

Peri-operative aspirin can prevent post-operative ischemia and thrombosis

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Summary Of the 30 million patients in the USA who undergo non-cardiac surgery every year, approximately 1.5 million suffer post-operative cardiovascular events. Surgical trauma and associated catecholamine release leads to platelet activation in the immediate post-operative period, as evidenced by a rise in circulating platelet release products. Platelet activation promotes platelet aggregation and hypercoagulability. Aspirin is widely used for its platelet inhibiting effects to prevent myocardial infarction and stroke. However, aspirin is not routinely started in the immediate peri-operative period, and even in high-risk patients already taking aspirin, aspirin is generally discontinued before elective surgery to improve intra-operative hemostasis. The risk-to-benefit ratios of administering vs withholding aspirin in the immediate peri-operative period have never been assessed and compared. We hypothesize that aspirin given pre-, intra- or immediately post-operatively will reduce post-operative ischemia and thrombotic events, including myocardial infarction and stroke, and that risk-benefit analysis would favor the administration of aspirin. This hypothesis can and should be tested in a prospective, randomized trial. © 2000 Harcourt Publishers Ltd

HYPOTHESIS

We propose that pre-, intra-, or immediate post-operative aspirin can be used to prevent intra- and post-operative platelet activation that contributes to ischemic and thrombotic events, and that the risk/benefit ratio of administering aspirin is more favorable than the current practice of withholding it.

RATIONALE

Cardiovascular, cerebrovascular, and thrombotic events are relatively common in the post-operative period in high-risk patients, despite all efforts to assess and

mitigate risk pre-operatively (1–3). Platelet activation is an important contributor to such events as evidenced by the role of platelets in thrombus formation, and the increase in platelet activation products measurable in serum during and following surgery (4). The utility of aspirin in platelet inhibition, and thereby in the prevention of ischemic events, has been well established in other settings. However, the standard practice at present is to withhold or discontinue aspirin pre-operatively to improve intra-operative hemostasis (5,6). The risks and benefits of this practice have never been formally compared to alternatives.

BURDEN OF SUFFERING

Approximately, 30 million patients undergo non-cardiac surgery every year in the USA (2,3). Of these, approximately 1.5 million patients suffer peri-operative cardiovascular morbidity, while many others suffer from transient cerebral ischemia or stroke, deep venous thrombosis (DVT) or pulmonary embolism (PE) (2,3). Overall,

Received 9 July 1999

Accepted 18 October 1999

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about 1.6–18% of patients undergoing non-cardiac surgery will suffer myocardial ischemia or infarction (2,7,8). The annual cost associated with these events exceeds \$20 billion (2,3).

Although studies published before 1980 showed a peak in the risk of myocardial infarction (MI) on about the third postoperative day (9), more recent series show that a combination of frequent electrocardiograms and cardiac enzymes including both CK, CKMB and cardiac Troponin detect many non-Q wave myocardial infarctions in the first 24 hours post-operatively (10–14). Myocardial oxygen demand and supply imbalances might explain early post-operative non-Q wave MIs, whereas platelet activation and hypercoagulability may account for a later peak in Q-wave infarction (10–14).

PLATELETS IN THE PERI-OPERATIVE PERIOD

Role of platelets in coronary thrombosis

Coronary atherosclerosis underlies virtually all acute MIs. The initiating event is a crack or fissure in the diseased arterial wall, which occurs as a result of loss of integrity of the fibrous cap overlying the plaque and partitioning of the atheroma from the arterial lumen (15). The fissure, or even frank plaque rupture, leads to exposure of sub-endothelial matrix elements such as collagen, stimulating platelet activation and thrombus formation (16). Furthermore, tissue factor which directly activates the extrinsic coagulation cascade and promotes the formation of fibrin, is released with arterial injury (16).

The thrombus that occludes the coronary artery is a mixture of white (platelet rich) and red (fibrin and erythrocyte rich) clot. The proportional contribution from platelet or fibrin in individual patients may differ (17). In some patients, there is a more dominant role of platelets, while in other predominantly fibrin-rich thrombus at the arterial injury site is found. The mural thrombus in patients without ST-segment elevation during MI is more apt to be platelet-rich, and not accompanied by stagnation as there is not sustained cutoff of coronary blood flow. Depending on the extent and duration of ischemia, the patient may or may not suffer any myocardial necrosis (unstable angina) or develop myocardial damage (non-ST segment elevation or non Q-wave infarction) (17,18).

Evidence of platelet activation during postoperative period – platelets physiology during and after surgery

There is a tendency towards thrombocytopenia both in the intra-operative period, and in the immediate post-operative period up to 1–3 days. This is followed by a thrombocytosis with a maximum level reached at 1–2 weeks after surgery (19). Other cell lines are affected as

well. Following surgical procedures, leukocytosis is prominent and the total white cell count returns to normal by the fifth post-operative day (20). Platelets and eosinophils show a similar response, with a pronounced decrease during and immediately after surgery, followed by a brief return to normal levels, then thrombocytosis and eosinophilia, with gradual return to pre-operative levels. This pattern is attributable to neurohormonal responses of the pituitary–adrenal axis to surgical stress. Postoperative thrombosis may be the result in part of the sudden and pronounced thrombocytosis (20).

Many studies confirm that the platelet count drops during and after surgery with a tendency to increase post-operatively, but these studies provide little information about platelet function (21). A drop in platelet count early in the post-operative period is at odds with the observation of highest risk of myocardial ischemia on about the third post-operative day. This pattern suggests that platelet activation and the fall in platelet count occur concomitantly. The homeostatic effects of surgery are not limited to platelets. The level of factor VIII (anti-hemophilic factor) increases in the post-operative state with maximal values obtained 1–15 days after surgery. The high level of factor VIII correlates with high fibrinogen concentration (22). Moreover, factor IX and factor XI also show a modest increase in levels in the first few days after surgery (22). The proportion of peri-operative cardiovascular events attributable to platelets or coagulation factor changes is not known. Both platelets and the coagulation cascade may be involved in the pathogenesis of post-operative ischemic events.

Evidence of platelet activation

The peri-operative increase in release products is proxy evidence of platelet activation in response to the physiological stress of surgery. Naesh et al. (4) studied the plasma concentration of beta-thromboglobulin (B-TG), thromboxane B₂ (TXB₂), 5-hydroxytryptamine (5-HT), intraplatelet 5-HT, serum cortisol and ADP induced platelet aggregation in ten patients undergoing elective cholecystectomy pre-, intra-, and post-operatively. They observed a highly significant increase in platelet release products during surgery. The increase in plasma levels of TXB₂, B-TG and 5-HT was closely related to the surgical stress, showing a peak concentration one to two hours after skin incision. Serum cortisol concentration was used as an index of the stress response, showing intraoperative increase and post-operative decrease. In the postoperative days P-TXB₂ and P-B-TG decrease to pre-operative levels in the clinically uncomplicated patients. Plasma 5-HT remain elevated with a tendency to increase during the postoperative period. Negatively correlated to this increase, platelet 5-HT decreases and this is taken as

evidence that the increased Plasma -5-HT may come from the activated platelets. This is in accordance with earlier observations by Shuttleworth et al. (23). The decrease in circulating platelet count during surgery, as noted by Naesh et al., and described in detail in the above section, results from intraoperative consumption of platelets (24,25).

Catecholamines may be involved in platelet activation. Plasma concentration of norepinephrine and epinephrine are known to increase significantly during major surgery (26–29), although other activating factors may be involved. Surges of epinephrine may have an important role in both plaque rupture and platelet activation. Sudden increases in the rate of MI during periods of acute stress (30,31) have been attributed to stress-induced catecholamine release. Release of epinephrine might provide an explanation for higher perioperative MI s in patients undergoing surgery under general anesthesia (26), while several studies have demonstrated the beneficial effect of beta-adrenergic blockers in reducing perioperative ischemia and MI (32).

Role of aspirin in coronary thrombosis

Aspirin prevents platelet aggregation by inhibiting platelet synthesis of cyclooxygenase A2. Because platelets are unable to generate new cyclooxygenase, inhibition of the enzyme lasts the lifetime of the cell (about 10 days). In the vascular endothelial cells aspirin prevents the synthesis of prostacyclin, which prevents platelet aggregation and acts as a vasodilator. However, because endothelial cells can recover cyclooxygenase synthesis, the inhibitory effect of aspirin may be of shorter duration.

A number of large trials have confirmed the beneficial effect of aspirin in patients with different cardiovascular disorders. Aspirin has demonstrated its usefulness in several trials in patients with unstable angina (33–36), acute myocardial infarction, (ISIS-2 Collaborative Group 1988–aspirin alone, ISIS-2 Collaborative Group 1988–aspirin with thrombolytic therapy) secondary prevention of acute myocardial infarction (37–40); primary prevention of MI (41); prevention of acute occlusion and myocardial infarction in patients undergoing percutaneous transluminal angioplasty (40,42) aortocoronary saphenous vein graft surgery (43,44); and reduction in the incidence of stroke in patients with transient ischemic attacks and in those with nonvalvular atrial fibrillation (45).

RESEARCH IMPLICATIONS

Although better anesthetic and improved monitoring technology have lowered the incidence of peri-operative cardiovascular events, such events are far from rare in high risk patients (2,7). Recent work supports routine use

of peri-operative beta-blockade (atenolol) in reducing death and cardiovascular complications (46). However, platelet activation is not specifically targeted during the peri-operative period and in fact, patients are instructed to stop their aspirin one-week prior to major surgery. Often these are the very patients, who are at the highest risk for cardiac events. Fear of excessive bleeding during surgery has resulted in this practice (5,6,47), despite a lack of evidence (5,47) and no reported study to date of alternative aspirin protocols that might reduce post-operative ischemia, while avoiding intra-operative complications of impaired hemostasis.

CONCLUSION

Surgical stress activates platelets which play an important role in the pathogenesis of post-operative ischemic and thrombotic events. The risk of such events could be reduced by the peri-operative use of aspirin. Further, if aspirin were administered intravenously at the close of surgery, platelet inhibition would begin immediately post-operatively, without compromising intra-operative hemostasis. The same effect could be achieved with aspirin suppository pre- or intra-operatively. We propose to study the risk/benefit ratio of peri-operative aspirin vs placebo in surgical outcomes among high risk patients.

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