# The potential efficacy of Survanta® and Seprafilm® on preventing intra-abdominal adhesions in rats[1]

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**ABSTRACT**

**PURPOSE:** To investigate the potential efficacy of beractant (Survanta®) and Seprafilm® on the prevention of postoperative adhesions.

**METHODS:** Forty Wistar-albino female rats were used. The rats were randomly allocated into four groups of 10 rats each as control group (CG), beractant group (BG), Seprafilm® group (SG), and combined group (COG). All rats underwent cecal abrasion via midline laparotomy. Before abdominal closure, isotonic saline, beractant, Seprafilm, and combined agents were intraperitoneally administered. Adhesions were classified macroscopically with Canbaz Scoring System on postoperative day 10. Ceacum was resected for histopathological assessment.

**RESULTS:** Macroscopic adhesion scores were significantly lower in BG, SG, and COG than CG ($p<0.05$); (45%, 15%, 25%, and 15%; respectively). Histopathological assessment revealed a reduced inflammation and fibrosis score in the study groups than CG ($p<0.05$). In BG, adhesion development, inflammation and fibrosis scores were lower than SG; however, it was not statistically significant.

**CONCLUSIONS:** Intra-abdominal application of beractant is significantly effective for the prevention of adhesion formation with no adverse effect by covering the whole peritoneal mesothelium with excellent gliding properties in a rat model. The combination of both agents is also effective in reducing adhesion formation, however, not superior to single beractant application.

**Key words:** Tissue Adhesions. Beractant. Seprafilm. Inflammation. Rats.

## Introduction

Postoperative adhesions (PA) still remain a major surgical problem that should be solved after abdominal surgery even though we are in modern surgical era. Intra-abdominal adhesions may cause chronic abdominal pain, intestinal obstruction, feeding intolerance, and infertility[1-6]. Unfortunately, 3-8% of these patients may undergo redo surgeries mainly for acute intestinal obstruction[6]. Particularly, bowel injuries while re-entering the abdominal cavity due to dense adhesions is the main complication of redo surgery[2]. This fact leads to high morbidity and mortality. For this reason, prevention of postoperative adhesion formation is still a popular topic among the investigators.

Seprafilm® is a biocompatible anti-adhesive material that is comprised of modified form of hyaluronic acid and carboxymethylcellulose. Because of its clinically proven efficacy on preventing abdominal adhesions, it has been commonly used by surgeons after abdominal surgery in recent years[3,7]. It should be noted that Seprafilm® reveals its potent efficacy on covered area, however adhesions may develop in uncovered traumatized surfaces. This deficiency of Seprafilm underlines the necessity of using liquid anti-adhesive agents to cover all traumatized surfaces. For this purpose, in parallel with understanding the chemical physiology of the peritoneum, pulmonary surfactants has been suggested to use as off-label drugs for preventing adhesion formation[1,7,8].

Beractant is a pulmonary surfactant that is used to treat respiratory distress syndrome in preterm infants. It is comprised of surface-active phospholipids, particularly phosphatidylcoline (PC) which is the main constituent of surface active material coating the peritoneal mesothelium[9]. PC is an excellent lumbricant and constitutes a temporary membrane by coating the whole traumatized peritoneum, thereby, it reveals its anti-adhesive effect[8,10]. In fact, the efficacy of beractant on preventing abdominal adhesions has been demonstrated in a recent single study[8]. However, according to our view, the potential efficacy of beractant should be confirmed by comparing with another potent anti-adhesive material.

In this study, we aimed to evaluate the potential anti-adhesive effect of Seprafilm® and beractant. To our knowledge, there is no comparative study comparing the potential effect of Seprafilm and beractant (Survanta) on reducing postoperative adhesions to date. Furthermore, in the present study, we aimed to investigate whether we able to enhance the anti-adhesive effect by using combination of both agents.

## Methods

This study was conducted at the Experimental Research Center of Mersin University after obtaining the ethical committee approval of Mersin University Medical Faculty (Approval number: 2014/32). This research was carried out in accordance with the Guide for the Care and Use of Laboratory Animals (NIH, 1985).

Forty Wistar-albino female rats, weighing 230 to 260 g were used in the present study. The animals were maintained at 21$^0$C, humidity at 40%-60% with a 12 h light/dark cycle and allowed free access to water and standard chow during the study. After adaptation, the animals were randomly assigned to four different groups of equal numbers.

### *Study design and surgical procedure*

After an overnight fast, the rats were anesthetized by intramuscular injection of ketamine 90 mg/kg (Ketalar®; Pfizer, Istanbul, Turkey) and xylazine HCL 10 mg/kg (Rompun; Bayer AG, Istanbul, Turkey). Animals were allowed to breathe spontaneously during the surgery. A heating lamp was used to preserve the body temperature at 37$^0$C. All operations were performed by the same surgeon to ensure technical uniformity. The abdominal skin of the rat was shaved, and under aseptic condition, a 3 cm midline incision was made. The abdomen was explored; the rat was excluded from the study if intra-abdominal adhesion was observed. The cecum was exteriorized. The anterior surface of the cecum was abraded with moderate pressure using a nylon bristle dental brush until a 1 cm$^2$ of the subserosal ecchymotic area developed. The cecum was replaced in its original position. The muscle-fascial layer was closed with a single layer continuous absorbable 3/0 suture (Vicryl, Johnson & Johnson). The skin was closed with interrupted 3/0 silk suture. Before closing the abdominal cavity, the following agents were applied in accordance with the groups:

Group I: Control group (C): Intraperitoneal administration of 2mL isotonic saline (0.9% NaCl, Eczacibasi, Istanbul, Turkey).

Group II: Beractant group (BG): Intraperitoneal administration of 100 mg/kg beractant. Beractant (25mg/mL) was diluted with 0.9% NaCl to 2 mL.

Group III: Seprafilm® group (SG): The abraded cecal area was covered by a 1.5 cm$^2$ piece of Seprafilm.

Group IV: Combination group (BG+SG): Beractant was administered as described in group II followed by covering the abraded cecal area by Seprafilm as performed in group III.

The postoperative course was assessed every 6 h within the first 48 h and every 8 h for 20 days as described Zantl *et al.*[11]. No perioperative antibiotics were used. No postoperative analgesics were used since we observed no symptoms associated with pain including discomfort, agitation or itching of wound side.

*Assessment of adhesions*

On postoperative day 10 (POD 10), all animals were euthanized by intraperitoneal overdose pentobarbital sodium. The abdomen was opened via a U-shaped incision based in the lower abdomen in order to view the entire adhesions and to perform accurate adhesion grading. The abdomen was explored with regards of adhesions by two of the investigators blind to the study groups. Intraperitoneal adhesions were graded from 0 (absent) to 4 (severe) according to the Canbaz Scoring System (CSS) (Chart 1). Grade 0 and 1 adhesions were considered as mild, grade 2 as moderate, grade 3, and 4 adhesions were considered as severe adhesions. The scores higher than grade 2 were accepted as clinically significant.

**CHART 1** - Adhesion grading according to Canbaz adhesion severity scoring method.

| Grade | Description of Grade |
|---|---|
| 0 | No adhesion |
| 1 | 1 adhesion band, no vessel, easily separated |
| 2 | 2 thin adhesion bands, no vessels, easily separated |
| 3 | 3 thin adhesion bands, no vessels, easily separated |
| 4 | > 3 thin adhesion bands, easily separated with no vessel or defused adhesion bands with vessels |

*Histopathological examination*

Adhesion-carrying tissues including cecum and peritoneum were excised en bloc and fixed in 10 % buffered formaldehyde solution. The samples were dehydrated, embedded in paraffin and cut in 5-µm thick slices. Each layer of the cecum (mucosa, submucosa, and serosa) was sampled separately. Histopathological sections were stained with hematoxylin-eosin (HE) and Masson-Tricrom (MT) for evaluating histopathological parameters including fibrosis, inflammation, and vascular proliferation. The parameters were rated on a modified semi-quantitive scale grading from 0 to 3[12,13]. The amount of fibrosis was scored as follows: 0, no fibrosis; 1, minimal, loose fibrosis; 2, moderate fibrosis; and 3, florid dense fibrosis. Inflammation was scored as follows: 0, no inflammation; 1, presence of giant cells, occasional lymphocytes, and plasma cells; 2, presence of giant cells, plasma cells, eosinophils and neutrophils; and 3, presence of many inflammatory cells and microabscesses. Vascular proliferation was scored as: 0, no vascular proliferation; 1, mild vascular proliferation; 2, moderate vascular proliferation; and 3; intense vascular proliferation. A conventional binocular Leica DM 2000 light microscope (Leica Microsystems, Wetzlar, Germany) was used for analysis. The samples were assessed in a blinded manner by two pathologists.

*Statistical analysis*

Statistical Med Calc 9.3.9.0 software was used for sample size calculation. The primary outcome variable was a reduction in adhesion formation with a 2 grades difference between the groups. Using a power, 80% α-error and 5% β-error, a sample size of 8 rats were calculated for each group to show a significant difference. Considering the possible casualties during the study, 10 rats were allocated for each group. Statistical analyzes were performed by using SPSS 20.0 for Windows. Numerical data were presented as mean ± standard deviation (SD). Categorical variables between the groups were analyzed by using Kruskal-Wallis test. The adhesion score between the two groups was compared by using Mann-Whitney U test and chi-square test. A *P* value less than 0.05 was considered statistically significant.

**Results**

All animals survived the surgery. No local or systemic complications related to Seprafilm or Survanta application were observed.

*Adhesion scores and rates*

Adhesion scores were calculated as 45%, 15%, 25% and 15% in group 1, 2, 3 and 4; respectively (Figure 1). Adhesion scores were found significantly lower in treatment groups than in control group. Macroscopic adhesion rates were significantly lower in group 2, 3, and 4 with a rate of 30%, 50%, and %30; respectively when compared with control group (90%) ($p<0.05$). Grade 2 ≤ adhesions, which we were accepted as clinically significant, were observed in the control group at a rate of 70% of which 40% of the adhesions were grade 3 or 4. On the other hand, there were no grade 3 or 4 adhesions in the study groups while grade 2 adhesion was detected at a rate of 10%, 20%, and 0 % in group 2, 3, and 4; respectively. Seprafilm application significantly reduced adhesion scores comparing with the control group ($p<0.05$). However, either single or combined Survanta application was presented similar adhesion scores as Seprafilm application ($p>0.05$). Beractant significantly reduced the postoperative adhesions when compared with control group ($p=0.002$, for each comparison). Grade 2 adhesion was observed only in one rat. Adhesion grades and rates of the groups were presented in Table 1.

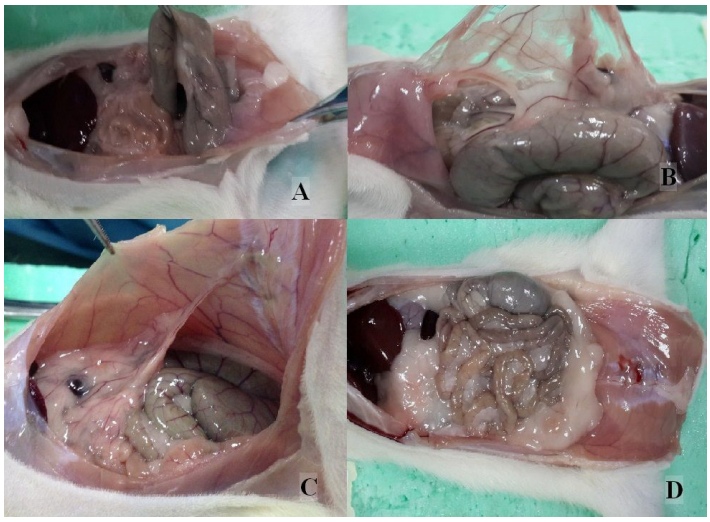


**FIGURE 1 -** Macroscopic imaging of the groups. **A**) Control group, **B**) Beractant applied group, **C**) Seprafilm applied group, **D**) Combination of beractant and Seprafilm applied group.

**TABLE 1 -** Macroscopic evaluation of postoperative adhesion grades, rates and statistical comparison of the groups. Adhesion rate is used to describe the presence of any adhesion in any grade.

| Groups | No. of the rats | Adhesion grade | | | | | Adhesion rate (%) | P value and comparison of the groups |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | | |
| 1.Control group | 10 | 1 | 2 | 3 | 2 | 2 | 9/10(90) | p=0.022<br>1-2<br>1-4 |
| 2. Beractant group | 10 | 7 | 2 | 1 | 0 | 0 | 3/10(30) | |
| 3. Seprafilm group | 10 | 5 | 3 | 2 | 0 | 0 | 5/10(50) | |
| 4.Combined group | 10 | 7 | 3 | 0 | 0 | 0 | 3/10(30) | |

*Histopathologic examination*

The histopathologic scores of adhesions differed significantly for each layer of the cecum among the control group and treatment groups with respect to mucosal, submucosal, and serosal inflammation (p=0.006, p=0.035, p=0.047; respectively) and fibrosis (p=0.001, p=0.033,p=0.043; respectively). However, no significant difference was detected between the groups in terms of mucosal, submucosal and serosal vascular proliferation (p=0.078, p=0.082, p=0.064; respectively). The control group revealed the highest scores for fibrosis and inflammation when compared with treatment groups. It is interesting that no statistical difference was detected between control and Seprafilm group with respect to inflammation and fibrosis (except mucosal fibrosis) even though low inflammation and fibrosis were observed in rats subjected to Seprafilm. However, in both beractant applied groups, the histological scores for inflammation and fibrosis were significantly lower than in the control group ($p<0.05$). The histologic scores of the specimen were summarized in Table 2.

**TABLE 2 -** Histopathologic examination of the specimen in terms of inflammation, fibrosis and vascular proliferation. *p<0.05 The significant difference between the groups.

| Histologic Feature | Groups | Scores 0 | 1 | 2 | 3 | p value |
|---|---|---|---|---|---|---|
| Mucosal inflammation | Control | 2 | 6 | 2 | 0 | **0.006**<br>1-2 |
| | Beractant | 9 | 1 | 0 | 0 | |
| | Seprafilm | 7 | 3 | 0 | 0 | |
| | Combined | 7 | 3 | 0 | 0 | |
| Submucosal inflammation | Control | 1 | 4 | 4 | 1 | **0.035**<br>1-4 |
| | Beractant | 4 | 6 | 0 | 0 | |
| | Seprafilm | 4 | 3 | 3 | 0 | |
| | Combined | 5 | 5 | 0 | 0 | |
| Serosal inflammation | Control | 0 | 4 | 3 | 3 | **0.047**<br>1-2 |
| | Beractant | 2 | 7 | 1 | 0 | |
| | Seprafilm | 2 | 6 | 1 | 1 | |
| | Combined | 1 | 6 | 3 | 0 | |
| Mucosal fibrosis | Control | 4 | 6 | 0 | 0 | **0.001**<br>1-2<br>1-3<br>1-4 |
| | Beractant | 10 | 0 | 0 | 0 | |
| | Seprafilm | 10 | 0 | 0 | 0 | |
| | Combined | 9 | 1 | 0 | 0 | |
| Submucosal fibrosis | Control | 2 | 5 | 3 | 0 | **0.033**<br>1-2<br>1-4 |
| | Beractant | 8 | 1 | 1 | 0 | |
| | Seprafilm | 5 | 4 | 1 | 0 | |
| | Combined | 7 | 3 | 0 | 0 | |
| Serosal fibrosis | Control | 1 | 2 | 5 | 2 | 0.043<br>1-2<br>1-4 |
| | Beractant | 3 | 6 | 1 | 0 | |
| | Seprafilm | 3 | 4 | 2 | 1 | |
| | Combined | 3 | 6 | 1 | 0 | |
| Mucosal vascular proliferation | Control | 2 | 4 | 4 | 0 | 0.078 |
| | Beractant | 7 | 2 | 1 | 0 | |
| | Seprafilm | 4 | 5 | 1 | 0 | |
| | Combined | 5 | 5 | 0 | 0 | |
| Submucosal vascular proliferation | Control | 1 | 2 | 5 | 2 | 0.082 |
| | Beractant | 1 | 7 | 2 | 0 | |
| | Seprafilm | 0 | 4 | 6 | 0 | |
| | Combined | 1 | 6 | 3 | 0 | |
| Serosal vascular proliferation | Control | 0 | 1 | 5 | 4 | 0.064 |
| | Beractant | 0 | 6 | 3 | 1 | |
| | Seprafilm | 2 | 3 | 2 | 3 | |
| | Combined | 0 | 6 | 4 | 0 | |

**Discussion**

Considering the recent reports in the literature, prevention of postoperative adhesion formation is still a popular topic among the investigators. Likewise, experimental adhesion studies that mimic clinical conditions are still essential for investigation and also testing the effect of a new anti-adhesive substance[5]. For this reason, this study was designed as an experimental model because of the difficulty of designing a controlled, randomized, prospective clinical study. In the present study, we evaluated the efficacy of beractant (Survanta®), which is a pulmonary surfactant, on the prevention of postoperative abdominal adhesions. To our knowledge, this is the first study comparing, as well as, evaluating the combined effectiveness of two antiadhesive agents (Survanta® and Seprafilm®) in reducing postoperative intra-abdominal adhesions. The macroscopic and histopathologic examination of the groups revealed that adhesion formation was significantly reduced in study groups (groups II, III, IV) when compared with the control group. Although, the adhesion scores of both beractant groups were calculated lower than SC, the difference did not reach significance. Whereas, on histopathological examination, mucosal inflammation and fibrosis of the specimen in both beractant groups were significantly lower than either SC or C groups.

Postoperative adhesion formation still remains a major clinical problem that may lead to undesirable redo surgeries resulting in high morbidity and mortality for every surgical specialty. Adhesion formation occurs as a consequence of the physiological wound healing process. Peritoneal injury related to surgical trauma, ischemia, thermal injury, infection, and foreign body trigger the steps of adhesion formation[3,15]. The fibrin-rich exudate is secreted followed by increased vascular permeability. Reduced tissue plasminogen activity and elevated inflammatory cytokines such as tumor necrosis factor, interleukins 1 and 6 play an important role in reducing fibrinolytic activity[16]. This may lead the fibroblasts to become organized into adhesions. Adhesion formation develops within 5-7 days after trauma and the optimal time for evaluating the adhesions in rats has been reported as on POD 7 or more days[4,14]. For this reason, adhesion formation was evaluated on POD 10 day in this study.

In parallel with understanding the pathophysiology of adhesion formation; numerous drugs and substances including fibrinolytics, barrier films, anti-inflammatory agents, anticoagulants, anti-oxidants, and phospholipids have been used locally or systematically for preventing adhesions[1,3,4,15,17]. However, the majority of tested agents have not been adopted for standard therapy due to the lack of biocompatibility of the studied agents. An ideal anti-adhesive agent should totally cover the traumatic region during the healing process and be biologically resorbable after that period. For this reason, research in preventing adhesion formation has mostly focused on adhesion barriers, fibrinolytic agents, and phospholipids. Seprafilm is a mechanical bioresorbable adhesion barrier that is comprised of modified hyaluronic acid and carboxymethylcellulose. It turns into a gel form within 24-48 hours after placement onto the gliding interfaces and stays in place for up to 7 days during the critical tissue healing period. The efficacy of Seprafilm on preventing abdominal adhesions has been extensively demonstrated in numerous well-designed randomized clinical trials[18]. In the present study, Seprafilm application significantly reduced adhesion formation comparing with the control group and presented similar results as previously reported by various authors. However, it should not be ignored that Seprafilm has a deficiency in preventing adhesion formation of whole abdomen because adhesions may develop in uncovered areas. For this reason, we speculated that liquid anti-adhesive agents may be more effective in preventing intra-abdominal adhesions since they cover all traumatized peritoneal lesions.

Beractant is a liquid pulmonary surfactant that is comprised of several phospholipids, particularly phosphatidylcoline (PC). Snoj[9] demonstrated that the surface-active material coating the peritoneum is chemically similar to pulmonary surfactant and rich from PC (81%). Chen *et al*.[19] revealed the absorption of phospholipids by mesothelium and subsequently the formation of a thin membrane like layer on whole peritoneum. The gliding property of this PC rich layer acts as a liquid barrier and reduces the adhesion formation during the healing process[8,19,20]. In view of this suggestion, we aimed to evaluate the antiadhesive effect of beractant in the present study. In fact, the potential effect of pulmonary surfactants in reducing abdominal adhesions has been well demonstrated in a recent report [8]. However, to our knowledge, no comparative study evaluating the potential effect of beractant on reducing intra-abdominal adhesions has been studied to date, thereby; we preferred to use Seprafilm for comparison with beractant. Furthermore, in the present study, we aimed to investigate whether we able to enhance the anti-adhesive effect by using combination of both agents. Our results revealed that beractant application significantly reduced the adhesion formation with a rate of 70% grade 0 adhesion score, while the adhesion was 50% grade 0 in Seprafilm applied group, comparing the with the control group. Although a 20% difference of adhesion score was observed between SG and BG, it was not statistically significant.

It is notable that adhesions were mainly observed in the uncovered areas in SG. In combined group, beractant enhanced the anti-adhesive effect of Seprafilm; we reached the similar adhesion scores of BG.

It is well known that high tissue inflammation, fibrosis and vascular proliferation are strongly associated with dense adhesion formation[3,17]. For histopathologic examination, single layer of the bowel segment has been evaluated for tissue healing in almost every study. In order to achieve more detailed results, each layer of the bowel segment was separately evaluated in terms of inflammation, fibrosis and vascular proliferation in the present study. On histopathologic examination, in both beractant applied groups, we observed significant low inflammation and low fibrosis in each layer of the bowel segment when compared with the control group. Furthermore, beractant application revealed better histologic results except mucosal fibrosis than Seprafilm application. Although vascular proliferation was observed less in both beractant groups than the other groups, the difference did not reach significance. According to these results we speculated that beractant revealed its anti-adhesive effect by reducing tissue inflammation and fibrosis due to its anti-inflammatory effect and anti-rubbing properties.

Beractant is a widely available, biocompatible drug that can be easily obtained when compared with the other pharmacologic agents previously studied for preventing adhesions. Moreover, because of its liquid formation, it can cover all traumatized surfaces and play a potent role in preventing adhesions. Considering these properties of beractant, it can be used easily in clinical practice whereas its relative cost and needing a cold chain system for carrying seem to be the disadvantages of beractant.

There were indeed several limitations of our study. Although we tried to accommodate the number of rats by using power analysis, the small sample size was the first limitation of our study. Another limitation was that the metabolism of beractant in rats is unknown. The pathophysiological aspect of the tissue healing may differ from humans. Furthermore, high surface volume of the abdomen in human may increase the need of beractant dose. Although no adverse effect related to beractant application was observed (100mg/kg) in the present study, in order to achieve the same results in human, high dose of beractant application may cause side-effects. Prospective clinical studies should be performed to overcome these concerns. Despite these limitations, we assumed that solely the anti-adhesive effect of beractant has been well demonstrated in this study.

## Conclusions

Intra-abdominal application of beractant (Survanta®) is significantly effective for the prevention of adhesion formation with no adverse effect by covering the whole peritoneal mesothelium with excellent gliding properties in a rat model. Furthermore, the combination of Seprafilm and beractant is also effective in reducing adhesion formation, however, not superior to single beractant application.

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