



Original research

# Influence of anti-adhesive agent on incidence of bile leakage after liver resection: A prospective cohort study



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## HIGHLIGHTS

- Use of anti-adhesive agent was not associated with increased risk of bile leakage.
- Larger area of cut-surface was significantly associated with bile leakage.
- Patients without history of hepatitis were at risk for bile leakage.

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## ABSTRACT

**Background:** Anti-adhesive agents are increasingly used to reduce the incidence of postoperative adhesions following abdominal surgery. Bile leakage after liver resection remains a major cause of postoperative morbidity. The aim of this study was to examine the effect of anti-adhesive agent on bile leakage after liver resection.

**Materials and methods:** 77 patients were enrolled to receive an anti-adhesive agent (study group) during liver resection between May 2012 and August 2013. The study group was compared to a match-paired control group. Clinical data were collected including bilirubin concentration in serum and drain fluid and bile leakage rate. In addition, a separate analysis was performed between patients with and without postoperative bile leakage.

**Results:** There was no difference in bile leakage rate or hospital stay between the study group (n = 77) and control group (n = 77). Of the total number of patients (n = 154), there were 29 patients with postoperative bile leak and 125 patients without bile leak. On univariate analysis, patients without history of hepatitis were significantly associated with bile leakage. In addition, liver resection with broader cut surface area was associated with bile leakage. Application of anti-adhesive agent was not associated with bile leakage. On multivariate analysis, resection with broader cut surface area (OR = 2.788, p = 0.026) and patients without history of hepatitis (OR = 5.153, p = 0.039) were significantly associated with bile leakage.

**Conclusions:** Larger area of cut-surface and patients without history of hepatitis were significant risk factors for bile leakage. The use of anti-adhesive agent was not associated with increased risk of bile leakage.

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## 1. Introduction

Postoperative adhesions are the main cause of intestinal obstruction in the developed world and account for approximately

70% of readmissions for small bowel obstruction. As a result, anti-adhesive agents are increasingly used to reduce postoperative adhesion in various fields of surgery. Specifically, anti-adhesive agents may have increasing value in liver surgery due to increased number of procedures that require reintervention after initial liver resection such as re-resection for colorectal metastasis and salvage liver transplantation for hepatocellular carcinoma (HCC) [1,2]. However, adhesions may have a potential benefit, including neovascularization of ischemic structures such as

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anastomoses [3].

Liver resection is widely accepted as the only potentially curative treatment in malignant or benign hepatobiliary lesions. In recent years, morbidity and mortality rates have markedly decreased due to the refinements in surgical techniques, improved selection criteria and advances in postoperative care. Among the various potential postoperative complications after liver resection, biliary leakage remains as one of frequent complications with a reported incidence ranging from 3.6 up to 12% [4–6]. Bile leakage after liver resection remains a major cause of postoperative morbidity, often leading to prolonged hospital stay, and need for additional diagnostic tests and interventions. Use of anti-adhesives can decrease unnecessary adhesion after liver resection, on the other hand, there are concerns that prevention of normally occurring adhesion process may increase incidence of bile leakage. Currently, various topical hemostatic agents such as fibrinogen-coated collagen patches as well as fibrin glues have been developed for surgical tissue management [7,8], although the main goal of using these agents is hemostasis of the resection surface.

Contrary to the increasing use of anti-adhesive agents in abdominal surgery, to our knowledge, no report exists regarding the possible unfavorable effect of anti-adhesive agents during liver resection such as poor sealing of biliary radicals leading to postoperative bile leakage. The aim of this study was to examine the effect of an anti-adhesive agent on bile leakage after liver resection.

## 2. Materials and methods

### 2.1. Patient selection

This study was approved by our Institutional Review Board. Written informed consent was obtained from all patients. A total of 77 patients were enrolled to receive an anti-adhesive agent (study group) during liver resection between May 2012 and August 2013. All patients undergoing liver resection were eligible except for patients requiring biliary reconstruction or concomitant surgery with other organs. Patients with severe liver cirrhosis (above child class A) or renal disease (requiring hemodialysis) were excluded. Also, patients with prior history of liver resection or autoimmune disease and patients requiring immunosuppressant therapy were excluded. The study group was compared to a control group consisting of patients who underwent liver resection without application of anti-adhesive agent and who met the inclusion criteria. The control group was retrospectively matched (1:1) with regard to sex, age, diagnosis (malignant vs benign) and size of cut surface area following liver resection. Within each group, patients receiving liver resection with a small cut surface area comprised the minor group, whereas patients with a large cut surface area comprised the major group. The minor group included patients receiving simple wedge resection, left lateral sectionectomy. The major group included patients receiving central bisectionectomy, right anterior sectionectomy, right posterior sectionectomy, right hemihepatectomy and left hemihepatectomy among others.

### 2.2. Study protocol

Six grams of poloxamer/alginate (Guardix-SG<sup>®</sup>, Hanmi pharmaceutical company, Seoul, Korea) was applied on the liver cut surface and right beneath the abdominal wound before wound closure. The total bilirubin concentration of the serum and drainage fluid was recorded on the first, third, fifth postoperative day and on the day of drain removal. The amount of drainage was also recorded. Bile leakage was defined as proposed by the international study group of liver surgery (ISGLS) [9].

### 2.3. Sample size calculation and statistical analyses

We hypothesized that there would be no difference in bile leakage rate between the study group and control group. Since Ijichi et al. reported a bile leakage of 5% when fibrin glue was applied after liver resection, a sample size of 69 patients per group was calculated using the Z test with pool variance with a type 1 error of 0.05 [10]. After adjusting for a 10% dropout rate, the final sample size was 77 patients per group. Group characteristics were compared with an independent *t*-test and Fisher's exact test.

A separate analysis was performed between patients with (bile leak group) and without (non-bile leak group) postoperative bile leakage. To reveal factors associated with bile leakage, univariate logistic regression analyses were performed using patient characteristics and surgery-related variables as independent variables and bile leakage as the dependent outcome. Thereafter, selected variables (*p*-value below 0.1 in univariate analysis) were entered into the multiple logistic regression analysis to investigate the factors related to bile leakage.

## 3. Results

### 3.1. Study group vs control group

The most common cause for liver resection was hepatocellular carcinoma in both groups (Table 1). There was no difference in total bilirubin concentration of serum and drainage fluid between the 2 groups (Fig. 1). In addition, there was no difference bile leakage rate (14.3% vs 23.4%, *p* = 0.174) between the 2 groups (Table 2).

### 3.2. Non-bile leak vs bile leak group

There were 125 and 29 patients in the non-bile leak and bile leak group, respectively. However, there were significantly more patients with underlying history of hepatitis in the non-bile leak group (Table 3). The two groups did not differ in terms of postoperative diagnosis, operative method, operative time and requirement for transfusion. However, the bile leak group tended to have patients undergoing liver resection with larger cut surface area (Table 3). In addition, the incidence of postoperative infection and intraabdominal abscess was higher in the bile leak group. However, the use of anti-adhesive agent did not differ between the 2 groups (Table 3). On multivariate analysis, liver resection with broader cut surface area and patients without underlying history of hepatitis were significant risk factors for bile leakage (Table 4).

### 3.3. Subgroup analysis within the bile leak group

Since ISGLS grade B or C bile leakage may be more associated with technical error, a subgroup analysis within the bile leak group was performed to analyze the effect of anti-adhesive agent on the so called "chemical bile leak". There were no significant differences in bilirubin concentration of drainage fluid, drain amount and time interval to drain removal between the 2 groups (Fig. 2).

## 4. Discussion

Adhesion occurs when the tissue damaged during surgery secretes factors that activate the blood vessels; inflammatory cells accumulate, and extracellular matrix formation is accelerated, leading to the formation of fibrotic clots. Collagen is secreted, and connective tissues are formed, all of which eventually result in tissue adhesion [11]. Based on this mechanism, studies have applied hyaluronic acid carboxymethylcellulose (HACMC) mixtures, both as physical barriers or liquid applications, at the site of

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