

## Adhesion prevention: a deal of gynecologists

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*Postoperative adhesions are related to the trauma caused by the surgical procedure itself. We can assume that the ideal surgical approach is the one which best preserves tissue integrity. Eventhough new techniques have been developed, adhesion formation is still an incipient result. Besides surgical techniques, a wide variety of agents such as chemical solutions or barriers have been tested, but none of them has been proven to be effective in solving the problem completely. In this review, the currently available methods in preventing adhesion formation have been summarized. [Journal of Turgut Özal Medical Center 1(3):213-218,1994]*

**Key Words :** Adhesion formation, prevention

### **Adezyon oluşumunun önlenmesi**

*Postoperatif adezyonlar cerrahi müdahaleye bağlı travma ile ilgilidir. Doku bütünlüğünün çok iyi korunmasını, ideal cerrahi yaklaşım olarak değerlendirebiliriz. Yeni tekniklerin gelişmesine rağmen adezyon formasyonu hala kaçınılmazdır. Cerrahi teknikler yanında kullanılan kimyasal solusyon yada bariyerler gibi fazla sayıda ajanlarla bu problemi tam olarak ortadan kaldıramamıştır. Bu makale ile, adezyon formasyonunun önlenmesinde günümüzde geçerli metotlar özetlenmiştir. [Turgut Özal Tıp Merkezi Dergisi 1(3):213-218,1994]*

**Anahtar Kelimeler :** Adezyon oluşumu, korunma

Adhesion formation stands as the most important problem for the gynecologists. Since the most effective procedure has not been developed yet, to find the etiology and prevention of adhesion formation are one of the best deals of investigators. A great effort has been dedicated to reduce adhesion formation because of the morbidity associated with adhesions and recent emphasis on cost containment. A wide variety of agents have been tried, and these agents worked to a limited degree<sup>1</sup>.

Recent studies demonstrated conclusively that microsurgical techniques alone will not prevent adhesion formation. Therefore, besides chemical substances, physical barriers that prevent adhesion formation by limiting tissue apposition during the critical stages of mesothelial repair have become

available for the general obstetrician-gynecologist<sup>2,3</sup>. The known pathophysiology of adhesion formation, chemical substances and barriers used for adhesion prevention, efficacy of surgical techniques and the future of adhesion prevention will be summarized in this review.

### **PATHOPHYSIOLOGY OF ADHESION FORMATION**

The pathogenesis of postsurgical adhesion formation has become better understood. Investigators have demonstrated that the production of ischemic tissue after surgical injury by coagulation, ligation or devascularization have all been associated with adhesion formation<sup>4,5</sup>.

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Anatomically, the mesothelial cells of the peritoneum cover connective tissue containing blood vessels, collagen, fibroblasts, macrophages, lymphocytes, plasma cells and mast cells<sup>6</sup>.

Injury to the mesothelial layer, in which the plasminogen activators located, results in exposure of the underlying connective tissue with peritoneal fluid. Peritoneal fluid leukotriene B<sub>4</sub> and prostaglandin E<sub>2</sub> levels are increased while plasminogen activator activity is inhibited after peritoneal trauma. Leukotriene B<sub>4</sub> and prostaglandin E<sub>2</sub> are involved in adhesiogenesis. Plasminogen activation is essential in the lysis of adhesions by plasmin. Plasmin is the principal agent of the fibrinolytic system. The inactive proenzyme, plasminogen, is converted to plasmin by plasminogen activator. Plasmin then induces fibrinolysis wherever it encounters fibrin and fibrin degradation products are then formed. Thus, formation and dissolution unbalanced, and adhesion formation progresses<sup>1</sup>.

#### CHEMICAL SUBSTANCES IN PREVENTION OF ADHESIONS

Various substances (saline solution, Ringer's lactate, dextran, heparin, phosphatidylcholine, proteinase inhibitors, calcium blockers, NSAID, corticosteroids, hyaluronic acid, etc) have been investigated to determine their influence on adhesion prevention, but until recently the results were controversial and lacked any implication for clinical use<sup>7,8</sup>.

The result of corticosteroid use in experimental models of intraperitoneal adhesion formation generally have not been encouraging; furthermore, clinical use of these drugs in a postoperative situation is limited by their pharmacologic properties, including immunosuppression and delayed wound healing<sup>7</sup>.

Prostaglandin inhibition with some nonsteroidal antiinflammatory drugs appear promising in the relief of some premenstrual symptoms and in the prevention of postoperative pelvic adhesion formation, but more studies are needed in women. Whereas these antiinflammatory drugs have the side effect of reducing fertility by impairing implantation and tubal motility<sup>9</sup>.

Dextran is a water-soluble glucose polymer. It is a volume expander and can be manufactured in different molecular weights. The most used one is

32% solution of dextran 70. When it is instilled into the peritoneal cavity, it produces an osmotic gradient resulting in a transient ascites<sup>10</sup>. The role of dextran 70 in reducing adhesion formation was observed in several animal models<sup>11</sup>. It was compared with Ringer's lactate, and it was prior to it<sup>12</sup>. Since serosal drying and tissue abrasion play an important role in adhesion formation, an animal study was designated by Frishman et al to test the hypothesis that the peritoneal instillation of 32 % high molecular weight dextran 70 before, rather than after, a surgical procedure results in less postoperative adhesion formation and reformation. It was concluded that preoperative instillation of 32 % high molecular weight dextran 70 did not offer any advantage over postoperative instillation in the prevention of either adhesion formation or reformation<sup>13</sup>.

On the other hand, Gauwerky claimed that with increasing molecular weight of dextran the maximum effect is achieved with smaller quantities of the solutions. Because of adhesion preventing properties, in cases of single also multiple applications dextran 60 should be preferred to other high molecular solution<sup>14</sup>.

However, dextran 70 has important side effects, such as vulvar edema, edema of the leg, pleural effusion, coagulopathy, disseminated intravascular coagulation, hypotension, anaphylactic shock or allergic symptoms<sup>2</sup>.

Shahakian et al. evaluated the effect of combining carbon dioxide gas (CO<sub>2</sub>) with normal saline versus CO<sub>2</sub> with lactated Ringer's solution on adhesion formation in the rabbit model. They found that lactated Ringer's solution had a protective effect against adhesion formation<sup>15</sup>.

Tulandi evaluated the effects of Ringer's lactate, fibrin sealant (Tisseel, Immuno, (Canada)Ltd, Vienna, Austria), Interceed (TC7) (Johnson and Johnson Medical, Inc., New Brunswick, NJ), Gore-Tex surgical membrane (W.L. Gore & Associates, Inc., Flagstaff, AZ) and amniotic membrane on postsurgical adhesion in rat model. Ringer's lactate efficacy was found to be superior to that of the commercially available adhesion barriers and amniotic membrane<sup>16</sup>.

Although several decades have passed since the first theories concerning normal healing and adhesion formation processes were proposed, the possible role of some factors is still under investigation. The development of recombinant tissue plasminogen

activator offers a unique alternative to augment the depressed endogenous fibrinolytic system. Intraperitoneal application of recombinant tissue plasminogen activator to injured animal models showed significant reduction in both de novo and reformation of adhesions. To assess the potential benefit of synergistic therapy for the prevention of postoperative adhesion formation, a combination of calcium channel blocker and recombinant tissue plasminogen activator was instilled to the rabbit's peritoneal cavity by means of an Alzet osmotic pump x 200 hours. The results were in favor of this combination<sup>17</sup>.

In two different prospective, randomized and blinded animal studies to determine the effectiveness of hyaluronic acid solution in preventing intraperitoneal adhesions, it was concluded that hyaluronic acid appeared to reduce postoperative intraperitoneal adhesion by coating the serosal surfaces and decreasing the extent of initial tissue injury<sup>18,19</sup>.

Activated granulocytes play an important role in propagation of the inflammatory response by production of reactive oxygen species and release of their granule content. Hyperactivation of these cells is suggested to result in deterioration of wound healing and probably increase of cicatrization. Pantothenic acid and its stable salt form, Ca-Pantothenate, were shown to significantly improve surgical wound healing. In a study, the modulating effect of Ca-pantothenic acid to subsequent stimulation with a variety of stimuli was investigated on isolated human PMN using functional assay systems; Lucigenin dependent chemiluminescence (CL), release of myeloperoxidase (MPO). Ca-Pantothenate significantly inhibited the CL response of PMN upon stimulation with the chemotactid peptide cytokines GM-CSF and TNF  $\alpha$  at a concentration range of 5 to 50 mM, but not upon stimulation with opsonized zymosan. Moreover, Ca-Pantothenate significantly inhibited the release of myeloperoxidase from PMN upon stimulation with f-met-leu-phe at a concentration of 5 mM. In contrast, Ca-Pantothenate did not directly activate PMN in the assay systems tested. These *in vitro* results support the concept of an antiinflammatory action of Ca-pantothenate *in vivo*<sup>20</sup>.

In an unpublished experimental study we investigated the efficacy of pantothenic acid in prevention of adhesion formation in rat model. We observed that daily intramuscular administration of 20 mg/kg pantothenic acid significantly diminished adhesion

formation as compared with the control group and intraperitoneal pantothenic acid group. There was not a significant difference between the control and intraperitoneal pantothenic acid group. It is concluded that intramuscular route is effective, but intraperitoneal route not in reduction of adhesions. This study suggested that pantothenic acid may help reduce adhesions<sup>21</sup>.

## MECHANICAL BARRIER METHODS

Contemporary adhesion prevention regimens for infertility surgery emphasize the use of barrier materials to effect physical separation of injured surfaces before reperitonealization<sup>22</sup>.

Although mechanical barrier usage has gained widespread attention it is not approved yet because of its important side effects such as ischemia or foreign body reaction. But recently oxidized regenerated cellulose (TC7) and polytetrafluoroethylen (PTFE) and poloxamer 407 have attracted much attention<sup>23</sup>. These recently developed barrier methods have been tested in animal models and appear promising in reducing both formation and reformation of adhesions<sup>24</sup>.

### Oxidized regenerated cellulose (TC7)

Oxidized regenerated cellulose (TC7), is most widely used and clinically approved barrier<sup>25</sup>. This material was either used in combination or compared with some solutions in various studies.

Sixty-three infertility patients in 12 investigational centers were included in a multicenter, randomized, controlled study from Japan. All had pelvic sidewall adhesions due to prior infection, surgery, endometriosis and unknown causes. After the lysis of these adhesions, the pelvic sidewall was covered with Interceed (TC7). The Interceed (TC7)-treated sidewalls contained significantly fewer adhesions than the control sidewalls<sup>26</sup>.

In the rabbit uterine horn model, the synergistic effects of interceed and heparin were assessed and a reduction in adhesion formation was noted<sup>27</sup>.

On the other hand, in a prospective, randomized, blinded clinical study of laparoscopic ovarian cauterization with application of interceed to one ovary followed by short interval second look laparoscopy. Periovarian adhesions of varying severity developed in all women after laparoscopic ovarian cauterization. Interceed showed no protective effect<sup>28</sup>.

### **Polytetrafluoroethylene (PTFE)**

PTFE was used to reconstruct the peritoneum or pericardium. Experiences have proven the PTFE membrane to result in minimal adhesion formation when used as a pericardial substitute<sup>29</sup>. However, satisfactory results were not shown in gynecological surgery<sup>30</sup>. Goldberg reported a study showing increased adhesions scores with Gore-tex<sup>31</sup>. On the other hand, in a clinical trial, at the time of second look laparoscopy, Gore-tex surgical membrane, previously placed on the myomectomy site was removed and it was seen that the extension of adhesion was minimal<sup>32</sup>.

Up to date, no human studies was designated to compare barrier agents in humans.

Effects of Ringer lactate, Interceed (TC7) and Gore-Tex surgical membrane on postsurgical adhesion formation were compared in a randomized animal study and adhesion score after Ringer's lactate instillation was significantly lower than those of control, Interceed (TC7), and Gore-Tex groups<sup>33</sup>.

Tissue coating following cecal abrasion failed to inhibit adhesion formation. However, tissue coating with polymer solutions prior to cecal abrasion significantly reduced the formation of postoperative adhesions. In this study polyvinylpyrrolidone (PVP) and carboxymethyl cellulose (CMC) solutions were used<sup>34</sup>.

Flowgel was evaluated as an intraperitoneal barrier for prevention of postsurgical adhesion formation. Results were satisfactory and this material was considered to have significant potential for use as an adjuvant in laparoscopic infertility procedures<sup>35</sup>.

Young et al used grafts of trypsin treated, gamma irradiated human amniotic membranes to cover injured uterine horns of nulliparous female rabbits to prevent adhesions. These specially prepared amniotic membranes dramatically reduced postoperative adhesion formation<sup>36</sup>.

Poloxamer 407 is a biocompatible polymer that displays reverse thermal gelation characteristics: that is, the material exists as a liquid at room temperature and as a solid at body temperature. These properties make it an ideal material for use in laparoscopic surgery<sup>37</sup>.

### **SURGICAL TECHNIQUES**

If the operating surgeon pays attention to be

meticulous in surgical techniques this will help reducing adhesion formation, although it will not prevent totally. Peritoneal surfaces should be handled with care, hemostasis should be maintained, while selecting and applying suture, resultant ischemia must be kept in mind. Otherwise, none of barriers or instilled solutions can prevent adhesion formation. Therefore, meticulous surgical attitude is not the only but necessary process in adhesion prevention.

Peritoneal closure seems to be reasonable on denuded areas. But animal studies and clinical reports demonstrate increased adhesion formation on suture lines<sup>38-42</sup>. Peritoneal incisions that are not closed primarily demonstrate diminishing tissue necrosis by 24 hours with complete disappearance of tissue necrosis by 7 days. The sites show less inflammatory reaction and more prompt reperitonealization, than sites primarily closed with even minimally reactive suture (polyglycolic acid). Therefore, especially in gynecologic surgery a great attention must be paid to avoiding routine peritoneal closure<sup>43</sup>.

### **CESAREAN BIRTH**

In a prospective study, the outcome of peritoneal closure at the time of cesarean birth was evaluated. It was concluded that, nonclosure of the visceral and parietal peritoneum after low transvers section had no adverse effects on recovery and adhesions and, decreased the operating time<sup>44</sup>.

### **LAPAROSCOPY**

Laparoscopic surgery is believed to reduce adhesion formation. But it has no longer have its previous reputation in this regard. Because the studies done in the past several years demonstrated that laparoscopic surgical techniques decreased the adhesion scores only 50% and of the areas where adhesions were lysed, 67% contained at second look<sup>45</sup>.

### **FUTURE**

Adhesion prevention will take a longer time than it is expected. To date, no unique treatment modality has been proven effective in preventing adhesion formation. However, the state of art in surgical technology is changing so rapidly that the future is hard to predict. It is already known that abdominal adhesions are due to a locally decreased peritoneal

fibrinolytic capacity occurring mainly in ischemic areas of the peritoneum. No optimal solution to the problem of adhesions has been found so far. Nevertheless, appropriate surgical technique can permit us to control adhesion formation to a certain degree<sup>16</sup>. In this regard, surgeons performing abdominal procedures must be aware of the adverse reproductive effects of common surgical procedures<sup>17</sup>.

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