

METHOD AND COMPOSITION FOR REDUCING POSTSURGICAL ADHESIONS

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates generally to methods and compositions for reducing postsurgical adhesions in the abdominal or thoracic cavity of mammals.

2. Description of the Prior Art

There is a need for a method and composition suitable for use in preventing adhesion formation/reformation in mammals following surgical injury to the peritoneal or pleural cavity, or organs situated therein.

According to Ellis in a reviewed entitled "The Cause And Prevention Of Post-operative Intraperitoneal Adhesions" in *Surgery, Gynecology and Obstetrics* for September 1971, volume 133, pages 497-509, at pages 502-503, the prevention of adhesions has been the subject of an enormous amount of work since the beginning of this century. According to Ellis, these attempts have included means of preventing the fibrin-coated walls of the intestine from reaching each other by distending the abdomen with oxygen or filling the abdomen with saline solution, paraffin, olive oil, lanolin, concentrated dextrose solution, macromolecular solutions of all sorts, and silicones.

Caspi, Halperin, and Bukovsky in an article entitled "The Importance of Periadnexal Adhesions in Reconstructive Surgery for Infertility" appearing in *Fertility and Sterility* for March 1982, volume 31, number 3, pages 296-300, at page 299 indicate that despite experimental and clinical efforts in the prevention of adhesion formation following surgery, no major advances have thus far been achieved. The authors discuss the use of post-operative intraperitoneal installation of a mixture of hydrocortisone acetate, promethazine, and ampicillin. As an alternative method of treatment, a low molecular weight dextran (a glucocorticoid) was also instilled intraperitoneally in another group of patients. The authors conclude that the intraperitoneal installation of high doses of glucocorticoids combined with early hydrotubations seems to be a worthwhile method.

Musich and Behrman in an article entitled "Infertility Laparoscopy In Perspective: Review of 500 Cases" appearing in *The American Journal of Obstetrics and Gynecology* for June 1, 1982, pages 293-303, at page 300 in the discussion section of the article disclose that there is a need to prevent adhesions subsequent to surgery in view of a study of 35 patients which indicated that 30 of these patients having serious tuboplasties had severe adhesions, one-third of which were judged to be inoperable.

High molecular weight dextran either alone or in combination with dextrose has been used in the prevention of peritoneal adhesions subsequent to surgery. Dextran is clinically standardized to a low molecular weight of about 75,000 by partial hydrolysis and fractional precipitation of the high molecular weight particles which normally have molecular weights of up to 200,000. Dextran is a polymer of glucose which has a chain-like structure and is produced from sucrose by *Leuconostoc* bacteria. In articles appearing in *Fertility and Sterility*, volume 33, number, 6, June 1980, pages 660-662, Holtz, Baker, and Tsai and volume 34, number 4, October 1980, pages 394-395, by Holtz and Baker, results are reported of the adhesion reducing effects of a 32% (aqueous) solution of dextran 70 containing 10%

dextrose (sold under the trade name HYSKON by Pharmacia, of Piscataway, N.J.). Holtz et al. postulate several mechanisms of action in the prevention of peritoneal adhesions utilizing HYSKON including a simple mechanical separation of adjacent surfaces, termed a hydroflotation effect.

Project coordinator diZerega and several contributors have reported the results of a large study in an article entitled "Reduction of Post-operative Pelvic Adhesions with Intraperitoneal 32% Dextran 70: A Prospective, Randomized Clinical Trial" in *Fertility and Sterility*, volume 40, number 5, for November 1983, pages 612-619. The authors, at page 618, indicate that the use of Dextran intraperitoneally has limitations such as the reported tendency of HYSKON to support bacterial proliferation and concern over the anaphylactoid potential of dextran. In addition, the benefit of Dextran 70 in preventing post-operative adhesions was shown to be limited to the more dependent regions of the pelvis.

Borten and Taymor in *Obstetrics and Gynecology*, volume 61, number 6, June 1983, pages 755-757 report in an article entitled "Recurrent Anaphylactic Reaction to Intraperitoneal Dextran 75 Used for Prevention of Postsurgical Adhesions". These authors indicate that anaphylactic reaction to Dextran administered intravenously is well documented and report such a reaction after intraperitoneal administration of Dextran.

Linsky in *The Journal of Reproductive Medicine* for January 1987, pages 17-20 in an article entitled "Adhesion Reduction in the Rabbit Uterine Horn Model Using an Absorbable Barrier, TC-7". These authors report that the use of a resorbable fabric barrier provides a significant reduction in post-operative adhesion formation and that no gross remnants of the fabric barrier material were noted, subsequent to initial placement, after a two week period.

Oelsner et al. in *The Journal of Reproductive Medicine* for November 1987, volume 32, number 11, pages 812-814, reported results of a comparison of sodium carboxymethyl cellulose, 32% dextran 70, and chondroitin sulfate to prevent the formation of postoperative adhesions in the rabbit uterus. The authors report superior results with chondroitin sulfate which is described as a member of a family of biochemical compounds referred to as glycosaminoglycans (formerly termed mucopolysaccharides), to which hyaluronic acid, heparin sulfate and heparin also belong.

The use of ethylene oxide/propylene oxide block copolymers as surfactants for use in surgical scrub solutions and the topical application of 10% solutions of these copolymers to wounds is described in Edlich et al in the *Journal of Surgical Research*, volume 14, number 4, April 1973, pages 277-284. The test results indicate that the copolymers having an ethylene oxide:propylene oxide ratio of 4:1 provide less inflammatory response in a wound to which the copolymer is applied in comparison with a copolymer having an ethylene oxide:propylene oxide ratio of 1:4. There is no indication in Edlich et al or any prior art that such copolymers are useful in reducing post-operative adhesions.

SUMMARY OF THE INVENTION

Compositions and a process are disclosed for reducing post-surgical adhesion formation/reformation in mammals following surgical injury to the organs of the peritoneal or pleural cavity. Both aqueous and non-aqueous compositions comprising a polyoxyalkylene