

METHOD AND COMPOSITION FOR PREVENTING SURGICAL ADHESIONS USING A DILUTE SOLUTION OF POLYMER

This application is a continuation of Ser. No. 555,377 filed Jul. 19, 1990, now U.S. Pat. No. 5,080,893 issued Jan. 14, 1992, which is a continuation of Application Ser. No. 07/199,087 filed May 31, 1988 now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the improvement of surgical techniques and tissue-protective surgical solutions.

2. Prior Art

Adhesions of the tissues involved in surgery occasioned by manipulative trauma of the tissue surfaces during the surgery and other causes such as drying and ischemic trauma constitute one of the most serious post-operative complications of surgical procedures.

Although a variety of techniques have been proposed to reduce adhesions, the problem continues to plague the art and seriously compromise even the finest and most scrupulously performed surgeries. Prior attempts to alleviate the problem and the disappointing results attendant are described in Davis et al, *Surgery*, Vol. 2, p. 877 (1937); Gozalez, *Surgery*, Vol. 26, p. 181 (1949); Hunter et al, *J. Bone Joint Surg.*, Vol. 53A, p. 829 (1971); Ellis, *Surg. Gynecol. Obst.*, Vol. 133, pp. 497-511 (1971); Lindsay et al, In Verdan, C. (ed); *Tendon Surgery of the Hand*, Lond, Churchill Livingstone, pp. 35-39 (1979); Potenza, *J. Bone Joint Surg.*, Vol. 45A, p. 1217 (1963); Verdan, *J. Bone Joint Surg.*, Vol. 54A, p. 472 (1972); St. Onge et al, *Clin. Orthop.*, Vol. 148, pp. 259-275(1980); Thomas et al, *Clin. Orthop.*, Vol. 206, pp. 281-289 (May, 1986); Weiss et al, *Bull. Hosp. Jt. Dis. Orthop. Inst.*, Vol. 46(1), pp. 9-15(1986).

Goldberg et al. [*Arch. Surg.*, Vol. 115, pp. 776-780 (1980)] describes the use of certain hydrophilic polymer solutions (Povidone polyvinylpyrrolidone K-30 PVP, and dextran) to coat tissue exposed to drying and/or manipulative peritoneal trauma as well as the surgical articles, etc., which contact the tissue before and during surgery to prevent adhesions. Although the materials and methods of Goldberg et al showed some improvement over other research studies in which hydrophilic polymer solutions were used to attempt to reduce the incidence of surgical adhesions, there still exists significant need for improvement.

A distinct disadvantage associated with the materials and methods of Goldberg et al and other prior art which has shown some benefit is the required use of highly concentrated solutions of the polymeric materials which makes practical use in surgery very difficult. Concentrated polymer solutions (greater than about 10-15%), for example, the 25% PVP and dextran solutions used by Goldberg et al, become sticky due to drying during surgery on the surfaces of tissue, surgeons' gloves, instruments, etc. This can seriously interfere with normal surgical procedures. High concentrations of PVP (K-30-molecular weight about 40,000) and dextran (molecular weight about 300,000) were required to achieve even some degree of tissue protection. Many studies prior to the report of Goldberg et al used lower concentrations of PVP, dextran, or other water soluble polymers which were even more ineffective. For example, Ellis [*Surg. Gynecol. Obst.*, Vol. 133, pp.

497-511] has stated that "use of PVP was accompanied by a slightly greater incidence of adhesions" in a rat peritoneal adhesions study. He also states that because "such macromolecular solutions as plasma or dextran are known to be absorbed rapidly through functional lacunas on the under surface of the diaphragm" and "it is therefore probable that any effect of PVP or any other macromolecular solution introduced into the peritoneal cavity could only be transitory". In the study by Berquist et al [*Eur. Surg. Res.*, Vol. 9, p. 321 (1977)] using 10% dextran-70 (molecular weight 70,000) and 1% hyaluronic acid (molecular weight unknown), it was reported that there was "no difference between control and treated groups" for adhesions in rat and rabbit studies. Even attempts to use the relatively low molecular weight dextran-70 at very high concentrations (32%), based on suggestions of some beneficial effect in reducing genital tract adhesions in female rabbits [Neuwirth et al, *Am. J. Obstet. Gynecol.*, Vol. 121, p. 420 (1974)] have not proven very successful. A commercial 32% (w/v) solution of dextran-70 was introduced as a hysteroscopy fluid about 1984, but recent studies have shown "no effect in reducing adhesions" using 32% dextran [Hadick et al, *Military Medicine*, Vol. 152, p. 144 (1987)].

Moreover, the use of such high concentrations may increase the expense of the surgical solutions and poses problems in preparing, purifying, stabilizing and storing solutions of such highly concentrated and often viscous solutions. For example, 32% dextran tends to crystallize "when subjected to temperature variations or when stored for long periods" [data sheet for commercial 32% dextran-70 solution].

Although the studies reported by Goldberg et al indicated some modest improvement in preventing adhesions using 25% PVP (mol. wt. 40,000) and a slight improvement with 25% dextran (mol. wt. 300,000) even using a surgical method involving coating of tissues and surgical implements before surgical manipulation, the materials and surgical solutions used were clearly impractical for clinical use in surgery.

It is, therefore, an object of the present invention to provide a significant improvement in compositions and method of use in surgery for preventing surgical adhesions.

SUMMARY OF THE INVENTION

The above and other objects are realized by the present invention which provides an improved method of preventing surgical adhesions in tissue by manipulation thereof during surgery comprising coating tissue surfaces involved in the surgery and/or the surfaces of surgical articles which contact the tissue surfaces during the surgery with an aqueous solution of a hydrophilic, polymeric material selected from the group consisting of water soluble, biocompatible, pharmaceutically acceptable polypeptides, polysaccharides, synthetic polymers, salts and complexes thereof and mixtures thereof prior to manipulation of the tissue during the surgery, the improvement wherein the hydrophilic, polymeric material is of high molecular weight (greater than 500,000) and the solution contains from about 0.01% to about 15%, by weight, of the polymeric material.

The invention further comprises certain compositions, specifically adapted for coating the surfaces of tissues involved in surgery and preferably also the surfaces of articles which contact the tissue surfaces during