Anti-platelet agents in pediatric cardiac practice

Sweta Mohanty, Balu Vaidyanathan
Department of Pediatric Cardiology, Amrita Institute of Medical Sciences and Research Centre, Kochi, Kerala, India

ABSTRACT

Pediatric patients with a variety of congenital and acquired cardiac conditions receive antithrombotic therapy. Many of the indications are empirical, and have either not been proven in controlled studies or are extrapolated from adult studies. This article reviews the current available literature regarding the use of anti-platelet drugs in the pediatric cardiac population.

Keywords: Anti-platelet drugs, anti-thrombotic therapy, pediatric cardiac practice

INTRODUCTION

Pediatric patients with a variety of congenital and acquired cardiac conditions receive antithrombotic therapy. Many of the indications are empirical and have either not been proven in controlled studies or are extrapolated from adult studies. This article reviews the current literature available regarding the use of anti-platelet drugs in the pediatric cardiac population.

MECHANISM OF ACTION OF ANTI-PLATELET AGENTS

Injury to the vessel wall leads to adherence of platelets and activation of platelets. Platelet aggregation is coordinated by several signalling pathways. Adenosine diphosphate (ADP), for example, activates purinergic receptor P2Y12 and evokes morphological changes of platelets. Thromboxane A_2 activates prostaglandin/thromboxane receptors and induces platelet aggregation and vasoconstriction.[1] There is a conformational change in the platelet GPIIb/IIIa receptor favouring binding of fibrinogen, the formation of platelet aggregates and the formation of thrombin.[2] Various drugs act on different targets to interfere with platelet function [Figure 1].

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Aspirin irreversibly acetylates cyclooxygenase and thereby prevents formation of thromboxane A_2. Aspirin also affects other processes, such as coagulation and inflammation.[3]

Ticlopidine and clopidogrel are thienopyridines, which cause irreversible blockade of the ADP receptor (P2Y12) on platelet cell membranes. This inhibits platelet aggregation by interfering with platelet activation and fibrinogen binding. This pathway provides an antiplatelet effect that is additive to the inhibition of the cyclo-oxygenase pathway by aspirin.

Dipyridamole acts by inhibiting phosphodiesterase and blocking uptake of adenosine to increase platelet cAMP, which potentiates PG_{12} and interferes with aggregation.

Newer drugs include Glycoprotein IIb/IIIa receptor antagonists like abciximab inhibit the platetlet GP IIb/IIIa receptor directly, thereby blocking the final step in platelet

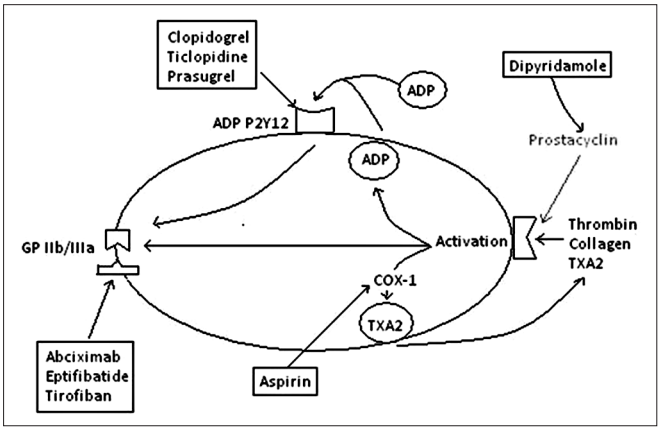

Figure 1: Mechanism of action of antiplatelet agents

Address for correspondence: Dr. Balu Vaidyanathan, Department of Pediatric Cardiology, Amrita Institute of Medical Sciences, Kochi, Kerala - 682 041, India. E-mail: baluvaidyanathan@gmail.com

aggregation. They are the most potent anti-platelet drugs currently available.

Pharmacokinetics

Pharmacokinetics of anti-platelet drugs in children is mostly extrapolated from adult studies. Aspirin is absorbed from the stomach and small intestines and rapidly deacetylated in the gut wall, liver and plasma, to release salicylic acid, the major circulating and active form. Aspirin acts by irreversible inhibition of thromboxane synthase. As platelets have no nuclei, after acetylation by aspirin, fresh enzyme cannot be synthesized. Thus aspirin mediated prolongation of bleeding time lasts for 5-7 days.

Ticlopidine and clopidogrel are prodrugs and are converted in the liver by cytochrome P_{450} enzymes to an active metabolite. Clopidogrel is hydrolyzed to clopidogrel carboxylate, and this metabolite does not have any therapeutic activity.[1] The active metabolite has an elimination half-life of about 8 hours.

Following an oral dose of Dipyridamole, plasma concentration is maximal after about 1-2 hours.[4] Dipyridamole is eliminated by hepatic biotransformation to monoglucuronide, which almost exclusively is subjected to biliary and faecal excretion.[5]

Abciximab is the Fab fragment of a chimeric monoclonal antibody against GpIIb/IIIa receptor. After a bolus dose, platelet aggregation remains inhibited for 12-24 hours, while the remaining antibody is cleared from blood with a half-life of 10-30 minutes.[6]

Dosage

Pediatric doses of aspirin are not based on studies of the effect on platelet function in children.[7] The dose of aspirin required for the optimal inhibition of platelet aggregation in pediatric patients is not known, although empiric low doses of 1-5 mg/kg/day have been proposed.[8]

Clopidogrel dose for children is not established. A dose of 1mg/kg/day was extrapolated from adult studies. In a single center retrospective study evaluating the safety and efficacy of clopidogrel in fourty six children with heart disease in a dose range of 0.1 to 0.7 mg/kg/day. Almost all patients received concomitant aspirin therapy. Skin bruising was reported by most patients. Nine patients permanently withdrew from treatment because of adverse events, including epistaxis, allergic reaction, hair loss, skin bruising causing parental concern, malena and haematological abnormalities like anemia and reduced white blood cell count. Two patients who were treated with concomitant warfarin had bleeding complications (severe epistaxis and gastrointestinal bleeding), and hematological abnormalities was documented in 1 patient.[9]

A prospective, multicenter, randomized, placebo-controlled trial evaluating the pharmacodynamics of clopidogrel in children by platelet aggregometry studies showed that clopidogrel at a dose of 0.20 mg/kg/day in children achieved a platelet inhibition level similar to that in adults taking 75 mg/day (mean 49.3% inhibition of 5-mcmol/l ADP–induced platelet aggregation), with no serious bleeding events.[10]

Dipyridamole has been used as an antiplatelet agent in children is in doses of 2-5 mg/kg/day. Ticlopidine is given in doses of 10 mg/kg/day; however, there are no data to support the use of this drug in children.[8]

Adverse effects

The clearance of aspirin is slower in neonates, potentially placing them at risk for bleeding for longer periods of time. An association between aspirin and 'Reye's syndrome', a rare form of hepatic encephalopathy has been noted.[6] Reye's syndrome is a risk in children who take salicylates during an episode of active infection with varicella or influenza and has been reported in patients taking high dose aspirin (>40 mg/kg) for a prolonged period after Kawasaki disease.

The most important adverse effect of clopidogrel is bleeding, which is increased when combined with aspirin.[6]

Contraindications

Aspirin is contraindicated in patients who are sensitive to the drug and in peptic ulcer, bleeding tendencies, in children suffering from chicken pox or influenza. Aspirin should be stopped 1 week before elective surgery.

Clopidogrel is contraindicated if there is hypersensitivity to the drug or any component of the product and in active bleeding.[11]

Interaction with drugs

Aspirin displaces warfarin, phenytoin and methotrexate from binding sites on plasma proteins and hence can increase the toxicity of these drugs. Its antiplatelet action increases the risk of bleeding in patients on oral anticoagulants.[6]

The concomitant use of ibuprofen antagonizes the irreversible platelet inhibition that is induced by aspirin; thus ibuprofen should be avoided in children with coronary aneurysms taking aspirin for its antiplatelet effects.

INDICATIONS AND CLINICAL EVIDENCE

Systemic to pulmonary artery shunt

Systemic to pulmonary artery shunts can undergo shunt thrombosis in the interim period prior to second stage palliative or definitive repair and can result in sudden death. Antiplatelet therapy has variably been used to prevent shunt thrombosis in such cases.

In an early retrospective study, Motz, *et al.*, studied the impact of aspirin therapy in thirty seven infants with systemic-to-pulmonary arterial shunt. Partial or complete occlusion of the shunt occurred in 2 of 15 (13%) infants taking aspirin, but occurred in 12 of 22 (54%) infants in whom aspirin was discontinued or not given. Of these, 3 died due to acute occlusion of the shunt.[12]

In a large prospective multicenter study including 1004 infants who underwent systemic to pulmonary artery shunts, after the exclusion of patients with early mortality, patients receiving aspirin were shown to have a lower risk of shunt thrombosis (hazard ratio, 0.13; $P = 0.008$) and death compared with those not receiving Aspirin.[13]

A recent randomized trial (CLARINET) to evaluate the efficacy of clopidogrel in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary shunt showed no significant benefit of clopidogrel use in reducing all cause mortality and shunt related morbidity.[14]

Kawasaki disease

During the acute phase, Kawasaki disease (KD) may cause medium and large vessel arteritis and aneurysms. Coronary artery aneurysms or ectasia may lead to myocardial infarction, sudden death or chronic coronary arterial insufficiency.[15,16]

High dose aspirin (80-100 mg/kg/day) is traditionally administered in patients with KD in the acute phase for its anti-inflammatory effect[17] However recent data suggests that Aspirin therapy in the acute phase may not have an incremental benefit over intravenous immunoglobulin therapy.[18]

A Cochrane review to evaluate the effectiveness of salicylate in treating and preventing cardiac consequences of Kawasaki disease in children identified only one randomized controlled trial. In this study, a total of 102 children were randomized to receive intravenous immunoglobulin (IVIG) with or without salicylate therapy; on follow up, no association between the addition of ASA to IVIG treatment on the rate of coronary artery abnormalities was reported.[19]

Low dose aspirin (3-5 mg/kg/day, given as a single dose) has an antiplatelet effect and should be continued until 6-8 weeks after disease onset if there are no or transient coronary artery abnormalities (Risk Levels I and II) or indefinitely if abnormalities are present (Risk levels III to V).[17] Adjunctive therapy with warfarin is recommended for patients with giant aneurysms.[20]

Primary prophylaxis for Fontan surgery in children

Thromboembolic events (TE) are a major cause of morbidity and mortality following the Fontan procedure. Prevalence of venous thromboembolism after Fontan operation ranges from 3-16% and that of stroke or arterial thrombi is 3-19%, with higher rates in more recent studies.[21] There is no consensus in literature as to the optimum type and duration of antithrombotic therapy after Fontan operation. The American College of Chest Physicians (ACCP) recommend therapy with aspirin (1-5 mg/kg/day) or therapeutic heparin followed by vitamin K antagonists to achieve a target (INR) of 2.5 (INR range, 2-3).[8]

Jacobs, *et al.*, assessed the impact of Aspirin in reducing thromboembolic events after Fontan operation, initiating aspirin therapy from the first post-operative day. On followup (mean duration fourty months amounting to 2,882 patients months), there were no documented thromboembolic events, hemorrhagic events or aspirin-related complications. It was concluded that low dose aspirin can be used safely and effectively in Fontan patients, and more aggressive anticoagulation may be unwarranted.[22]

In a systematic review and meta analysis of twenty studies involving 1075 patients, Marrone, *et al.,* reported no significant difference in the prevalence of overall thromboembolic complications between patients receiving anticoagulation therapy compared with those on antiplatelet therapy after extracardiac Fontan operation.[23]

A recent multicenter, randomized trial showed comparable results with respect to thromboembolic episodes between ASA and heparin/warfarin groups.[24]

Prosthetic heart valves

Aspirin may be used in combination with oral anticoagulants for prevention of systemic thromboembolism or valve thrombosis, particularly in patients who have additional risk factors such as systemic embolism.

In a meta analysis of eleven randomized clinical trials that involved 2428 patients, combination therapy with an oral anticoagulant and anti-platelet agent (either aspirin or dipyridamole) was associated with a significant reduction in thromboembolic event rates (relative risk reduction of 42% for thromboembolism and 58% for mortality) compared to monotherapy with oral anticoagulants alone. Major bleeding events increased significantly with combination therapy.[25]

Intracardiac devices or stents

Antiplatelet medications may be administered for several months in patients after transcatheter closure of atrial septal defect, until endothelialisation of blood exposed parts is complete. Most trials have used aspirin alone or aspirin along with clopidogrel or ticlopidine for duration of 6 months post-procedure.[26]

In a restrospective review of twenty four patients who received aspirin after hybrid pulmonary artery stent

implantation, no episode of stent thrombosis was reported over a mean follow up period of nineteen months.[27]

Dilated cardiomyopathy

Low cardiac output, poor contractility and concomitant atrial fibrillation predispose to thromboembolic events (TE) in patients with dilated cardiomyopathy. Most studies have been performed in adults with heart failure and pediatric data is lacking.

A 2002 Cochrane systematic review found no evidence from long term randomized controlled trials (RCTs) to recommend use of aspirin to prevent thromboembolism in patients with heart failure in sinus rhythm.[28]

Arterial ischemic stroke

Childhood Arterial ischemic stroke (AIS) is rare and common etiologies include sickle cell disease, congenital heart disease, arterial dissection, prothrombotic conditions, preceding viral infections or idiopathic.[29] There is a paucity of data supporting current treatment approaches in childhood AIS.[30] As recurrent stroke is very rare after AIS in the neonatal period, ACCP recommend against anticoagulation or aspirin therapy for neonates with a first episode of AIS. For children with non–sickle-cell disease related acute AIS, ACCP recommends unfractionated heparin or low molecular weight heparin or aspirin (1-5 mg/kg/day) as initial therapy till dissection and embolic causes have been excluded and daily aspirin prophylaxis (1-5 mg/kg/day) for a minimum of 2 years once these causes are excluded.[8]

Other uses

Antiplatelet agents have been used with left ventricular assist device.[31] There is no standardized antithrombotic regime; however, based on adult data and to prevent circuit occlusion or embolic complications, anticoagulant therapy in combination with antiplatelet therapy has been preferred over no therapy.[8]

Antiplatelet agents have also been used for treatment of vasculitis in children and adolescents, such as in Takayasu disease.[32,33]

Randomized control trials in pediatric cardiac practice

Role of acetylsalicylic acid in primary thromboprophylaxis after the Fontan procedure

A multicenter international randomized trial of primary prophylactic anticoagulation after Fontan surgery compared the safety and efficacy of acetylsalicylic acid (ASA) and warfarin for thromboprophylaxis after the Fontan procedure. One hundred eleven patients were randomized to receive either ASA (5 mg/kg/day, no heparin phase) or warfarin (started within 24 hours of heparin lead in; target international normalized ratio 2.0-3.0) for a period of 2 years. There were thirteen thromboembolic events in the heparin/warfarin group and twelve events in the ASA group. Overall freedom from thrombosis 2 years after Fontan surgery was 19%, with no significant difference between ASA and heparin/warfarin groups. This data suggests that both thromboprophylaxis strategies were suboptimal in Fontan patients and alternative approaches may need to be considered in this subset of patients.[24]

Dosing of clopidogrel for platelet inhibition in infants and young children trial

This was a prospective, multi-center, randomized, placebocontrolled trial enrolling one hundred sixteen patients with a cardiac condition at risk for arterial thrombosis. Ninety two patients were randomized to receive either clopidrogel or placebo; seventy three patients completed the study. Compared with placebo, clopidrogel in a dose of 0.20 mg/kg/day resulted in a mean 49.3% inhibition of the maximum extent of platelet aggregation and a mean 43.9% inhibition of the rate of platelet aggregation. No serious bleeding events occurred. The trial concluded that Clopidogrel 0.20 mg/kg/day in children 0-24 months of age achieves a platelet inhibition level similar to that in adults taking 75 mg/day and is well tolerated in infants and young children at this dose.[10]

Efficacy and safety of clopidogrel in neonates/ infants with systemic to pulmonary artery shunt palliation trial

In this multi-center, randomized controlled trial was conducted to determine whether the addition of clopidogrel, 0.2 mg/kg/day, reduces all cause mortality and shunt related morbidity in infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt.[14] Nine hundred six infants were randomly assigned to receive clopidogrel (467 patients) or placebo (439 patients) in addition to conventional therapy (88% received concomitant aspirin therapy). There was no significant difference in the primary composite endpoint (death, shunt thrombosis or a cardiac procedure before 120 days of age following an event considered of thrombotic nature) between the Clopidogrel and placebo groups (19.1% vs. 20.5%; $P = 0.43$). Post-traumatic and surgical bleeding tended to be more common in the clopidogrel group[14]

Newer agents

GP IIb/IIIa antagonists, a new class of potent platelet aggregation inhibitors, are chemeric monoclonal antibody fragments (abciximab), peptides (eptifibatide) or non peptide small molecules (tirofiban), which act by binding to platelet surface GPIIb-III a receptor.[6]

Abxicimab has been used to treat patients with Kawasaki disease who have large coronary aneurysms not

responding to standard therapy. Abciximab in addition to standard therapy has demonstrated greater regression in coronary aneurysm diameter compared to patients receiving standard therapy alone[20,34,35] suggesting that abciximab treatment might be associated with favourable vascular remodelling in patients with large coronary artery aneurysms.

CONCLUSIONS

Aspirin continues to be the most widely used anti-platelet agent in the pediatric age group for a variety of indications. Though preliminary data with newer anti-platelet agents have shown their safety in the pediatric age group, more data are required for their use in the pediatric age group.

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