits of Aspirin

Aspirin is conventionally used as a primary and secondary prevention of cardiovascular disease which is the leading cause of worldwide morbidity and mortality (World Health Organization, 2012). Numerous randomized trials and meta-analyses studies demonstrated a statistically significant reduction of morbidity, including cardiovascular disease, cardiovascular events, and all-cause mortality (Guirguis-Blake et. al., 2016; Hennekens, et. al., 1997). This includes significant reduction of 22 percent in myocardial infarction over 10 years (RR 0.78, 95% CI 0.71- 0.87), six percent significant reduction in all-cause mortality (RR 0.94, 95% CI 0.89 – 0.99) (Guirguis-Blake, et. al., 2016). Aspirin has also been shown to have secondary prevention of cardiovascular disease in high-risk patients with acute myocardial infarction, acute stroke, transient ischemic attacks, unstable angina, peripheral artery disease, coronary artery bypass graft surgery, percutaneous coronary intervention, atrial fibrillation, and vascular disease. The meta-analysis study concluded that daily aspirin, ranging from 75mg to 325mg, significantly reduced the relative risk of MI, stroke, and vascular death by about 22 percent (Antithrombotic Trialists' Collaboration, 2002). In some studies, aspirin has been shown to significantly reduce cancer incidence and mortality (Rothwell, et. al., 2010; Rothwell, et. al., 2012). The 2012 American College of Chest Physician (ACCP) guidelines suggest a daily dose of aspirin (75mg to 100mg) for persons who are 50 years or older without the symptomatic cardiovascular disease. Daily aspirin has been demonstrated to increase mortality in certain population (Vandvik, et. al., 2012).

Aspirin is a well-studied antithrombic management in the arterial system, and its benefits have also been suggested in long-term management for the prevention of VTE recurrence after patients experience a PE or DVT. The estimated annual incidence of VTE is one per 1000 people between the years 1980 and 2000, and there has been a two-fold increase in the pulmonary embolism incident from 2007 to 2009 (Naess, et. al., 2007; Park, et. al., 2017). After coronary heart disease and stroke, VTE is the third most common cardiovascular disease (Naess, et. al., 2007). People who experience VTE require pharmacological management of anticoagulants which is conventionally treated at least three, six or twelve months. The American College of Chest Physicians (ACCP) 2016 antithrombic guidelines recommends aspirin as an alternative extended anticoagulant therapy in patients with unprovoked VTE (Douketis, 2016).

Investigating Aspirin as a Medical Management for Venous Thromboembolism

Research has demonstrated that previous medical management of VTE does not affect the recurrence rate of VTE after the anticoagulant is discontinued (Agnelli, et., al., 2001). The risk of recurrence of VTE after discontinuation of anticoagulation in patients with first unprovoked VTE is 10 percent at the first year after anticoagulation discontinuation and 30 percent at five years (Keron, et. al., 2012). Another systematic review concluded VTE recurrence rates of 7.4 percent per patient-year at 24 months in people who were recently treated for three months of anticoagulation (Iorio, et. al., 2010). Another systematic review concluded a 30 percent risk reduction in VTE with daily aspirin management in comparison with placebo and observation (Castellucci, et. al.,

2013). Other oral anticoagulants have also been considered for secondary prevention in high-risk patients. Such studies include factor Xa inhibitor, rivaroxaban. In a randomized trial of 3385 patients, daily rivaroxaban 10mg, rivaroxaban 20mg and aspirin 100mg were administered beyond the common practice of three to six months of treatment to different groups. In comparison to the extended treatment of daily aspirin 100mg, with VTE recurrence rates of 4.4 percent, daily Rivaroxaban of 10mg and 20mg demonstrated lower VTE recurrence rates of 1.5 and 1.2 percent, respectively.

Although the risk of bleeding is a concern of anticoagulation medication therapy, similar major and nonmajor bleeding risks were found in patients who were treated with rivaroxaban or aspirin (Weitz, 2017). In a systematic review, vitamin K antagonists demonstrated to have the greatest VTE risk reduction in recurrent venous thromboembolism as well as the greatest risk of major bleeding (Castellucci, et. al., 2013).

In a randomized control trial of 120 patients, 60 patients were given aspirin and the other 60 patients were given low molecular weight heparin (LMWH) or rivaroxaban after undergoing total knee replacement. This study concluded that aspirin had same effect as the other anticoagulants. Moreover, aspirin had significant lower cost than LMWH and rivaroxaban (Mistry, et. al., 2017). Thus, aspirin can be a cost-effective management in comparison to other anticoagulants.

Current management for the prevention of secondary VTE with prolonged anticoagulation treatment will depend on the individual assessment as well as the patient's values and preference. Such consideration includes but is not limited to the

individual's bleeding risk, current medications, renal failure, liver failure, age, noncompliance with medication, PE risk, and DVT risk.

Conclusion

The investigation of aspirin preventing VTE will likely need to be further elucidated. The ACCP 2016 antithrombic guidelines provide a weak recommendation (2C) for aspirin as an alternative antithrombotic management in people with unprovoked VTE (Douketis, 2016). A Cochrane Review of six available randomized controlled trials which ranged from low to moderate quality concluded there is insufficient evidence due to the limited research available (Robertson, et. al., 2017). Another systematic review which consists of 16 moderate quality studies found no significant evidence between different oral prophylactic anticoagulation, including aspirin, for secondary prevention in patients following hip or knee surgery (Forster and Stewart, 2016). Although recent studies suggest aspirin's antithrombotic role in preventing reoccurrence of VTE, further research that is of longer duration, larger scale, and high quality will provide a definitive conclusion of aspirin's role in VTE management.

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Table 1: Anti-thrombic effects of Acetylsalicylic acid

Irreversibly inhibits cyclooxygenase-1 (COX-1) by acetylating Ser529
Suppresses the generation of prostaglandins H2
Inhibits thromboxane A2
Promotes fibrinolysis by acetylating fibrinogen
Inhibits platelet activation
Inhibits platelet aggregation
Inhibits the release of platelet factors, fibrinogen, thrombospondin, von Willebrand factor
Suppresses thrombin formation
Reduces coagulation factors in the liver

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Table 2: Recurrence rate of venous thromboembolism

	First Year	Annual rate after First Year
First episode of unprovoked VTE	10 %	5%
Second episode of unprovoked VTE	15%	7.5%

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