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ORIGINAL ARTICLE

ROLE OF STATINS IN PREVENTION OF INFECTION IN HERNIA MESH REPAIR; PROSPECTIVE STUDY

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Abstract

Background: There was good evidence suggests that statin may reduce the risk of infections and infection-related complications in all medical fields including surgery. Our objective was to assess the association between statin usage and risk of infections and related outcomes in inguinal hernia open mesh repair.

Method: In this study, a total of 609 Egyptian patients, with different types of hernia underwent hernioplasty with mesh repair during period from May 2010 to April 2011. Review of their drug history divided them into two groups: Group A included 67 patients who were taken statin tablet regularly for at least 9 months and group B who included 542 patients with no drug intake. We documented any postoperative wound infection and compare between incidences of wound infection in the two groups.

Results: In Group A, only 2 cases (2.9%) were found to have wound infection while in Group B, there were 22 cases (4%) that were found to have wound infection postoperatively. A significant difference is present between the two groups. ($\rho = 0.05$).

Conclusions: Our results suggest that statin usage is associated with a beneficial effect in preventing postoperative wound infections in open mesh repair for hernias.

Keywords: Antihypertensive, post-operative infection, clean operation.

INTRODUCTION

Sepsis is considered one of the leading causes of mortality in hospital staying. Although some advances have been made in treating patients with sepsis, the mortality of patients with sepsis remains extremely high.(1)

A number of important abnormalities occur during sepsis, including endothelial dysfunction and apoptosis, activation and increased production of cytokines and other pro-inflammatory mediators, activation and extra-vascular transmigration of leukocytes, and activation of platelets and coagulation and complement systems.(2-3)

Because of this multiple pathway involvement in the pathogenesis of sepsis, targeting a single component is likely to be insufficient to halt the septic process. In fact, a number of pharmacological agents have been tested in the setting of severe sepsis over the past 2 decades, and all failed except recombinant activated protein C, which showed encouraging results.(4)

Statins, Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, are the treatment of choice in the majority of patients with hyperlipidemia for their ability to lower cholesterol levels. It is currently used for hyperlipidemia control and considered useful for protection from cardiovascular events. In addition, there is increasing evidence for the potential use of statins in preventing and treating infections.[2]

Although the exact mechanism(s) behind the observed association remains unknown, it could be attributed to several factors, including the immune-modulator and anti-inflammatory effect of statins and their impact on endothelial function.[5-6]

Statins inhibit 3-hydroxy-3 methylglutaryl coenzyme A (HMG CoA) reductase, were developed as lipid level–lowering agents, and have been studied extensively in relation to atherosclerosis. However, statins, not only reduce cholesterol level but also decrease the levels of intermediate products of cholesterol synthesis, mevalonate, farnesylpyro phosphate, and geranylgeranylpyro phosphate, which play a crucial role in several intracellular signaling pathways.7 Apparently, this effect is the major explanation for the observed pleiotropic effects of statins, which include the modulation of both innate and adaptive immune system and anti-inflammatory effects (reviewed by Kwak et al 8), as well as their role in counteracting the deleterious effects of sepsis on the coagulation system by inhibiting tissue factor expression and reducing prothrombin fragment levels 9 and by strongly increasing the expression of thrombomodulin. 10 In addition, statins have been shown to have direct inhibitory effects on pathogenic microorganisms.[11-17]

Statins also affect leukocyte-endothelial interaction and transmigration of leukocytes through the endothelial layer.[8] This may explain the observed protective effect of statins in the context of sepsis, a process that is well known to be associated with maladaptive dysregulated immune response. Second, statins also exert an anti-inflammatory response independent of their lipid level–lowering properties.[18]

For example, it has been shown that simvastatin inhibits the inflammatory response to Staphylococcus aureus alpha toxin in rats.[19] Third, clinical trials in the context of atherosclerosis have shown that statins improve endothelial function (reviewed by Jain and Ridker).[18] In fact, sepsis is associated with endothelial dysfunction and apoptosis, which is associated with deranged homeostasis.20 It has also been shown that statins up-regulate endothelial nitric oxide synthase, which is well known to have a number of favorable effects.[21]

Finally, statins exert direct effects on pathogenic microorganisms; for example, lovastatin reduces the intracellular growth of Salmonella typhimurium in cultured macrophages.[11] Similarly, a number of studies found that statins exhibit direct antifungal activity.[12-14]

The direct antimicrobial effects and the immune-modulatory properties of statins may explain the observed preventive effects against infection in a number of observational studies.

Having all these properties, statins have been suggested as an adjunct in the treatment of patients with sepsis. Although there have been reviews regarding various aspects of statin use in patients with sepsis, to our knowledge, there has been clinically related studies. Thus, we sought to critically examine the use of statins for patients with high sepsis potentiality.

Therefore, statins may be good candidates as novel therapeutic agents for the treatment and prevention of sepsis because they target a number of pathways that are dysregulated during the sepsis process and because of their direct antimicrobial effects. Indeed, in a murine model of sepsis, simvastatin was shown to profoundly improve survival.[15]

PATIENTS AND METHODS

From May 2010 to April 2011, a total of 609 patients with different types of hernia had undertaken hernioplasty operation with mesh repair in Main Alexandria University Hospital. Sixty seven of them were received statin as a lipid-lowering agent or as a protective from cardiovascular events for at least last 9 months.

Patients' demographics, clinical and pathological characteristics of hernias were recorded and compared between statin receiving group & none statin group.

Standard mesh repair was performed to all the patients, removing the hernia sac, performing herniorrhaphy using polyprolene none absorbable mesh. Wound infection was reported 4 weeks of postoperative period.

Postoperative wound infection is an infection in the tissues of the incision and operative area. It is defined by presence of one or more of following criteria were assessed: pain at rest, persistent pyrexia, continuing wound erythema or discharge, increased erythrocyte sedimentation rate, increased white blood cell count, positive deep cultures and radiological changes suggestive of infection.

All patients had signed an informed consent to be enrolled in this study & protocol of the research had been approved by Alexandria Faculty Medical Ethics Committee. SPSS for windows, version 11.0 (SPSS Inc., Chicago) was used for statistical analyses using $\chi 2$ test and Fisher exact test wherever appropriate. A $P > 0.05$ was considered to indicate a significant difference.

RESULTS

Studied group who were on statin medical treatment included 67 patients, 49 of them (73.1%) were males and 18 (26.9%) were females. Their ages ranged from 44 to 81 year, the median was 61.3 years. The hernia was primary in 51 patients (76.1%) and recurrent in 16 patients (23.9%). 31 patients (46.3%) were diagnosed as inguinal hernia, 10 patients (14.9%) were paraumblical hernia, 17 patients (25.4%) were incisional hernia, 6 patients (9%) were epigastric hernia, and 3 patients (4.5%) were femoral hernia. Concomitant diseases were hypertension in 59 patients (88%), diabetes mellitus in 31 patients (46.3%) and ischemic heart diseases in 17 patients (25.4%). 55 patients (82%) were smokers or ex-smoker. The duration of preoperative statin treatment differed and ranged from 9 to 46 months with median of 25 months. The operations were done under general anesthesia in 42 patients (62.7%) and spinal anesthesia in 25 patients (37.3%). Of those 67 cases, two cases (2.9%) were found to have wound infection.

609 controlled patients had a comparable demographic clinical data as shown in Table 1. 22 of them were found to have postoperative wound infection. It revealed a significant difference. ($P < 0.05$).

DISCUSSION

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, namely statins, are a class of drugs used for their ability to lower cholesterol levels. Statins are the treatment of choice in the majority of patients with hyperlipidemia. Their primary indication is the prevention of cardiovascular disease. Recently, there is an increasing interest about the use of statins for other purposes apart from their original one. Part of this trend is the hypothesis that statins might play a role in the prophylaxis and treatment of infections. Statins have been attributed anti-inflammatory and immunomodulatory pleiotropic effects and suggested as an adjunct in the treatment of patients with sepsis.

Multiple studies have been published on the efficacy of statins as anti-inflammatory in patients with sepsis, bacterimeia, viral infection, MODS, pneumonia and other infections. Some also studied their effect on the mortality rate from the infection.

Statins have been attributed anti-inflammatory and immunomodulatory pleiotropic effects. They inhibit the synthesis of products of mevalonate pathway such as isoprenoids and geranyl-geranylpyrophosphate.[7] In addition; they modify the intercellular interactions and the cellular chemotaxis of the immune system.

Furthermore, statins reduce the release of cytokines and acute-phase proteins. They demonstrate antioxidant properties, although they reduce ubiquinone (CoQ10) levels, which is an important endogenous antioxidant.[22]

They may also exert an anti-apoptotic action, contribute to the stabilization of the atheromatic plaque, modify cell activity by inhibiting the expression of certain genes and participate in various other mechanisms of the inflammatory response.

Table 1. Clinical data of Statin received group of patients versus control group of patients.

	Statin-Received group	Control group
Age (yr)		
Median	61.3	53
Range	44 to 81	19 to 83
Gender		
Male	49 (73.1 %)	420 (69 %)
Female	18 (26.9 %)	189 (31 %)
Duration of preoperative statin use (months)		
Range	9 – 46	
Median	25	
Concomitant diseases		
Hypertension	59 (88%)	428 (70.3 %)
DM	31 (46.3%)	213 (35 %)
IHD	17 (25.4%)	159 (26.1 %)
Smokers	55 (82%)	481 (79 %)

Table 2. Hernia types and operation performed for Statin received group of patients versus control group.

	Statin-Received group	Control group
Type of Hernia		
Inguinal	31 (46.3%)	314 (51.6%)
Paraumblical	10 (14.9%)	87 (14.3%)
Epigastric	6 (9%)	40 (6.6%)
Femoral	3 (4.5%)	13 (2.1%)
Incisional	17 (25.4%)	155 (25.5%)
Primary vs. Recurrent		
Primary	51 (76.1%)	423 (69.5%)
Recurrent	16 (23.9%)	186 (30.5%)
Type of anesthesia		
General	42 (62.7%)	412 (67.8%)
Spinal	25 (37.3%)	197 (32.2%)

Statins like all medications have potential for adverse effects (AEs). Being a widely used group of drugs, it is important to be aware of possible AEs and drug-drug interactions. AEs are dose dependent, and risk is amplified by drug interactions that functionally increase statin potency, often through inhibition of the cytochrome P450 (CYP) 3A4 system. Statins' adverse effects ranged from myositis, myalgia, rhabdomyolsis and cognitive functions affection. The best recognized and most commonly reported AEs of statins are muscle AEs,[23,24] and include muscle pain, fatigue and weakness as well as rhabdomyolysis. Muscle effects arising on statins do not uniformly resolve fully with statin discontinuation.[25] Statins have also exacerbated known muscle conditions, such as myasthenia gravis.[26]

Rhabdomyolysis occurs when muscle damage is severe, leading to a marked elevation of CK (e.g. in excess of 10 times the upper limit of normal) often accompanied by evidence of renal dysfunction and occasionally renal failure and death.[27-29,32] Cognitive problems are the second AEs to muscle problems among patient reports of statin AEs.[33] Brain tissue shares with muscle tissue a high mitochondrial vulnerability as both are post-mitotic tissue with high metabolic demand.34 Drug interactions arise when drugs inhibit metabolic pathways of statins, compete for metabolism with statins, or cause similar or interacting toxicity. Several widely used statins – atorvastatin, simvastatin, and lovastatin are metabolized by the cytochrome P450 (CYP) 3A4 pathway.[35]

Concurrent administration of statins with CYP3A4 inhibitors may raise statin concentrations and risk of toxicity, including rhabdomyolysis.36 The CYP3A4 pathway is inhibited by a variety of agents including cyclosporin, erythromycin, azole antifungal, and antiretroviral such as ritonavir.[37,38]

In this study, we searched for the efficacy of the preoperative statins administration in prevention of the wound infection in patients undergo standard mesh repair of different types of hernia. We found that preoperative statins use had a beneficial effect in preventing wound infections after hernia mesh repair. It is thought to be applied for different types of surgical wounds.

There is a need for prospective studies and randomized controlled trials in order to draw a safe conclusion regarding the consideration of statins use as a prophylactic of surgical wound infection.

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