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The effect of oral simvastatin on fibrinolytic activity after colorectal surgery—a pilot study

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ABSTRACT

Background: Studies conducted in animal models have shown that statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) reduce adhesion formation by upregulating fibrinolysis. The aim of this study was to determine the effect of orally administered statins on the promoters and inhibitors of the fibrinolytic pathway.

Methods: In a previously described double-blinded clinical trial, 144 patients undergoing elective colorectal resection, or reversal of Hartmann's procedure were randomized to receive 40 mg once daily oral simvastatin 3-7 d before surgery or placebo. For the purposes of the present study, peritoneal drain fluid was collected postoperatively from patients to measure active tissue plasminogen activator (tPA), tissue plasminogen activator total antigen, active plasminogen activator inhibitor-1 (PAI-1), plasminogen activator inhibitor total antigen (PAI-1TA), plasminogen activator inhibitor-1 and tissue plasminogen activator complex (PAI-1/tPA). These were analyzed using ELISA. The number of hospitalizations and complications related to small bowel obstruction (SBO) were recorded at 2 y after surgery.

Results: A total of 95 patients (72%) had sufficient peritoneal drain fluid suitable for ELISA analysis. Of them, 46 patients (48%) were from the oral simvastatin group. Mean tPA and tPA total antigen concentrations in peritoneal fluid were similar between the two groups. Mean PAI-1 and PAI-1 TA concentrations in the statin and placebo group were also similar. Mean PAI-1/tPA complex concentration was similar between the two groups. The number of hospitalizations from SBOs were 5 and 4 in the statin and placebo groups respectively ($P = 0.46$). The overall mortality at 2-year post-surgery was similar between the two groups ($P = 0.59$).

Conclusions: In this pilot study involving humans, oral simvastatin had no measured effect on the peritoneal fibrinolytic pathway in the first 24 h after colorectal surgery. Analysis of clinical outcomes also showed that oral simvastatin did not reduce hospitalizations for SBO in the 2 y after surgery. Further studies may be useful to evaluate whether fibrinolytic pathways beyond 24 h are altered after systemic administration of statins and to evaluate the use of higher doses of statins, perhaps used intraperitoneally rather than systemically.

This study was completed while the primary author was a medical student during his research elective with the Department of Surgery, The University of Auckland.

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Introduction

Postoperative adhesions (PAs) develop in up to 100% of patients after major abdominal surgery.[1] Significant PA can lead to small bowel obstruction, chronic pelvic pain, and infertility.[2] PA can further complicate future abdominal surgery by inhibiting access. Colorectal patients are at greater risk with up to a third readmitted for adhesion-related complications over a 10-y study period.[3] Despite recent advances to reduce PA such as laparoscopic surgery[4] and adhesion prophylaxis,[5] they remain a significant cause of morbidity, mortality, and carry a substantial financial burden to society.[6]

PAs develop when the peritoneum suffers an insult such as major abdominal surgery. When this occurs, a number of biological processes occur to allow for healing at the site of injury. Initially, peritoneal injury causes desquamation of injured mesothelial (peritoneum) cells, producing an inflammatory reaction characterized by cellular infiltration and formation of a serosanguineous exudate.[7] Macrophages adhere to the wound surface and upregulate the expression of tissue factors. This eventually leads to the formation of a fibrinous matrix that forms fibrin bands, which under normal circumstances are broken down by fibrinolysis.[8]

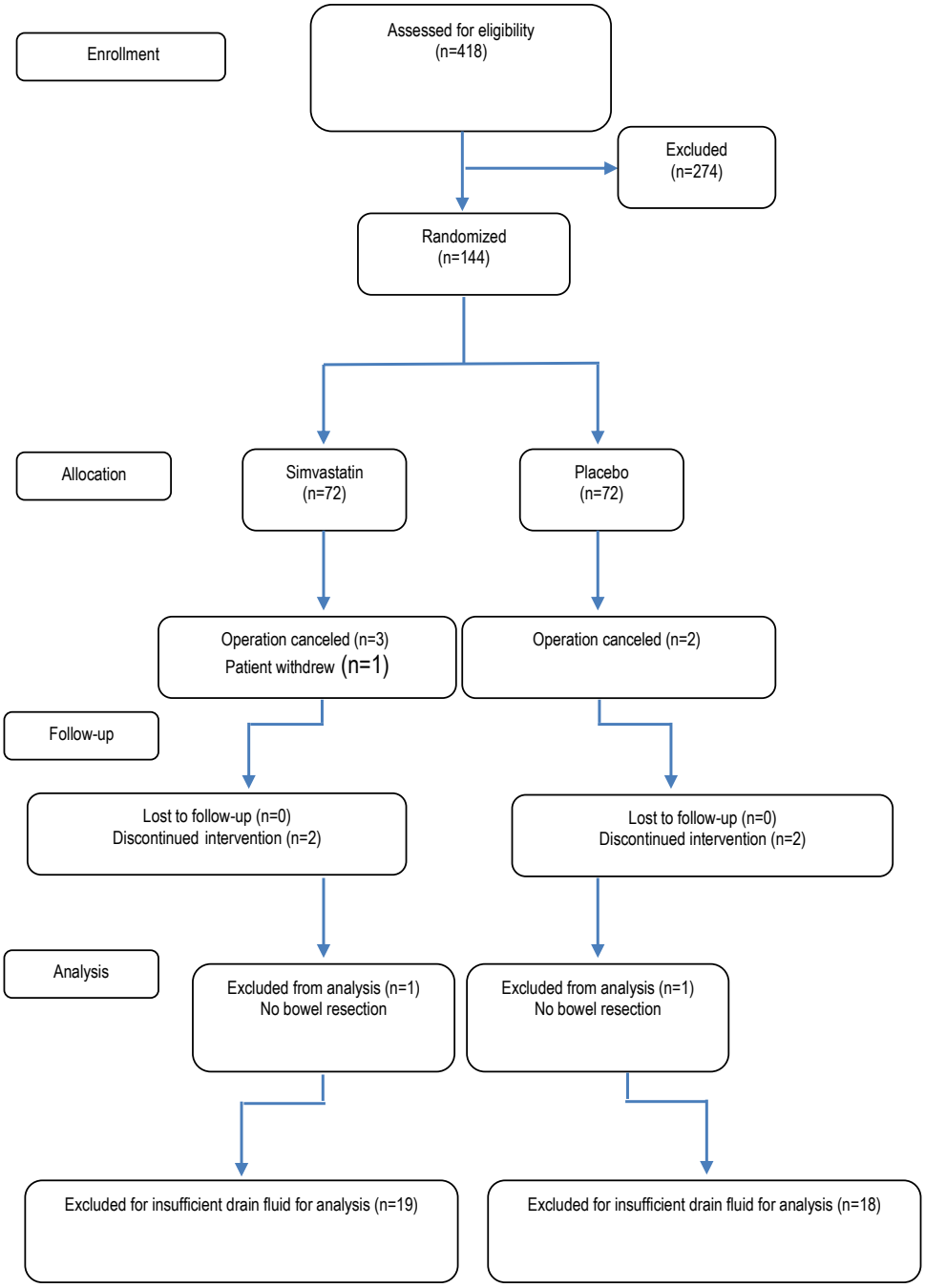

Figure – Patient flow. (Color version of figure is available online.)