
Can statins improve outcome in colorectal surgery? Part I

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ABSTRACT: Statins are recommended for people who have high serum cholesterol, and this role of statins has been well documented. However, some activities of statins, independent of their lipid-lowering effect, in conditions such as systemic inflammatory response syndrome, nephropathy, and other anti-inflammatory activities that reduce proinflammatory cytokines, are called “pleiotropic” effects of statins. For this reason, many candidates for surgical treatment are users of statins. As a result, benefits are observed in these patients, such as minimized postoperative complications, especially in cardiac or coronary surgery. This study was designed with the purpose of determining the current status of the use of statins as an adjuvant in the prevention of postoperative complications in colorectal surgery. Ongoing studies and future researches will help clarify the potential impact of statins on the prophylaxis of postoperative complications.

Keywords: statins; postoperative complications; colorectal surgery.

RESUMO: As estatinas são drogas com o poder de inibir a hidroximetilglutaril coenzima A redutase (HMG-CoA redutase), enzima que age na ativação da cadeia metabólica do colesterol. Portanto, sua principal ação, entre outros efeitos, é diminuir a concentração sérica total desse lipídeo. Por essa razão, muitas pessoas candidatas ao tratamento cirúrgico são pacientes usuários das estatinas. Seus outros efeitos, independente de sua capacidade para baixar os lipídeos circulantes, são denominados “efeitos pleiotrópicos” e estão, principalmente, relacionados à ação de bloqueio das atividades pró-inflamatórias, sobretudo minimizando, nos cardiopatas ou coronariopatas submetidos às operações cardíacas ou coronarianas, a prevalência da síndrome da reação inflamatória sistêmica, inclusive quando desencadeada por infecção. Estudos recentes têm sido elaborados para maiores conhecimentos dos mecanismos de ação das estatinas, especialmente em pacientes cardiopatas submetidos a tratamentos cirúrgicos não cardíacos ou em outros pacientes com o propósito de fazer a profilaxia das complicações pós-operatórias, inclusive as relacionadas diretamente com os agentes infecciosos. O presente manuscrito foi delineado com o objetivo de se conhecer a situação atual do uso das estatinas como adjuvante na prevenção das complicações pós-cirúrgicas em operações colorretais.

Palavras-chave: estatinas; complicações pós-operatórias; cirurgias colorretais.

INTRODUCTION

HMG-CoA (hydroxy-methyl-glutaryl-Coenzyme A or HMG-CoA reductase) – the enzyme that catalyzes the reduction reaction – is part of the metabolic pathway that produces cholesterol and targeted by several blocking substances when the purpose is to reduce the production of this lipid.

The inhibitors of HMG-CoA reductase are drugs known as statins, which belong to the group of drugs used in the prevention of cardiovascular dis-

eases caused by elevated total circulating cholesterol. Statins are widely used, and most candidates for surgical treatments, including colorectal surgery, especially patients with neoplastic diseases, due to their age, are users of statins.

Statins reduce the serum levels of low-density lipoproteins (LDL) and triglycerides and promote increased levels of high-density lipoproteins (HDL)¹. Plainly explained, increased LDL leads to more fatty deposits and formation of platelets in the endothelium of arteries, producing thicker walls and narrowed lu-

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men of vessels (atherosclerosis) with functional involvement of several organs. Statins reduce LDL, as well as the size of platelets in coronary arteries²⁻⁴.

Several studies have been highlighted to show that statins reduce the incidence of coronary artery diseases and cerebrovascular lesions, and improve the survival rate of patients with coronary artery diseases⁵⁻⁸; benefits can be obtained even in the beginning of the treatment³.

This study was designed with the purpose of determining the current status of the use of statins as an adjuvant in the prevention of postoperative complications in colorectal surgery.

Other benefits of statins (pleiotropy)

Statins also have an anti-inflammatory effect, particularly regarding the incidence of cardiovascular infection and complications during surgical procedures and they control the metabolic response to stress, facts that suggest the preventive use of statins in candidates for surgery⁹, and not only in patients to be submitted to cardiac surgeries due to several types of lesions, but also in cardiac patients undergoing non-cardiac operations. These conclusions resulted from the observation that the benefits provided by statins do not only depend on its LDL-lowering effect, but also on the impact of these drugs on organs, systems and morbid status, regardless of its original mechanism of action, which are properties called "pleiotropic effects".

These effects, promoted by several mechanisms, suggest the extended therapeutic action of statins, including: the anti-inflammatory power, as they reduce the plasma concentration of cytokines – tumor necrosis factor-alpha (TNF- α) and interleukins (IL-6) – and positively act in situations with significant elevation of C-reactive protein (CRP)^{1,3,9-20}.

Sepsis

On the other hand, there are evidences²¹⁻²⁴ and controversies²⁵⁻²⁹ that require a better definition that statins, independent of their primary action, help reduce mortality in the treatment of sepsis^{21,25,30}, supposedly for inhibiting the synthesis of products of the cholesterol metabolic pathway just before mevalonate is produced, preventing the production of substances such as isoprenoids and geranylgeranyl pyro-

phosphate³¹. In addition, they modify the intercellular interaction and the chemotaxis of the immune system; have antioxidant properties, although reducing the levels of ubiquinone (CoQ10), an endogenous oxidant³²; act against apoptosis; inhibit the action of certain genes, changing the cellular activity; and participate, in other mechanisms, of the inflammatory response³⁰, facts that intensify their capability to control the systemic inflammatory response syndrome and protect cardiac patients from complications of non-cardiac surgeries³³⁻³⁵ or in similar situations triggered by the infection^{22-24,36,37}. However, most studies testing the effect of statins in the treatment of severe diseases present methodological limitation and are retrospective studies³⁰.

Almog et al.²¹, in a prospective study with the participation of several researchers, consecutively enrolled 361 patients admitted with presumed or documented acute bacterial infection. These patients presented high rates of severe sepsis and transference to the intensive care unit. Eighty-two patients (22.7%), treated with statin before the admission, constituted a group that was compared to another group of 279 people that did not receive statin. The similar aspect of both groups was the severity of diseases that led to hospital admission. Acute sepsis affected 19% of the patients in the second group (without statin) and only 2.4% of the patients in the first group (treated with statin) ($p < 0.001$). The statin group was associated with the relative risk of developing severe sepsis of 0.13 (95% CI, 0.03 to 0.52) and reduced absolute risk of 16.6%. The global admission rate at the intensive care unit was 10.2% (37/361): 12.2% in the non-statin group and 3.7% in the statin group ($p = 0.025$), meaning that the treatment with statin may be associated with a reduced rate of severe sepsis and admission to the intensive care unit.

Surgeries

The systemic inflammatory response syndrome can affect 30 to 40% of the patients submitted to coronary artery bypass surgery³⁸ or other types of cardiac or non-cardiac surgeries in patients with heart problems or coronary artery diseases; and these facts, based on the probable benefits of statins, encouraged the American Heart Association to highlight in 2007 the evidences that supported the use of statins during

the surgeries to prevent cardiac complications resulting from non-cardiac surgeries³⁹.

The incidence and increased risk of postoperative infectious or non-infectious complications depend on a relatively high variety of factors, especially in colorectal surgeries for the treatment of large bowel cancer⁴⁰⁻⁴², whose discussion is not included in the scope of this study.

However, the purpose today is to know whether the current surgical treatment practices supported by technical, mechanical or other developments, considering the global support to health, and combined with improved skills of surgeons, and by scientific investigations on methods used during the surgery that recommend to discard unnecessary and harmful “traditional practices”⁴³ – such as preoperative mechanical preparation of the large bowel, use of nasogastric probe, cavity drainage, extended bed rest, gradual introduction of diet, among others^{44,45} – can, associated with a statin-like drug, promote improved results after colorectal surgeries, just as those that have been observed in cardiac surgeries⁴⁶⁻⁴⁸.

Statin in colorectal surgeries

Recently, Khan et al.⁴⁹ and Singh et al.²⁰, interested in reducing postoperative morbidity, studied the immediate effect of statin during colorectal surgeries. Among the first authors, the group of patients enrolled in the study had 21.7% of statin-treated patients – who were much older than the other patients (74.7 vs. 69.2 years old; $p=0.022$), had more associated disorders and used more antidiabetic agents or other cardiovascular drugs. No difference was observed in relation to mortality between both groups or in the incidence of hospital infection or postoperative sepsis. However, regarding the aspect of being or not admitted to Intensive Care Unit (ICU), the statin-treated patients were significantly less inclined to develop systemic inflammatory response syndrome or surgical wound infection or to ICU admission as a result of inflammatory or infectious sequelae. The second authors studied a group of 269 patients, 86 (32%) of them received statin during the surgery and the others (68%) did not. The statin-treated patients

were older (72 vs. 69 years old; $p=0.021$), with predominance of male over female patients (53 vs. 40%; $p=0.049$), and included more patients in class III of American Society of Anesthesiology (ASA) classification (55 vs. 22%; $p<0.001$), whose classes range from I to IV. No significant difference was observed in the total number of complications or in the hospital length-at-stay and both groups presented comparable functional recovery. However, they observed that statin-treated patients showed a significantly lower number of anastomotic dehiscence cases (1 vs. 7%; $p=0.031$). In addition, they concluded that the statin-treated group presented more deficient health and high surgical risk than the others, but obtained a similar global result to non-statin group, suggesting that this therapy produced a protective result.

Another relevant aspect refers to recent observations that highlight the relation between the local or systemic inflammation process and the pathogenesis of solid tumors^{50,51} in which pro-inflammatory macrophages, cytokines and chemotactic cytokines, acting as factors that predispose the subsequent progression, growth, invasion and metastasis of tumors, would determine the bad prognosis in the treatment of these patients⁵². In this sense, Gunter et al.⁵³, in 2006, showed the relation of chronic inflammatory process, evidenced through a persistently elevated dose of CRP, with colorectal cancer. On the other hand, some genetic epidemiological studies showed that elevated CRP does not cause cancer, but it increased the risk of death caused by cancer^{54,55}, suggesting that not only the intrinsic properties of tumors determine their behaviors. Therefore, for these reasons, the prevention of pro-inflammatory activities should be part of the adjuvant therapeutic arsenal in cancer treatment and in prophylaxis of general postoperative complications⁵⁰⁻⁵².

The studies available are still not sufficient to ensure a better evaluation of the pleiotropic effects of statins and their probable benefits in colorectal surgeries, but the University of Auckland, New Zealand⁵⁶, is interested in the topic and has assigned a group to start a multi-center cohort study to help clarify the impact of pleiotropic effects of statins on the prophylaxis of postoperative complications.

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