REVIEW ARTICLE

The Perioperative Effects of Statins in Non Cardiac Surgeries

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Background: Statins (3-Hydroxy-3-methylglutarylcoenzyme-A (HMG-CoA) reductase inhibitors) decrease cardiovascular mortality and morbidity. This article reviews the role of perioperative statins in non cardiac surgery.
Methods: A literature review was done on all English published articles till February 2015 about this subject using pubmed. Then the reference list of relevant articles was reviewed for additional resources.
Results: Current evidence shows that not only statins decrease perioperative morbidity and mortality in patients undergoing non cardiac surgery, but also they seem safe during perioperative period.
Conclusion: A properly designed randomized control trial should be performed to assess the perioperative benefits of statins in non cardiac surgery.
keywords: statins; non cardiac surgery; perioperative periods

Vascular complications are one of the most common reasons of perioperative morbidity and mortality, especially in vascular surgery field [1]. The prevalence of vascular complications is 5.6% in non-cardiac surgeries [2]. Myocardial infarction [3], ventricular arrhythmias [4], pulmonary edema [3] and atrial fibrillation [5], are the main causes of perioperative morbidity and mortality in patients with major elective noncardiac operations. Perioperative myocardial infarction (MI) and acute coronary syndromes are the most common cardiac complications happening especially after cardiothoracic surgery. The incidence of perioperative MI among patients undergoing major non-cardiac surgery is 2-3 % [6], but this can reach to 34% in major vascular surgeries [7]. Perioperative MI is associated with longer hospital stay and mortality rate is as high as 25-40 % [8].

The exact nature of perioperative MI and whether it is different from typical nonsurgical MI is not entirely clear but it is believed that the mechanism of perioperative MI is multifactorial and resemble nonsurgical MI [9]. The probable main cause of preoperative MI is rupturing of the unstable coronary atherosclerotic plaque, thrombus formation, arterial stenosis and occlusion of the artery.

Surgical stress imposes more workload that causes dynamic imbalance between myocardial oxygen supply and demand. This extra cardiac workload is due to perioperative blood loss, tachycardia, blood pressure lability, pain, release of catecholamines because of inflammatory response during surgery, platelets activation and aggregation, reduced fibrinolitic activity and vasospasm. Resultant plaque instability, thrombus formation, and vessel occlusion constitute potential underlying pathophysiologic mechanisms for cardiovascular complications in patients undergoing non cardiac vascular surgery [10]. Patients with cardiac disease are in more hazards for perioperative cardiac complications so trying to find these patients have a great value to reduce the perioperative complications.

Preoperative cardiac assessment can help to determine patients with high cardiac risk, but many of these assessments are not necessary and have a poor predictive value. In a study which evaluates the efficacy of preoperative cardiac assessment in vascular surgery, stress echocardiography can only show ischemia in half of the patients; and stress echocardiogram could not predict the region of infarct in 36% of the patients [11]. A lot of surgeries are urgent so it cannot be possible to do coronary revascularization. Many surveys showed that percutaneous coronary angioplasty and stenting are not useful in these patients [12] and even can be hazardous. Because MI is related more to plaque instability than degree of stenosis [13], so it is better to be less rigid in the criteria to identify high risk patients and try to improve outcome by medical therapy to control heart rate and blood pressure, decrease inflammation, and stabilize coronary plaques [14].

The beneficial cardiovascular effects of Statins

Statins, 3-Hydroxy-3-methylglutarylcoenzyme-A (HMG-CoA) reductase inhibitors, inhibit HMG-CoA reductase in rate limiting manner. This leads to decrease hepatic cholesterol synthesis, up-regulation of LDL (low density lipoprotein) receptor, and so decrease plasma LDL cholesterol [15]. Statins also decrease plasma triglycerides and increase modestly high–density lipoprotein cholesterol. The full therapeutic effect is achieved in 4-6 weeks [16]. Besides their lipid lowering effects it was shown they have pleiotropic effects including vasodilation, anticoagulation, platelet inhibition, antioxidant, anti-inflammatory function, and decreased lymphocyte action. Statins stabilize plaques

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by modulation of macrophage, antithrombogenic, and antiplatelet and anti inflammatory actions [17-18]. Many of these effects happen in 24 hours from statin initiation due to the improvement in endothelial function, before the significant reduction in cholesterol level [19]. For more than two decades, statins have been used clinically for lowering the cholesterol and decreasing the atherosclerosis risk [20]. Large multi-centre randomized controlled trials have shown that statins are safe and effective in reducing LDL cholesterol and are useful in the primary and secondary prevention of ischemic heart disease [21-26].

The Efficacy of Perioperative statin therapy

In the perioperative setting, a lot of studies have shown that preoperative statin is associated with a reduced incidence of postoperative cardiac morbidity and mortality in high-risk patients undergoing major vascular and other major non cardiac surgeries [27-28].

Lindenauer and colleagues performed a retrospective cohort study for 2 years involving 780,591 patients who underwent major noncardiac surgery. The results showed that the perioperative mortality rate was 2.96% and, although the patients in statin group were older, had more associated diseases than those patients who were not treated with statin, the patients on statins showed a 1% reduction in hospital mortality [29]. This reduction in mortality was repeated in Polderman and Noordzij studies too [27-30].

To assess the clinical outcomes of perioperative statin treatment, a systematic review on 16 randomized clinical trials involving 2275 patients was done. The results showed a significant reduction in mortality (in 30 days and more), in perioperative myocardial infarction, in perioperative atrial fibrillation, and decrease in length of hospital stay in patients treated with statins. There was not any significant reduction in the incidence of perioperative stroke in patients on statins [31].

In another meta –analysis which contained 29 RCTs, the results showed a reduced risk of myocardial infarction at 0-30 days and a trend for a reduced mortality at 1 year when a statin was added before surgery [32].

In patients, candidate for vascular surgeries, systemic atherosclerotic process has affected different organs such as coronary, cerebral and renal circulation and these patients have multiple comorbidities, in addition the vascular surgeries, by themselves, are complex procedures and the perioperative morbidity and mortality is high in these patients. Many studies showed the statin efficacy in this group of patients. The results of a systematic review [33] on 24 studies which contain vascular and endovascular surgeries showed a significant reduction in all causes mortality, myocardial infarction and stroke in patients receiving statins periperatively. The composite of myocardial infarction, stroke and death was significantly reduced in patients on statins. No significant differences in cardiovascular mortality and the incidence of kidney injury between these two groups were identified. Because of significant decrease in perioperative mortality and morbidity in this meta-analysis the authors advised that statin therapy should be applied as an integral part of the pharmacologic strategy for secondary prevention in patients undergoing vascular or endovascular surgery [33].

Perioperative statin therapy is also associated with favorable perioperative outcomes unique to vascular surgery, include: reduced infrarenal aortic aneurysm growth [34], preserved renal function after suprarenal aortic clamping [35], decreased amputation rate [36], improved graft patency [36] and shorter length of stay [37] after infrainguinal bypass surgery, and better carotid endarterectomy outcomes as measured by improved carotid artery anatomic durability [38] and reduction in mortality and stroke [39].

In a study on 7777 patients undergoing non cardiac surgeries, the effect of statins on perioperative non cardiac complications was assessed; the results showed the preoperative use of statins was associated with a 37% decrease in major noncardiac complications. On multivariable analysis, the use of statins was associated with decrease in respiratory complications, VTE and infectious complications [40]. These results are consistent with pathophysiologic mechanisms mentioned by other studies, particularly by decrease in inflammation [41]. The decrease in infectious complications, including organ space infection may be mediated through improved wound healing from statins' angiogenic or immunomodulatory properties [42].

The 38% decrease in respiratory complications in preoperative statin users may be because of decreasing airway hyperreactivity [43]. This may cause a decrease in reintubation rate, decreases the risk for pneumonia and prolonged ventilation. Decreased inflammation may have a role in preventing prolonged mechanical ventilation. The rate of decrease in perioperative DVT in statins group was far greater than that reported in medical patients, this impact of statin in this study may show that because of increased hypercoagulability in perioperative period, the surgical patients achieve more benefit from statins in DVT protection [40].

Statins may have a role in sepsis treatment with increasing endothelial nitric oxide synthase [44].

Some pleiotropic effects of statins such as antioxidant activity and improvement in atherosclerosis process may have the beneficial effects in sepsis. One of the mechanisms of statins in decreasing perioperative complications is reduction of inflammation. The reduction of C-reactive protein, interleukin 6 [45], decrease in myocardial superoxide anion and peroxynitrite [46] was reported in various studies.

Targeting perioperative statin

The surgical patients with symptomatic atherosclerosis such as the patients with history of ischemic heart disease, cerebral vascular accident and peripheral vascular disease achieve benefits from perioperative statin therapy especially if the surgery by itself is high risk [47-48]. Current American College of Cardiology Foundation/American Heart Association coronary revascularization guidelines recommend statins in all patients undergoing CABG at a dose sufficient to reduce LDL cholesterol below 100 mg/dL(or 70 mg/dL in high risk patients) and achieve at least a 30% reduction in LDL [49]. All hypercholesterolemic patients and patients with metabolic syndrome should also be included as candidates for statin treatment [50]. Any patient who develops a perioperative acute coronary syndrome and is not on statin should be initiated on statin therapy as soon as possible [51].

Time course and safety of perioperative statin therapy

Although the cholesterol lowering effect of statins needs at least a month to establish [17], but the effect of statins on endothelial function and the coagulation cascade occur rapidly for example, atorvastatin 20 mg daily can improve endothelial function and NO availability in forearm vasculature after three days of therapy in hypercholesterolemic patients [52]. Wassmann et al. have shown that a single oral 40 mg of pravastatin significantly improved endothelium-dependent coronary vasomotion within 24 hr in the absence of significant cholesterol reduction [53]. In a meta analysis [32], the results showed that administration of high dose statin shortly before the surgery could produce protection against perioperative myocardial infarction [32]. Preoperative endothelial dysfunction is a predictor of postoperative cardiovascular events in patients undergoing vascular surgery and it is possible that statins, even when started in the immediate preoperative period, can have acceptable impact on postoperative cardiovascular outcome after non cardiac surgeries but there are not any obvious recommendations as to when the drug should be started. Discontinuation of statin after major vascular surgery is associated with high cardiac complications, so statin therapy should be continued or resumed early postoperatively [54]. It would be reasonable to continue statins for at least 3 days after surgery as this is the time that can be associated with an acute coronary event [2]. It is likely that continued statin administration will improve outcome in patients who experience acute coronary syndromes, and in patients with vascular problem [55].

In general, statins are safe and are effective drugs but muscular and hepatic adverse effects are commonly reported. The incidence of muscular pain and weakness, which are usually due to an increase in serum creatine kinase, is 1% to 5% in patients receiving statin. Myopathy happens in 0.1% to 0.2% of these patients and rhabdomyolysis is very rare (0.05%). Rhabdomyolysis is thought to cause 0.15 deaths per million statin users [56].

Another side effect of statins is liver toxicity, asymptomatic elevations of transaminase, as a sign of liver dysfunction is seen in 0.1% to 2% of patients with statin therapy. The adverse effects are dose related and higher doses of statins may increase the risk [57]. Increased age, medical conditions, high statin dose, and concomitant medications affecting statins pharmacokinetics are risk factors that may increase muscular and hepatic side effects [58]. In one study on patients undergoing major vascular surgeries, statin therapy did not increase the risk of myopathy [59]. The results of another study on patients undergoing hip or knee arthroplasty showed that long term statin therapy seems to be safe [58]. As in the nonoperative setting, statins should not be initiated in patients with chronic liver disease, inflammatory muscle disease, severe renal disease, on concurrent treatment with cyclosporin, fibrates, or high dose niacin, or in females with child bearing potential [9].

Conclusion

Anesthetists should consider standard dose of statin before surgery to patients undergoing cardiac surgery. Although many researches showed useful effects of statins in preoperative time and seemed to be safe medications, but we still need a well designed clinical trial to establish efficacy and safety of statins during non cardiac surgery. So till now there are insufficient data to support final recommendations on perioperative statin therapy for patients undergoing non cardiac surgery.

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