COMPOSITION AND METHOD FOR PREVENTION OF ADHESIONS BETWEEN BODY TISSUES

This invention relates to novel compositions containing a combination of hyaluronic acid and dextran and to their use as an agent for preventing adhesions, e.g. in order to avoid problems caused by unwanted adhesions between tissue surfaces.

Many surgical operations are complicated by the formation of unwanted adhesions between body tissues. Indeed, the effective prevention of adhesions is often an essential prerequisite for the ultimate success of the surgical procedure. Examples of surgery where adhesions are common and troublesome complications include abdominal surgery, where peritoneal adhesions between the intestines and/or abdominal wall may seriously impair gastrointestinal function; in urogenital surgery, where adhesions may occlude or otherwise impair the normal function of the ureters, bladder, uterus, fallopian tubes, etc, and in neurosurgery, where excessive granulation tissue may affect nerve function. In tendon surgery, the tendon and its sheath or other adjacent tissue will often tend to grow to a state of mutual adhesion during the postoperative period of immobilization and healing.

Considerable efforts have been made, without success, to prevent this problem by using various suturing techniques and passive movement of the tendon during the healing process. In microsurgery of the eye and inner ear, too, the prevention of adhesions may be of paramount importance. In thoracic and open heart surgery, the number of re-operation cases has been increasing, which has particularly highlighted the problem of pericardial and retrosternal adhesions. After heart surgery, adhesions often form between the epicardium and surrounding structures such as the pericardium, mediastinal fat, pleura and sternum. These adhesions make re-operations both difficult and hazardous. They increase the risk of damage to the heart during resternotomy and obscure the underlying coronary anatomy. Tight pericardial adhesions may also tend to cause coronary artery narrowing and to thus impair myocardial function.

One way of trying to prevent adhesions is based on holding apart the surfaces of tissues for a sufficient period of time after surgery. This can be achieved by placing some form of a barrier between the surfaces. Later this barrier can be removed either by a minor operation or, preferably, by natural in vivo degradation and phagocytosis.

One example of such a suitable barrier with inbuilt biodegradability is given in Swedish patent No. 456346 which describes a biocompatible gel of hyaluronic acid.

The above mentioned gel or film is one example of a material having a reasonable degree of mechanical strength. But in some cases, for example in hip surgery, demands in this respect are greater and a number of synthetic materials such as prostheses of plastic or titanium etc have been developed for such applications.

In other cases, however, it may be difficult to apply a pre-shaped material so that it covers all essential surfaces; and it may be especially difficult to hold such a material in place for a sufficiently long period of time. In such situations materials in liquid form are preferable.

Among the substances in liquid form which have been advocated and tested as adhesion prophylaxis agents, certain polysaccharides deserve special mentioning, especially glycosaminoglycans such as hyaluronic acid. Hyaluronic acid is available within a wide molecular weight interval, depending upon the source material and purification method. Highly purified hyaluronic acid of a weight average molecular weight ($\overline{M}_w$) exceeding 750,000 is described by Balazs in U.S. Pat. No. 4,141,973 and a hyaluronic acid preparation of a $\overline{M}_w$ of about 3 millions (Healon ® from Pharmacia AB, Uppsala, Sweden) is commercially available.

In the patent mentioned above (U.S. Pat. No. 4,141,973), Balazs indicates a number of applications for the product, including its use to prevent adhesions, and refers to some of the medical applications mentioned above. Hyaluronic acid has also been tested in various experimental models such as that of Weiss C et al (1986) which revealed good results in experimental tendon surgery. No adhesions were found in 55% of the treated group whereas only 5% of the control group were adhesion-free. Hyaluronic acid also had a pronounced effect on the nature of the adhesions — strong adhesions formed in only 18% of the treated group but in 62% of the controls.

Dextran is another polysaccharide which appears to reduce the risk of tissue adhesions in some models. This substance is well known in several therapeutic applications, e.g. as an important component of intravenous infusion solutions.

Among experimental studies which have been performed to investigate this effect of dextran, a trial by R. J. Robinson et al 1984 on prevention of pericardial adhesions is worthy of special mention. The work was performed on rabbits, whereby one group received intrapericardially 6% dextran 70 (Macrodex from Pharmacia AB, Uppsala, Sweden) and another operated group served as controls. Complete absence of adhesions was noted in 70% of cases in the dextran group, compared with only 10% in the control group.

It is thus clear that prior art literature indicates that both hyaluronic acid and dextran are able to reduce the risk of postoperative adhesion complications. In certain very complicated surgical operations, however, the possibility of achieving a final success may be greatly reduced, down to zero, due to adhesion formation. In such cases, an only partial reduction of this risk is not clinically sufficient; every effort must thus be made to completely eliminate this risk.

In this connection we have particularly studied pericardial adhesions in an attempt to resolve this problem. The experimental evaluation has been performed on a rabbit model analogous to that used by R. J. Robinson et al (1984) but with some very important differences: First, we induced a more pronounced standard tissue injury; and, secondly, we submitted the exposed surfaces to longer and more intensive drying. The subsequent experiments yielded very interesting results — it was evident that hyaluronic acid had a good effect (but did not prevent adhesions in all cases) whereas dextran in our standardized model provided no protection at all.

A composition containing both dextran and hyaluronic acid provided virtually complete protection against adhesion in this particular standardized model. The effect was substantially better than that of hyaluronic acid alone and, as mentioned above, dextran alone provided no protection at all. A clear synergistic effect was thus noted.

The present invention relates to a novel composition in liquid form for the prevention of adhesions between