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Nitroglycerin and Sodium Nitroprusside: Potential Contributors to Postoperative Bleeding?

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ABSTRACT

Postoperative bleeding is common in patients undergoing cardiac surgery with cardiopulmonary bypass. Most cases of severe postoperative bleeding not due to incomplete surgical hemostasis are related to acquired transient platelet dysfunction mediated by platelet activation during contact with the synthetic surfaces of the cardiopulmonary bypass equipment. Antihypertensive agents nitroglycerin and sodium nitroprusside have been shown to have platelet inhibitory properties, yet the clinical consequence in terms of postoperative bleeding has been little studied. Knowing that cardiopulmonary bypass causes platelet dysfunction, it is prudent for physicians to be aware of the additional platelet inhibition caused by these commonly used antihypertensive agents.

INTRODUCTION

Postoperative blood loss is a common complication in patients undergoing cardiac surgery with cardiopulmonary bypass. A recent large prospective randomized controlled trial evaluating transfusion requirements after cardiac surgery found that the number of packed red blood cell (PRBC) units transfused after cardiac surgery was an independent risk factor for worse outcomes, including mortality [Hajjar 2010]. Overall, 30% of patients receive postoperative PRBC transfusions [Karkouti 2001], and severe bleeding, classified as requiring greater than 10 units of PRBCs, occurs in 3% to 5% of patients [Woodman 1990]. Antifibrinolytic agents, platelet transfusions, fresh frozen plasma, cryoprecipitate, and desmopressin have been employed to decrease blood loss and correct coagulation abnormalities [Harker 1980]. Among patients with severe postoperative bleeding not due to incomplete surgical hemostasis, most cases are related to acquired transient platelet dysfunction [Czer 1989], which is mediated by platelet activation during contact with the synthetic surfaces of the cardiopulmonary bypass equipment as well as perioperative thrombin generation [Czer 1989; Karkouti 2001]. Antihypertensive agents nitroglycerin (NTG) and sodium nitroprusside (SNP) are often used intraoperatively and postoperatively for blood pressure control in patients undergoing cardiac surgery. Each of these agents has been shown to demonstrate platelet inhibitory properties, yet the clinical consequence in terms of postoperative bleeding is not known. Knowing that cardiopulmonary bypass causes platelet dysfunction, it is prudent for physicians to be aware of the additional platelet inhibition caused by these commonly used antihypertensive agents. The aim of this review is to outline the existing scientific evidence demonstrating the mechanism and clinical implications of platelet inhibition by NTG and SNP.

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METHODS

Data were compiled using the PubMed electronic database using the search terms "nitroglycerin," "sodium nitroprusside," "platelet inhibition," "bleeding," and "perioperative hypertension." References from review articles were reviewed for relevant publications. The last search was completed in July 2011. Only published literature in peer-reviewed journals was considered for inclusion in this review. Personal communications, manuscripts in preparation, or other unpublished data were not included.

NORMAL PLATELET FUNCTION

Damage to the vascular endothelium results in a series of biological events termed primary hemostasis, which involves the interaction of platelets and the coagulation cascade. The role of platelets in primary hemostasis is the formation of a hemostatic plug at the site of endothelial damage, which then interacts with the coagulation cascade to create a stabilized clot. The hemostatic plug is formed by 3 subsequent platelet actions: adhesion, activation, and aggregation. Damaged endovascular endothelium exposes collagen, which mediates the adhesion of numerous platelet receptors to various arterial wall receptors. Following adhesion, activation occurs, resulting in platelet shape change and degranulation of storage granules, releasing vasoactive substances that aid in recruiting

additional platelets to the site of injury. Platelet aggregation is the final step in forming the platelet hemostatic plug as fibrinogen links platelets together, forming aggregates. Once formed, the platelet plug interacts with the coagulation cascade to incorporate fibrin into the clot in order to provide stabilization for vascular remodeling [Parise 1979].

PLATELET INHIBITION BY NITROGLYCERIN

Since the 19th century, NTG has been used as an antianginal agent [Murrel 1979], and over time its use has evolved to include therapy for congestive heart failure [Helfant 1976; Taylor 1976], hypertensive emergency [Rhoney 2009], reduction of infarct size from acute myocardial infarction [Epstein 1975], and blood pressure reduction during coronary artery bypass [Kaplan 1976] or general [Fahmy 1981] surgery [Hill 1981]. Studies have shown that the perioperative use of intravenous NTG is independently associated with an increase in 30-day mortality rates in patients undergoing coronary artery bypass graft surgery (CABG) [Shroyer 1999], the reason for which could not be delineated by the study. Research has demonstrated NTG to have platelet inhibitory properties, but the clinical relevance, particularly when used in cardiac surgery, is not as well studied.

NTG is metabolized to nitric oxide (NO), which generates cyclic guanosine monophosphate (cGMP) [Chen 2002] that results in the dilation of veins, arteries, and coronary arteries by causing relaxation of vascular smooth muscle [Abrams 1998]. The increased level of cGMP produced by NO is the mechanism by which NTG inhibits platelet activation [Gries 1998]. Inhibiting calcium-mediated responses, reducing platelet P-selectin expression [Gries 1998], and modulating prostaglandin synthesis [Mollace 2005] are also thought to play a role in NTG's inhibitory effect on platelet function.

The inhibition of platelet function by NTG was initially shown by in vitro studies that demonstrated inhibition of agonist-induced platelet aggregation [Hampton 1967] in a dose-dependent manner [Schafer 1980], but the inhibitory doses in vitro were much higher than those used clinically. Subsequently, Loscalzo demonstrated NTG to inhibit platelet aggregation at pharmacologically achievable concentrations in vivo, therefore giving NTG's antiplatelet effect clinical relevance [Loscalzo 1985]. In addition to inhibiting platelet aggregation, NTG has been shown to inhibit other prothrombotic platelet functions. In the presence of deep arterial wall injury, Lam et al demonstrated that NTG given intravenously at a dose sufficient to lower mean arterial pressure by 9% significantly decreased platelet adhesion to the mechanically injured endothelium. These experiments also showed that intravenous NTG not only decreased platelet adhesion, but also blunted the vasoconstrictive response to arterial wall injury as measured by the percent diameter narrowing on angiography. Lam's work was the first reported in vivo effectiveness of NTG in the reduction of platelet deposition after deep arterial wall injury [Lam 1988]. In other work demonstrating the potential in vivo relevance of these platelet inhibitory mechanisms, Folts et al examined the effect of intravenous nitroglycerin infusion on periodic platelet thrombus formation in stenotic canine coronary arteries. The results showed that administration of 10 to 15 mg/kg per minute of nitroglycerin reduced platelet thrombus formation significantly and did so without a significant change in coronary artery blood flow. These results led to the conclusion that one mechanism by which intravenous nitroglycerin improves ischemia in acute coronary artery syndrome may be as much by inhibition of platelet thrombus formation as by dilation of diseased stenotic coronary arteries [Folts 1991].

Since there is evidence that intravenous NTG provides a mortality benefit in acute myocardial infarction (AMI) [Yusuf 1988], many of the existing clinical studies have focused on the potentially beneficial effects provided by the platelet inhibition of NTG. In a study of 40 patients with AMI or unstable angina (UA) who were initially given aspirin, platelet receptor expression was measured before and after administration of NTG. The findings showed that platelet activation persists in AMI and UA despite aspirin treatment and that this can be inhibited by the use of NTG [Langford 1996]. A different study involving 10 patients with AMI or UA quantified platelet aggregation response before, during, and after a 45-minute infusion of NTG and documented significant and reversible platelet inhibitory effects using bedside platelet aggregation assays [Diodati 1990]. In regards to stable angina pectoris, Diodati et al showed that rapid atrial pacing in patients with stable coronary artery disease causes platelet hyperaggregability during blood passage in the coronary circulation and that this platelet activation can be blunted with pretreatment doses of intravenous NTG and SNP, therefore demonstrating that these drugs inhibit platelet function during stable angina pectoris [Diodati 1995]. A protocol was designed to evaluate whether these antiplatelet effects could be detected using transdermal NTG. In a randomized, double-blinded, controlled parallel trial, 22 patients received transdermal NTG (0.6 mg/h) or placebo, and platelet aggregation and thrombus formation were assessed. The results showed that transdermal NTG significantly inhibits platelet aggregation and mural thrombus formation in patients with angina pectoris, documenting the transdermal formulation of NTG to have the same antiplatelet properties [Locoste 1994]. Langford et al showed that despite routine pretreatment with aspirin, nitroglycerin, and heparin, percutaneous coronary angioplasty (PTCA) causes an increase in platelet activation as measured by an increase in platelet surface expression of P-selectin and glycoprotein IIb/IIIa. This study showed that giving an additional NO donor medication significantly inhibited the PTCA-induced increase in platelet surface expression of P-selectin and glycoprotein IIb/IIIa [Langford 1994]. Evidence clearly exists to support the use of NTG when platelet inhibition is desirable, but the consequences of platelet inhibition when this effect is not ideal are less well documented.

The phenomenon of vascular tolerance to NTG has long been known [Abrams 1986], with reports indicating that tolerance can be demonstrated within the first 12 hours after administration of sustained concentrations of NTG [Elkayam 1987]. Using porcine aortic media, one study observed the antiplatelet effect of NTG in the presence of hemodynamic

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tolerance. After 48 hours of continuous transdermal NTG therapy, mean arterial pressure returned to baseline, yet platelet aggregation and platelet deposition remained decreased. This study demonstrated the dissociation between hemodynamic tolerance and persistent platelet inhibition, and it is now known that the use of NTG may provide less than maximal hemodynamic efficacy over time yet still result in decreased platelet function [Hebert 1997]. It is especially important to be aware of this phenomenon in those patients who are nonresponders to NTG or who develop early hemodynamic tolerance to the drug because they would not be receiving the intended effect of vascular relaxation while still receiving the platelet inhibitory effect.

NTG has been shown to prolong bleeding time. In a study of healthy males aged 25 to 40 years of age, bleeding time was prolonged when measured 6 minutes after the administration of 0.5 mg NTG sublingually. Interestingly, this study found that the administration of aspirin inhibited the effect of NTG on bleeding time, which indicated that NTG's effect on bleeding time may be mediated by prostacyclin rather than a general inhibition of platelet aggregation [Ring 1983]. A dose-related prolongation of bleeding time correlating with a drop in blood pressure was shown in a study of 17 patients receiving intravenous NTG for blood pressure control during coronary artery bypass surgery. Platelet function was not affected in this particular experiment, leading the authors to speculate that the increased bleeding time may be attributed to vasodilation and increased venous capacitance, proposing the idea that a dilated vessel would require larger platelet aggregates [Lichtenthal 1985]. A possible methodological dilemma with this study is that peripheral venous blood samples were used for testing, which may not represent the overall systemic blood samples and could be the reason the study was unable to demonstrate a correlation between change in platelet function and prolongation of bleeding time. Though bleeding time is the traditional in vivo assay to evaluate platelet function, it is not the ideal endpoint by which a platelet-inhibiting drug should be evaluated for bleeding risk. In a comprehensive review of 862 articles, Rodgers and Levin state that bleeding time is affected by a large number of diseases, drugs, physiologic factors, test conditions, and therapeutic actions (not all of which are platelet related) and that the test is poorly reproducible, insensitive, and not able to predict accurately abnormal bleeding in surgical patients [Rodgers 1990]. Further studies using advanced techniques to test platelet function are needed, as well as prospective randomized data evaluating the bleeding risk of therapy with perioperative NTG.

PLATELET INHIBITION BY SNP

SNP acts directly on vascular smooth muscle producing venous and arterial vasodilation [Friederich 1995]. Once infused, SNP immediately dissociates, releasing cyanide and NO [Smith 1974; Ivankovich 1978]. The released NO acts in the same fashion as previously described, producing vasodilation by increasing cGMP levels [Mocada 1991], which also results in platelet inhibition [Mollace 2005]. NTG contains a nitrate group, and SNP contains a nitrosyl group [Friederich 1995]. Despite these molecular differences, the functional result pertinent to this discussion is the same: release of NO with subsequent inhibition of platelet function. Acknowledging that the mechanism of platelet inhibition is the same for both SNP and NTG [Loscalzo 1992], it is reasonable to use the aforementioned evidence to suggest that the platelet inhibitory effects of SNP might be similar. Indeed, there are studies looking specifically at the platelet inhibitory effects of SNP. Initially, SNP was shown to decrease platelet aggregation in vitro. These studies demonstrated that SNP inhibits adenosine diphosphate, epinephrine, and collagen-induced platelet aggregation [Glusa 1974; Saxon 1976]. Similar to early experiments with NTG, these in vitro studies lacked physiologic relevance because the dosages of SNP used were considerably higher than those used clinically. However, in the same landmark experiment looking at NTG by Loscalzo et al, SNP was shown to inhibit platelet function at pharmacologically achievable concentrations in vivo [Loscalzo 1985]. Pharmokinetically, Anfossi and colleagues defined the dose- and time-dependent effects of SNP showing inhibition of platelet response lasting for hours after drug exposure [Anfossi 2001].

In a prospective study of patients undergoing cardiac surgery requiring cardiopulmonary bypass, the effect of SNP on platelet function and bleeding time was measured. Nineteen patients received SNP as clinically indicated to maintain a mean arterial blood pressure of 80 mmHg, and 10 patients served as a control population, receiving 30 mg/kg of fentanyl anesthesia without SNP. Any patient receiving preoperative medication known to interfere with platelet function was excluded from the study. The results showed a significant dose-related reduction in platelet aggregation that was accompanied by a concomitant increase in bleeding time. Platelet aggregation and bleeding time studies performed in the control group did not show any deviation from the baseline [Hines 1989]. Two studies were conducted that compared the use of SNP with nicardipine for induced hypotension during surgery. One study demonstrated SNP to cause significantly more blood loss than nicardipine. Although the study was not designed to determine the reason for differences in blood loss, the authors hypothesized that the greater blood loss seen with SNP might be attributed to the antiplatelet properties of SNP [Hersey 1997]. A similar study showed no difference in blood loss or need for transfusion between the 2 drugs, and it was therefore concluded that SNP's effect on platelet aggregation produces no increase in blood loss compared with nicardipine [Lustik 2004]. Since nicardipine alone has been reported to have some platelet inhibitory properties of its own [Yamada 1989], this study comparing bleeding complications of nicardipine and SNP did not examine how SNP affects bleeding complications when compared to control.

CONCLUSION

Intraoperative and postoperative hypertension is reported to occur in up to 61% of patients undergoing cardiac surgery [Whelton 1980], which is likely due to the physiologic

response to cardiopulmonary bypass causing increased plasma levels of catecholamines, glucocorticoids, and antidiuretic hormone [Stanley 1980]. Perioperative hypertension has been associated with stroke, renal dysfunction, perioperative MI, and increased mortality, though these findings have often been retrospective, using a small sample size lacking statistical power [Levy 2007]. Therefore, there are few formal guidelines for choosing antihypertensive agents, thresholds for initiation of treatment, and goals of treatment, and there is significant variability in selecting the optimal perioperative antihypertensive agent [Vuylsteke 2000].

Among the many choices, NTG and SNP are commonly used to control perioperative hypertension. Certainly the use of these agents may be beneficial in reducing postoperative blood loss because postoperative hypertension has been associated with surgical bleeding [Viljoen 1976]. Additionally, there are interesting data that suggest that inhibiting platelets during the course of cardiopulmonary bypass may attenuate the potential for bleeding by preserving platelet function [Bernabei 1995; Suzuki 1998]. The fact remains that the effects of these medications on postoperative bleeding is largely unknown. This review outlines current evidence demonstrating that NTG and SNP inhibit platelet function in a clinically relevant manner, which is important to take into consideration when giving these medications to patients undergoing cardiopulmonary bypass, a procedure itself known to cause platelet dysfunction. The relevance of this data is of particular importance given the availability of alternative antihypertensive agents, which do not have documented platelet inhibitory properties. With further studies, it may be shown that other antihypertensive agents without the platelet inhibitory properties of NTG and SNP result in less postoperative bleeding or lessen the requirements for antifibrinolytic agents, platelet transfusions, fresh frozen plasma (FFP), cryoprecipitate, and desmopressin, each of which may have negative consequences for patients treated with these agents.

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