



Does TGF beta suppressing effect of simvastatin lead to protection against surgical adhesion band formation?

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Abstract

Intra-abdominal adhesions are the most common cause of small bowel obstruction. Infertility in women and chronic abdominal-pelvic pain are the other problems of adhesiogenesis which impose a great economic burden on the population health. On the other hand, increased levels of transforming growth factor beta1 (TGF- β) are shown to play a role in formation of adhesion bands and can impair peritoneal fibrinolysis. Moreover, simvastatin, an immunomodulator agent, can down-regulate TGF- β . Although it is shown in previous studies that simvastatin antagonizes the interaction between TGF- β and connective tissue growth factor (CTGF), no human study exists on the effect of simvastatin on surgical adhesion band formation. We hypothesize that simvastatin, through its effect on reducing the level of TGF- β , may be useful in preventing adhesion band formation after surgical procedures. Surely, this hypothesis should be assessed in several experimental and clinical trials.

Keywords

Simvastatin, Intra abdominal adhesion bands, Bowel obstruction, Transforming growth factor beta

Introduction

Intra-abdominal adhesion bands are one of the most important complications of surgical procedures. They are the most common cause of small bowel obstruction (1). Infertility in women and chronic abdominal-pelvic pain are other complications of adhesiogenesis, which impose a great economic burden on the population health (2). Adhesions account for approximately 50% of all small bowel

obstructions. Therefore, trying to find strategies to prevent their formation has great importance.

Transforming growth factor beta (TGF- β) is a fibrogenic cytokine. As a result of surgical injury, activated macrophages and peritoneal mesothelial cells secrete pro-inflammatory cytokines including TGF- β (3, 4). Increased levels of TGF beta1 is shown to play a role in intestinal diseases (5, 6) and

in the formation of adhesion bands and can impair peritoneal fibrinolysis (7). Moreover, simvastatin, which is an immunomodulator agent that reduces the levels of circulating immune complexes can also down-regulate TGF beta (8). However, no research has hypothesized or used simvastatin as an antifibrotic agent in post-surgical adhesions. In this study, we propose the potential benefits of this drug in such situations. First, we introduce simvastatin, then we will explain our hypothesis and evaluate it.

Simvastatin and its safety

Simvastatin is safe for lowering LDL and cholesterol in heart transplant recipients (9). Combination treatment with fenofibrate and low dose simvastatin is generally safe and effective for treatment of combined hyperlipidemia in patients with normal hepatic and renal function (10). Overall, HMG-CoA reductase inhibitors appear to be remarkably safe. Over 50000 patients have been treated with HMG-CoA reductase inhibitors for over 5 to 6 years as a part of large RCTs and no increase in any major non cardiac diseases have been seen in these individuals (11, 12, 13). Contraindications of this drug are: hypersensitivity to it, active liver disease or unexplained persistent elevated liver function tests, pregnancy (category X) and lactation.

There are some works for anti fibrogenic effect simvastatin but they are not for its effects on peritoneal adhesiogenesis in humans. The starting dose of simvastatin for the treatment of hyperlipidemia is 20 mg with the maximal dose that reach 80 mg (12,13).

Since there is no clinical trial for evaluating the anti fibrogenic effects of simvastatin in peritoneal adhesiolysis, a pilot study to determine the probable effective and safe dose of the drug before conducting large randomized clinical trials (RCTs) is suggested (14, 15).

The hypothesis

Our proposed hypothesis is based on two sets of experimental data:

Firstly, TGF- β is a fibrogenic cytokine and increased levels of this substance could lead to adhesion band formation and secondly, simvastatin could down-regulate TGF- β .

Theoretically, administrating simvastatin during and after surgical procedures, especially those

which are in high risk of adhesiogenesis could be used to decrease the chance of adhesion band formation and its subsequent complications.

Evaluation of the hypothesis

Our hypothesis should be assessed in experimental studies on laboratory animals. One mouse models of peritoneal adhesiogenesis and intestinal obstruction could be used.

In addition, double blind RCTs could evaluate this hypothesis in human studies. We propose that simvastatin should be administered before, during and after the surgery in different groups of patients who have undergone surgical procedures. The route of drug administration could be intra-peritoneal, oral and via injection. The differences of various times of drug administration and its routes should be examined. If clinically confirmed, a practical guideline for high risk surgeries may be recommended.

Discussion

Current therapy

The best treatment of adhesions is primary prevention (16). The treatment of intestinal obstruction due to postoperative adhesiogenesis or other causes is controversial. Since strangulated small bowel is always complete, operation should always be done after suitable preparation. Before surgery, the patient should be hydrated and the electrolyte balance should be restored. A nasogastric tube should be instituted to decompress the patient's stomach. Broad spectrum antibiotics should be administered. Non operative therapy is best applied for patients with repeated episodes of partial obstruction and recent post operative peritoneal obstruction (17).

The surgical techniques are laparoscopic versus laparotomy. The potential advances of laparoscopic surgery may include less post operative adhesion formation as well as fewer wound infection and less post operative pain. But laparoscopic adhesiolysis is associated with a considerable risk of bowel perforation. Adhesiolysis carries a mortality risk of 5% to 30% for simple obstruction and strangulated bowels, respectively. Non operative conservative treatments are not always enough powerful to remove the need for surgery but increase the risk of later adhesion band formation. Of course surgery has its complications (16, 17, 18).

So trying to find anti adhesiogenesis agents for decreasing the risk of adhesion band formation after surgery in a normal patient (primary prevention) and in a patient with previous abdominal adhesiogenesis (secondary prevention) should be seriously persuaded.

Cellular mechanisms

CTGF is a fibroblast mitogen and promoter of collagen deposition (19) that has been implicated in the pathogenesis of fibrosis including that of the lung liver and kidney (20, 21, 22). Studies implicate that TGF- β through a Rho mechanism could up regulate the CTGF expression (23).

Simvastatin could exert its inhibitory effect on CTGF expression through two routes: the direct inhibitory effect on CTGF gene expression and interrupting the action of TGF- β on CTGF. Watts et al have shown that simvastatin reduces the activity of the CTGF promoter irrespective of the presence of TGF- β in lung fibroblasts. In addition, modulator effects of simvastatin on TGF- β /CTGF interactions depend on blocking Rho prenylation and its subsequent signaling (8).

Therefore, CTGF expression and induction by TGF- β is abrogated by simvastatin via a Rho signaling mechanism.

Conclusion

According to aforementioned information, we hypothesize that simvastatin, may be useful in prevention of adhesion band formation after

surgical procedures. Surely, this hypothesis should be assessed by clinical trials. Our hypothesis could be assessed in clinical trials after surgeries that are in high risk for adhesiogenesis such as perforated appendicitis, diverticulitis, major abdominal surgery and peritonitis. As a lateral benefit, decreasing the peritoneal adhesiogenesis could decrease the risk of infertility in women after abdominal and pelvic surgeries, which may have great economical, social and psychological effects in the community.

In a recent study, it was shown that simvastatin may have anitfibrotic effect on animal surgery (24), but this effect is explained in the light of tissue plasmin activator change. Since it has been reported in other studies that TGF- β increment induces fibrinogenesis (7), we think this putative anti-fibrinogenic effect of simvastatin may be produced through reduction of TGF- β . We propose that in animal studies on abdominal surgery, it is wise to measure TGF- β plasma level. If our hypothesis can be verified experimentally, then a novel therapeutic protocol will be accessible.

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