ORIGINAL ARTICLE

Effect of Intraperitoneal Antiadhesive Fluids in a Rat Peritonitis Model

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Hypothesis: Phospholipids and icodextrin reduce peritoneal adhesions resulting from general peritonitis without promoting abscess formation.

Design: Evaluation of adhesion reduction fluids in a randomized animal study using a standardized peritonitis model.

Setting: Experimental animal model in a university laboratory.

Interventions: In 60 rats, experimental peritonitis was induced using the cecal ligation and puncture model. On day 1, the abdominal cavity was rinsed with 10 mL of isotonic sodium chloride solution and the cecum was resected. Animals were randomly assigned to 3 groups: the RL group, which received Ringer lactate intraperitoneally; the PL group, which received phospholipids intraperitoneally; and the ID group, which received icodextrin intraperitoneally. In each group, 50% of the animals were humanely killed at day 11 and 50% at day 21.

Main Outcome Measures: The areas of adhesions were measured and the abscess formation was scored according to location and size. Abscesses, abdominal fluid, and blood were sampled for microbiologic workup.

Results: The median area of adhesions was significantly lower in the PL groups (PL_{11}, 43.7 mm^2; PL_{21}, 20.4 mm^2) than in the RL groups (RL_{11}, 163.8 mm^2; RL_{21}, 120.9 mm^2) and ID groups (ID_{11}, 418.5 mm^2; ID_{21}, 218.6 mm^2). Abscess formation was increased by icodextrin but not influenced by phospholipids, whereas microbiologic investigations did not reveal any differences among these 3 groups.

Conclusions: In this model of general peritonitis, phospholipids significantly reduced adhesion formation without promoting septic complications. Icodextrin enhanced adhesion and abscess formation in this peritonitis model. Phospholipids may be beneficial for adhesion control in general peritonitis.

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ADHESIONS CAUSE recurrent and chronic abdominal complaints, pain, and secondary female infertility. When reentering the abdominal cavity, they lead to intraoperative complications and prolonged operating time. Inadvertent enterotomy at adhesiotomy occurs in 19% of additional operations. Intestinal obstruction, the most life-threatening adhesion-related disease, has mortality rates of up to 15%.[1-4] Various approaches for prevention of adhesions have been used. All efforts directed at reduction of surgical trauma by using laparoscopic access, powder-free gloves, subtle preparation, and meticulous hemostasis, however, have been of only limited success. With increasing longevity and growing numbers of surgical procedures, the clinical workload and the socioeconomic costs of adhesion-related diseases are constantly rising.[5-8]

These facts call for adjuvant means directed at prevention and control of peritoneal adhesions. Fibrinolytic agents, nonsteroidal anti-inflammatory drugs, and corticosteroids carry the risk of hemorrhage, ulcers with subsequent bleeding, immunosuppression, and healing disorders. Saline solutions are too rapidly absorbed, and hydroflotation by macromolecular solutions shows significant adverse effects, such as fluid shifting, impairment of liver function, and even rare cases of disseminated intravascular coagulation and anaphylactic shock. Barriers in the form of patches are working efficaciously for local protection of the female reproductive organs, but they are not suitable for covering the disseminated mesothelial lesions afflicted by retractors, towels, and desiccation.[5,9-12]

Phospholipids were identified as a surfactant-like substance in the effluent of peritoneal dialysis.[13] These phospholipids, which have excellent release and lubricating properties, adsorb as an oligolamellar lining to the mesothelium.[14] Experiments with different settings demonstrated a significant reduction of adhesion formation after single intra-abdominal administration without any adverse effects.[12,15-18]

Icodextrin is an iso-osmolar, biodegradable, α-1,4-linked glucose polymer solution. Since icodextrin is only a substrate for amylase, which is not present in the abdominal cavity, it is stable for 3 to 5 days after intraperitoneal application until absorption via the lymphatic system. When it enters the systemic circulation, icodextrin is rapidly metabolized by amylase to oligosaccharides.[19-21] The hypothetical mode of action keeps the surfaces apart by flotation.

Abdominal and pelvic operations carry the risk of bacterial spillage from intestinal or gynecologic organs. Antiadhesive agents contact residue from contaminated fluids left after the procedure or secondarily from anastomotic leakage. Therefore, adhesion preventive drugs and devices must prove their safety in an infectious experimental setting.

Tzianabos et al[22] showed that a gel formulation of chemically modified sodium hyaluronate (HA) and carboxymethylcellulose (CMC) resulted in the propagation of intra-abdominal infection in a rat model in contradiction to a solid membrane of HA-CMC. Reijnen et al[23] demonstrated reduced adhesion and abscess formation using 0.4% HA solution. The HA-CMC membrane, however, showed adhesions and abscesses similar to controls receiving isotonic sodium chloride solution. In another study,[21] using a bacterial inoculum challenge in the rat, application of Ringer lactate solution resulted in a higher overall abscess score than instillation of icodextrin or no medication at all. This study was designed to investigate whether intraperitoneal application of antiadhesive fluids is capable of reducing abdominal adhesions in a contaminated environment and promoting abscess formation.

METHODS

A total of 60 female Sprague-Dawley rats (Department of Laboratory Animal Science, Rhenish-Westphalian Technical University, Aachen) were housed in standard cages under standard laboratory conditions with unrestricted access to a balanced pellet diet and water. The study protocol was approved by the local Animal Use and Care Committee, and the experiments were conducted in accordance with animal protection laws. After adaption, bacterial peritonitis was induced using the cecal ligation and puncture model according to Wichterman et al.[24] Animals were anesthetized by subcutaneous injection of a combination of 100 mg/kg of ketamine hydrochloride (10% Ketamin; Sanofi-Ceva GmbH, Düsseldorf, Germany) and 5 mg/kg of xylazine hydrochloride (2% Rompun; Bayer AG, Leverkusen, Germany). After weighing, shaving, and skin disinfection, a 3-cm midline incision was made. The cecum was filled with feces and ligated just below the ileocecal valve with a 3-0 polyglactin suture, permitting bowel continuity. The antimesenteric cecal wall was punctured with a 21-gauge needle, and the bowel was replaced into the abdominal cavity. After closing the abdomen in 2 layers with 3-0 polyglactin sutures, the animals received 0.1 mg/kg of buprenorphine hydrochloride (Temgesic; Essex Pharma GmbH, Munich, Germany) and 10 mL of isotonic sodium chloride solution subcutaneously for analgesia and hydration.

On day 1, animals were weighed and the abdomen was reopened under general anesthesia as described herein. Peritoneal fluid samples were collected and blood samples were obtained for microbiologic examination. The abdominal cavity was rinsed with 10 mL of isotonic sodium chloride solution, and the cecum was resected. Before closing the abdomen, the animals were randomly assigned to 3 groups for intraperitoneal instillation of a constant volume of 5.0 mL/kg of phospholipids (75 mg/kg; the PL group) (Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany); 4% icodextrin (the ID group) (Adept; ML Laboratories PLC, Liverpool, England); or Ringer lactate solution (the RL group) (Delta-Pharma GmbH, Pfullingen, Germany).

On days 11 and 21, approximately half of the animals in each group were weighed and humanely killed using an overdose of isoflurane (Baxter Deutschland GmbH, Unterschleissheim, Germany), resulting in 9 animals in the RL_{11} group, 8 in the ID_{11} group, 8 in the PL_{11} group, 9 in the RL_{21} group, 7 in the ID_{21} group, and 10 in the PL_{21} group for evaluation. (Nine animals died prior to the end of the observation period.) The abdominal cavity was opened via a U-shaped incision for complete exploration. Adhesions were examined and registered. Peritoneal adhesions were meticulously dissected, and the intestine was opened along the mesenteric attachment for planimetry. Specimens were placed without tension on a plain surface for transfer of the adhesion areas to a translucent foil. The latter was scanned together with a reference of scale. Images were analyzed and areas were computed (square millimeters) using digital photomicrography software (DP-Soft 3.0, version 3.0; Olympus Optical Co [Europe] GmbH, Hamburg, Germany).[18,25] The presence and size of abscesses were registered using the following scores: 0, no abscess present; 0.5, 1 very small abscess; 1, several small abscesses; 2, 1 medium abscess; 3, 1 large or several medium abscesses; and 4, 1 very large or several large abscesses present.[26] Swabs from abscesses and venous blood samples were collected for microbiologic examination.

MICROBIOLOGIC EXAMINATION

Swabs

Peritoneal fluid samples were taken from all animals on revision laparotomy for verification of the induced peritonitis. The swabs (SWUBE; Becton Dickinson GmbH, Heidelberg, Germany) were immediately introduced into a transport medium (Port-A-Cul; Becton Dickinson GmbH), transferred to the bacteriologic laboratory, and processed within 60 minutes after sampling.

Blood Culture

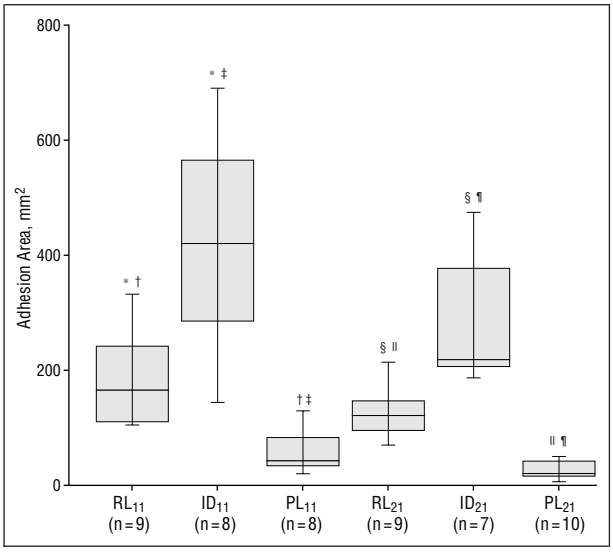
For screening of bacteremia, 1 mL of blood was drawn from the tail vein and injected into a pediatric blood culture bottle (BacT/ALERT PF; bioMérieux, Durham, NC) and cultivated for 7 days using an automated blood culture system (BacT/ALERT; bioMérieux).

Cultivation

Swabs were squeezed out in 5 mL of bouillon (mixture of brain heart infusion and thioglycolate broth, ratio 1:1). Then 500 µL of the bouillon was transferred to another tube containing 5 mL of the same bouillon (Becton Dickinson GmbH) using a sterile pipette. After thoroughly vortexing, this procedure was repeated 9 times. Following 24 hours of cultivation under anaerobic atmosphere using Anoxomat (MART GmbH, Bocholt, Germany) at 37°C, the 2 tubes with the highest dilution showing growth were plated onto blood agar (Fluorocult MacConkey agar; Merck KGaA, Darmstadt, Germany), colistine/nalidixine acid agar, Rogosa SL agar (Difco Laboratories, Sparks, Md), and Schaedler agar (Becton Dickinson GmbH). The 2 highest-dilution tubes were incubated for 72 hours under anaerobic condition, whereas the other ones were incubated under aerobic condition to cultivate the predominating microbiologic flora.

Identification

Identification of grown bacteria was achieved using standard microbiologic procedures established in a clinical laboratory. Gram-



Box-and-whisker plot of adhesion areas for the Ringer lactate (RL), icodextrin (ID), and phospholipids (PL) groups of animals humanely killed at days 11 and 21 (subscript numbers appearing with group name). Data are given as median (range). Asterisk indicates $P<.007$ for RL_{11} vs ID_{11}; dagger, $P<.001$ for RL_{11} vs PL_{11}; double dagger, $P<.001$ for ID_{11} vs PL_{11}; section mark, $P<.01$ for RL_{21} vs ID_{21}; parallel mark, $P<.001$ for RL_{21} vs PL_{21}; and paragraph mark, $P<.001$ for for ID_{21} vs PL_{21}.

negative bacilli were identified using the Api 32E gallery (bioMérieux), strips containing miniaturized biochemical tests. In case of suspected *Escherichia coli* (ie, fluorescent colonies on Fluorocult MacConkey plates), a spot indole test was performed. Enterococci were further identified using the PYRase test and plating on a Clauberg plate (BAG-Biologische Analysensystem GmbH, Lich, Germany). Staphylococci were identified using a latex test (Pastorex StaphPlus; Bio-Rad Laboratories, Munich, Germany) to discriminate *Staphylococcus aureus* from coagulase-negative staphylococci. Lactococci (ie, typical growth on Rogosa SL agar plates) were identified by gram stain and tested for vancomycin resistance. Obligate anaerobic bacteria were identified using the Api 32AN gallery (bioMérieux) (different galleries were used to detect different bacteria).

HISTOLOGIC FINDINGS

Adhesion-carrying tissues were excised en bloc and fixed in formaldehyde solution. Sections with a thickness of 5 µm were stained with hematoxylin-eosin for light microscopy to evaluate the structure of the connective tissue and the healing process.

STATISTICAL ANALYSIS

All data are expressed as median and range or mean±SD. The Mann-Whitney *U* test for independent samples was used for statistical analysis. With regard to the repeated comparisons, the level of significance was adjusted according to Bonferroni. Differences were considered significant at $P<.05$.

RESULTS

The mean±SD body weight of the rats was 237.3±12.9 g at the time of the first operation. The rats lost weight during peritonitis (231.8±12.9 g) and recovered weight by the end of the experiment (273.7±21.5 g). Performance of the initial surgical procedure was uneventful in all animals. All animals showed signs of peritonitis-like reduced activity, piloerection, and ocular exudates. One day after resecting the necrotic cecum and peritoneal lavage, all symptoms resolved. One animal died from narcotic disturbance during the second anesthesia (RL group). Another 8 animals died from peritonitis and sepsis within 36 hours following cecal resection (1 in the RL group; 5, ID group; 2, PL group).

The median (range) area of adhesions in the RL group (RL_{11}) at day 10 after peritonitis amounted to 163.8 mm^2 (105.5-330.7 mm^2) compared with 418.5 mm^2 (141.0-687.8 mm^2) in the ID group (ID_{11}) and 43.7 mm^2 (20.6-128.4 mm^2) in the PL group (PL_{11}). No animal in this PL group had adhesions exceeding 130 mm^2, in contrast to all of the animals in the ID group and 70% in the RL group. After an interval of 20 days following resection of the cecum, the extent of adhesions reached 120.9 mm^2 (67.9-352.0 mm^2) in the controls (RL_{21}) vs 218.6 mm^2 (184.8-643.9 mm^2) in the icodextrin group (ID_{21}) and 20.4 mm^2 (6.75-50.2 mm^2) in the PL group (PL_{21}). Only 1 animal in the PL_{21} group had an adhesion area of more than 50 mm^2 vs all of the animals in the ID or RL groups (**Figure**).

The comparisons of the control groups (RL) vs the lipid groups (PL), both 11 days (163.8 vs 43.7 mm^2, $P<.001$) and 21 days after peritonitis (120.9 vs 20.4 mm^2, $P<.001$), were significant. The differences between the RL and ID groups (11-day groups: 163.8 vs 418.5 mm^2, $P<.007$; 21-day groups: 120.9 vs 218.6 mm^2, $P<.01$) were significant. We found significant differences between the ID and PL groups at both time points (418.5 mm^2 for the ID_{11} group vs 43.7 mm^2 for the PL_{11} group, $P<.001$, and 218.6 mm^2 for the ID_{21} group vs 20.4 mm^2 for the PL_{21} group, $P<.001$). There were no differences between the median adhesion areas after both intervals following application of the same agent.

The scores concerning degree and severity demonstrated significant differences between PL and all other groups regarding the different time points after peritonitis. No differences were found between the RL and ID groups (**Table**). Abscesses were found predominantly at the site of cecal resection. Significant differences were only found between the RL_{11} and ID_{11} groups. The detailed scores are given in the Table. After 21 days, only the ID group showed abscesses.

In all animals, bacteria typical for enteral flora, for example, *E coli*, *Enterococcus* species, and *Lactobacillus* species, could be cultivated in all groups (data not shown), thus substantiating the presence of peritonitis due to an endogenous infection. Additionally, in up to 50% of the animals, bacteremia could be detected (data not shown) mostly due to *E coli*, *Enterococcus* species, or *S aureus*.

Histologic examination of the adhesions (days 11 and 21) revealed an unspecific inflammatory-reparative tissue response, characterized by a mixed inflammatory infiltrate of polymorphonuclear and mononuclear leukocytes, fibroblasts, hyperplastic mesothelial cells, and numerous capillaries. Qualitatively, no histologic differences were found among the RL, PL, and ID groups.

COMMENT

Damage to the mesothelial lining of the peritoneal cavity is inflicted by surgical trauma, such as ischemia, desiccation, thermal injury, foreign bodies, and infection. These peritoneal lesions lead to oozing from a fibrinous exu-

Adhesion and Abscess Scores*

Study Groups†	Adhesion Score				Abscess Score	
	Severity	*P* Value	Degree	*P* Value		*P* Value
RL_{11}	2.70 ± 0.16	***P*<.02 vs PL_{11}** *P*>.05 vs ID_{11}	2.90 ± 0.10	***P*<.001 vs PL_{11}** *P*>.05 vs ID_{11}	0.15 ± 0.08	***P*<.04 vs ID_{11}** *P*>.05 vs PL_{11}
RL_{21}	2.33 ± 0.24	***P*<.02 vs PL_{21}** *P*>.05 vs ID_{21}	2.56 ± 0.17	***P*<.001 vs PL_{21}** *P*>.05 vs ID_{21}	0	*P*>.05 vs ID_{21} *P*>.05 vs PL_{21}
ID_{11}	2.63 ± 0.18	***P*<.03 vs PL_{11}** *P*>.05 vs RL_{11}	2.63 ± 0.18	***P*<.001 vs PL_{11}** *P*>.05 vs RL_{11}	0.81 ± 0.30	***P*<.04 vs RL_{11}** *P*>.05 vs PL_{11}
ID_{21}	2.57 ± 0.20	***P*<.008 vs PL_{21}** *P*>.05 vs RL_{21}	2.71 ± 0.18	***P*<.001 vs PL_{21}** *P*>.05 vs RL_{21}	0.14 ± 0.14	*P*>.05 vs RL_{21} *P*>.05 vs PL_{21}
PL_{11}	2.00 ± 0.18	***P*<.02 vs RL_{11}** ***P*<.03 vs ID_{11}**	1.38 ± 0.18	***P*<.001 vs RL_{11}** ***P*<.001 vs ID_{11}**	0.25 ± 0.13	*P*>.05 vs RL_{11} *P*>.05 vs ID_{11}
PL_{21}	1.50 ± 0.22	***P*<.02 vs RL_{21}** ***P*<.008 vs ID_{21}**	1.20 ± 0.13	***P*<.001 vs RL_{21}** ***P*<.001 vs ID_{21}**	0	*P*>.05 vs RL_{21} *P*>.05 vs ID_{21}

Abbreviations: ID, icodextrin group; PL, phospholipids group; RL, Ringer lactate group.

*Adhesion scores concerning severity and degree and abscess score according to study groups. Data are given as mean ± SD. Significant values are given in boldface.

†Subscript numbers indicate the day the animals were killed.

date. Postoperatively, however, tissue plasminogen activator activity is reduced, and the levels of inflammatory cytokines (tumor necrosis factor, interleukins 1 and 6) and plasminogen activator inhibitors 1 and 2 are elevated.[27,28] van Goor et al[29] reported a reduced fibrinolytic activity in general peritonitis with significantly elevated activity of plasminogen activator inhibitor 1 until day 8. In the early stages of peritonitis and soon after colonic surgery, the tissue plasminogen activator antigen is increased, but the activity is severely depressed in peritonitis.[30] Intra-abdominally administered recombinant tissue plasminogen activator prevents adhesion formation in a peritonitis model in rats. However, early bacteremia and increased mortality rule it out from intra-abdominal use in peritonitis.[31] Because of the resulting impairment of the fibrinolytic activity, these fibrinous adhesions are organized. Invasion of fibroblasts leads to deposition of collagen and subsequent formation of permanent fibrous adhesions. Experimental inhibition of plasminogen activator inhibitor 1 significantly reduced the extent of adhesions.[32]

Although a number of substances have been developed to prevent postoperative adhesions, no reliable agent exists for prophylaxis of postoperative adhesions potentially involving the entire peritoneal surface. Many drugs tested effectively in animal studies carry the hazard of severe adverse effects, ruling them out for general clinical application.[3] Bioabsorbable membranes, such as oxidized regenerated cellulose or HA-CMC, can separate traumatized tissues during the sensitive period. They may only be useful in circumscript regions, such as the small pelvis in gynecologic procedures or intra-abdominally implanted meshes.[33] However, mesothelial lesions initiating adhesions are potentially spread throughout the whole abdominal cavity.[12]

Phospholipids, polar phosphoric acid diesters, are the natural constituents of abdominal cavity fluid and cell membranes. Human mesothelial cells were found to rapidly synthesize and secrete this surfactant-like substance. Phospholipids are zwitterions with a positively charged quaternary ammonium ion that are able to bind to negative charges of epithelial surfaces.[34] Chen and Hills[35] were able to show adsorption of dipalmitoyl phosphatidylcholine to normal rat peritoneal mesothelium in an oligolammellar layer. This offers the possibility of covering the whole surface of the visceral and parietal peritoneum by a small amount of fluid during healing of the serosal defects.[13,36-38] Phospholipids proved to reduce adhesion formation in different settings, including general peritonitis, most probably by separating opposing areas of the peritoneal surface by a thin membranelike film. Previous studies[12,17,39,40] have shown the beneficial effect of phospholipids with a dosage of only 70 mg/kg without further enhancement of the adhesion preventing capacity by larger doses.

Verco et al[21] evaluated icodextrin in 2 rabbit models, both with 7-day intervals. A 4% solution in a volume of 20 mL/kg achieved a 78% reduction in the score in the uterine horn model. In the sidewall abrasion model, de novo adhesion formation could be reduced by 93% and adhesion reformation by 66% vs surgical controls.

Every adhesion preventive drug or device to be used within the abdominal cavity may be contaminated with bacteria left after surgical procedures or released by postoperative complications. Before clinical use of such additives, it has to be shown that they do not cause propagation of peritonitis and abscess formation. Reijnen et al[23] found that 0.4% HA reduces adhesion and abscess formation in the cecal ligation and puncture model of bacterial peritonitis. On the contrary, HA-CMC impaired adhesions, abscesses, and mortality in the same model. In another study, Reijnen et al[41] assessed the use of HA and CMC solutions in the same model. A reduction of both adhesion and abscess formation was achieved with CMC and low concentrations (0.2% and 0.04%) of HA, whereas 1% HA did not influence the scores. Tzianabos et al[22] compared the HA-CMC preparations as gel and membrane formulations in bacterial peritonitis. The bioresorbable membranes did not alter the disease process. The gels' preparations from chemically modified HA-CMC with carboximide or ferric ion increased the peritonitis and mortality. In this study, there was no lethality because of the substances added at revision laparotomy. All deaths occurred within the first 2 days of peritonitis.

Statement of Clinical Relevance

The development of adhesions is a major cause of morbidity in patients undergoing abdominal or gynecologic surgery. Several adhesion reduction devices have been approved for clinical use, and new generations of these devices are currently under development. Surgical manipulation in the peritoneal or pelvic cavities takes the risk of disruption to the bowel and the release of colonic contents into these normally sterile spaces. The effect of these devices on the propagation of bacterial peritonitis in these cases is unknown. Previous studies of other groups showed different outcomes concerning propagation of bacterial peritonitis with different antiadhesive agents or different compositions or preparations of the same product. The data indicate that adhesion reduction devices should be tested in appropriate models of concomitant bacterial contamination. We examined the effect of 2 fluid adhesion reduction devices in a rat peritonitis model. Results from this study demonstrated that one device resulted in the propagation of intra-abdominal infection and an increase in the severity of disease; the other had positive effects.

Verco et al[21] analyzed 4% icodextrin in a bacterial peritonitis after inoculation in rats. The abscess score was similar with surgical controls, but the RL group showed an increased score. In our study, the ID group had significantly more abscesses and adhesions than all other groups. A possible explanation is that we used another model. Verco et al did not evaluate adhesion formation in the peritonitis experiment. We found an increase of adhesion areas by 233% and 180% compared with the RL groups after 11 and 21 days, respectively. It seems that icodextrin, produced on a glucose basis, promotes infection and should not be used in peritonitis.

Phospholipids proved effective and safe in this experimental setting. Adhesion formation was reduced by 76% and 83% in the RL group after 11 and 21 days, respectively, without supporting abscess formation. Therefore, phospholipids may qualify to be used even in the presence of infectious microorganisms.

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