

Postoperative Intraoperative Adhesions, Are they Preventable? What are the benefits of Seprafilm® as a method of adjuvant therapy?

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Abstract: Postoperative Intraoperative adhesions are a burden for patients and physicians, by far there are no available laboratory tests or imaging to predict them³ and their complications costs estimated to be more than 5 billion U.S dollars annually⁷. The development of postoperative peritoneal adhesions has been studied thoroughly but up to date there is no definitive guidelines for prevention. This literature review aims to identify the Types, pathophysiology, complications, triggering factors of abdominal adhesions and the best evidence based methods for prevention with focus on Hyaluronic acid/carboxymethylcellulose (Seprafilm). A literature search in TRIP database, PubMed, Cochrane library, Medline, Embase was performed. Postoperative abdominal adhesions occur in up to 97% in patients who undergo open gynecological pelvic surgeries¹. (93-100%) of patients after upper abdominal surgeries and (67-93%) after lower abdominal laparotomies². 80% formed between the wound and the omentum, 50% are formed between intestines¹. Laparoscopic approach has showed a marvelous decrease in the incidence of adhesions by 45%². Ischemia is the most important pathological factor leading to Adhesions formation, balance between fibrin deposition and fibrinolysis is needed for normal healing. Literature review proved that Seprafilm is an effective method of prevention of adhesions, it is cost beneficial for healthcare system and patients. Furthermore, the use of specific surgical techniques has a significant effect on adhesions prevention. Adhesions are inevitable complications of intra-abdominal surgery. The most important factor in treatment of peritoneal adhesions is prevention. Seprafilm was found to be the best adjuvant method to prevent adhesions according to the literature review. I believe that in the near future Seprafilm should be considered as a guideline for postoperative adhesions prevention. Surgeons most often underestimate the concept of adhesions and do not have full awareness of the problem⁸⁰. I believe that postoperative adhesions prevention should start with the first skin incision.

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1.Introduction

Postoperative Intraoperative adhesions are a burden for patients and physicians. They have a huge impact on life quality. They are defined as fibrous bands of healed scar tissue that extend between surfaces of internal organs that are normally separated and attach them together. The development of postoperative peritoneal adhesions have been studied thoroughly, but up to date there is no definitive guidelines for prevention and the diagnosis or prediction of adhesions formation is challenging. By far there are no available laboratory tests or imaging that could predict the occurrence and the

severity of adhesions³. Intra-abdominal adhesions were firstly discovered in a post-mortem examination in 1836⁸. Postoperative abdominal adhesions incidence is high as they occur in up to 97% in patients who underwent open gynecological pelvic surgeries¹. 93-100% of patients after upper abdominal surgeries and 67-93% in patients who had lower abdominal laparotomies². 80% of the adhesions are formed between the wound and the omentum and 50% are formed between intestines¹. Laparoscopic approach has showed a marvelous decrease in the incidence of adhesions by 45%².

Table 1: Types of adhesions

1A: no previous operations at the site of adhesion	2A: no previous procedures at the site of adhesions besides adhesolysis
1B: previous operation at the site of adhesions	2B: other procedures at the site of adhesions besides adhesolysis

Adhesion can be divided into two main types. Type 1 (de novo) represents adhesions formed in a site that was previously free of adhesions, Type 2 represents adhesions reformation⁸¹. (Table 1)

Intra-abdominal adhesions are the leading cause of secondary infertility in women^{4,5}, and precipitate other complications like small bowel obstruction, chronic pelvic pain, infertility, hospital readmission and prolonged operation time. All these complications lead to frequent hospital admissions and patients commonly require to be operated for adhesiolysis. This operation is time consuming and carries the risk of accidental enterotomy, adhesions reformation and de novo adhesion formation⁶.

The financial costs related to frequent hospital admissions and adhesiolysis operations are very high. A study was performed to calculate these costs in the United States healthcare system and it estimated more than 5 billion U.S dollars annually⁷. In Sweden another study was conducted and results also were high as the total cost was estimated to be 13 million dollars annually⁹. According to all the previous points discussed, the most important factor in treatment of adhesions is prevention. Literature review demonstrated that there are many methods to for prevention of adhesions. Multiple researches approved the efficacy of some of these methods that will be mentioned in details in this article.

2. Method

A literature search in TRIP database, PubMed, Cochrane library, Medline, Embase was performed. In this article the aim is to investigate the main pathophysiology behind the formation of Postoperative Adhesions and the best evidence based prevention method with more focus on Sefrafilm.

3. Results

3.1 Pathophysiology

An injury to the normal peritoneal tissue resulting from surgery, inflammation, infection, trauma and foreign material such as gloves powder, talc, lint from abdominal packs could lead to the development of adhesions. The formation of adhesions is considered as a pathological part of the healing process most commonly due to abdominal surgery^{10,11}. Healing results from proliferation and regeneration of the mesothelial cell layer of the peritoneum. Surgical trauma to the mesothelium covering the peritoneum surface precipitates disruption of mast cells, leading to the release of vasoactive substances like histamines and kinins consequently increasing vascular permeability, which in turn leads to collection of exudate that covers the injured area¹². Fibrin gel matrix in the exudate will form fibrin bands between the injured areas and

simultaneously fibrinolysis will take place preventing extensive fibrin deposition¹². The balance between fibrin deposition and fibrinolysis is important in order to have a normal healing without adhesions⁸. Incomplete degradation of fibrin eventually leads to proliferation of fibroblast and angiogenesis resulting in deposition of collagen, which precipitate adhesions formation. In contrast, complete degradation of fibrin gives rise to normal peritoneal healing free of adhesions^{8,12}.

Fibrinolysis must occur within 5 to 7 days after the peritoneal injury, otherwise the temporary fibrin matrix transforms into collagen secreting fibroblasts and adhesions are formed^{15,16}. Fibrinolytic system functions through converting plasminogen into plasmin that degrades fibrin into fibrin degradation products (FDPs). It can be activated by tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) that are found on endothelial cells of blood vessels, mesothelial cells and macrophages⁸. Activation of fibrinolytic system is done 95% by (tPA)¹⁵.

Ischemia is the most important factor leading to Adhesions formation¹³. A thorough study of fibroblasts found in peritoneal adhesions compared to others found in normally healed peritoneal areas, showed different phenotypes and these changes were proved to be induced by hypoxia¹³. A lower rate of apoptosis was also observed in the fibroblasts found in adhesions¹⁴.

Cyclooxygenase enzyme 2 (COX2) has shown to be of a great importance in the formation of adhesions through regulating the steps of inflammation and angiogenesis, a study revealed that in the adhesion's fibroblasts, the level of COX2 was markedly increased compared to normal fibroblasts¹⁷. Multiple studies conducted on animal models have proved that COX-2 inhibitors such as Celecoxib, Refecoxib can reduce the formation of postoperative adhesions^{18,19,20}.

Reactive Oxygen Species (ROS) such as oxygen ions, peroxides have been proved to have an important role in the pathophysiology and the formation of adhesions^{21,22,23}. They are molecules containing oxygen and formed as a byproduct from oxygen metabolism by cells, they play an important role in homeostasis of the cell²⁴. Oxidative stress is an increase in the level of ROS in the cells that occurs in stressful conditions such as surgery, this event leads to structural cell damage²⁴. It was demonstrated that there is a positive correlation between the level of oxidative stress and the severity of adhesions^{25,26}.

Intra-abdominal influx of neutrophils postoperatively demonstrated an important role in formation of adhesions²⁵. A study on animal model using anti-neutrophils serum compared to the control

group has shown significantly decreased adhesions formation by 38%²⁵.

3.2 Prevention

The most important factor in treatment of peritoneal adhesions is prevention. In the past century many studies have been carried out extensively to investigate methods of preventions of postoperative abdominal adhesions, in this literature review some of these methods have proven their efficacy and successfully prevented the formation of adhesions and many others still under trials. In conclusion the preventive methods can be divided into four main categories²⁷:

- 1- General principles.
- 2- Surgical techniques.
- 3- Adjuvant therapy with mechanical barriers.
- 4- Adjuvant therapy with pharmacological agents.

3.3 General principles & surgical techniques

William Stewart Halsted (1852-1922), an American surgeon who first described these principles and techniques "Halstedian principles"²⁸. The use of aseptic techniques, gentle tissue handling, sharp anatomic dissection of tissues, meticulous hemostasis with the minimal use of non-irritating sutures, closure of dead spaces and avoidance of tension²⁸. Additionally, continuous irrigation, keeping the tissues moist, the use of micro and atraumatic instruments has been proved to be effective²⁹.

The use of starch-powdered gloves demonstrated an increased risk of formation of postoperative adhesions³⁰.

Peritoneal closure vs. non-closure has been a debate over the years as some studies found out that closure increased the risk of adhesions, in contrast, other studies found it to be beneficial to decrease adhesions formation. A study on the outcome of peritoneal closure in patients who underwent radical hysterectomy showed increased adhesions formation among patients who had peritoneal closure (8.9% closure group – 5.8% non-closure group)³¹. Another study also demonstrated a significant increase in the incidence of formation of adhesions post-closure ($p < 0.05$)³².

In a 16 years prospective randomized control study on 360 patients undergoing lower segment cesarean incision were divided in 3 groups (group A: peritoneum was left unclosed, group B: closure of parietal peritoneum, group C: closure of both peritoneal layers) 65 out of 360 patients underwent second cesarean section, 20 from group A, 20 from group B and 25 from group C, adhesions were compared and showed higher incidence among group C (3 of 25), group B (1 of 20) and group A (1 of 20)³³. Other studies also supported the non-closure of the peritoneum^{34,35}.

On the contrary, a randomized study following 45 patients (22 closure vs. 24 non-closure patients), total of 31 patients were evaluated in their second caesarian section, the results were 54% of non-closure group developed adhesions compared to 15% of closure group. A prospective cohort study evaluated 173 patients and demonstrated adhesions formation in 52% of patients with prior closure compared to 73% of patients with non-closure, adhesions were present most commonly between the omentum and the fascia in non-closure group (30%) and between the fascia and the uterus in the closure group (12%)³⁶. However some studies also demonstrated no differences^{37,38}. On the other hand suturing peritoneal defects may lead to peritoneal ischemia and consequently decreased fibrinolytic activity that eventually leads to adhesions formation³⁹.

Laparoscopy vs. laparotomy, laparoscopic surgery has been proved to have more advantages compared to the traditional laparotomy over the past years^{41,42,43,44}. It provides small incisions in the peritoneum and minimizes tissue handling with atraumatic instruments. In a prospective randomized study 105 patients with ectopic tubal pregnancy were evaluated, and the outcome was significant decrease in adhesions formation among the laparoscopy group compared the laparotomy group⁴⁰. Another study demonstrated that the incidence of developing umbilical adhesions after laparotomy is 50% compared to 1.6% after laparoscopic procedure⁴⁵. Laparoscopic colectomy confirmed to have lower incidence of postoperative adhesions compared to open colectomy⁴⁶. Another advantage of laparoscopy is decreased rate of hospital readmission as demonstrated by Trastulli et al[47] in a meta-analysis of randomized clinical trial comparing open versus laparoscopic rectal cancer removal. In contrast CO₂ pneumoperitoneum caused by gas insufflation during laparoscopic surgery plays a role in adhesions formation as the CO₂ used is dry and cold which is irritant to the peritoneal cavity, it was reported that the adhesions formation increase with the duration of CO₂ pneumoperitoneum and insufflation pressure^{48,49}. Further detailed study demonstrated that CO₂ pneumoperitoneum increases postoperative adhesions according to duration of operation and pressure of insufflation, this increase could be reduced by adding 2-4% O₂⁵⁰. The use of heated humidified CO₂ at 37° reported many benefits such as less adhesions formation, short recovery room stay, less postoperative pain and less tumor growth^{48,51,16}.

3.4 Adjuvant therapy

Adjuvant therapy is further divided into two main categories⁵²:

1- Drugs that prevent excessive fibrin deposition.

2- The use of mechanical barriers to separate the serosal surfaces in early stages of healing.

Mechanical Barriers functions by separating the peritoneal surface in early stages of re-mesothelialisation in the first 5-7 days, Ideal barrier is biodegradable and should stay in place without staples or sutures, non-immunogenic and non-inflammatory^{29, 15,16,53}.

3.5 Hyaluronic acid/carboxymethylcellulose (Seprafilm®)

A mechanical barrier product by Genzyme Corporation, Cambridge, MA, United States. It was FDA approved in 1996 and it is available worldwide. Seprafilm has been indicated for the use of adults undergoing Abdominal and pelvic surgeries, it was reported that up to date, more than 2 million patients have been treated with it to *reduce the incidence of postoperative adhesions*⁵⁴. The optimum time for application and successful results is (5-7 days)⁷⁹. After placement of Seprafilm on the peritoneum, it becomes a hydrophilic gel and creates a coat around the injured tissue for 7 days during the entire phase of re-mesothelialisation⁵⁵. It can be used in the presence of blood and excessive irrigation unlike other barriers like Interceed, it is completely cleared from the body by the 28th day^{55,56}. The efficacy and benefits of Seprafilm has been confirmed by many studies and researches.

In multicenter prospective randomized controlled study on 183 patients undergoing total proctocolectomy with ileo-anal anastomosis, restorative pouch and temporary ileostomy, 175 patients were evaluated during ileostomy closure (90 control group vs. 85 received Seprafilm over the midline incision), the results were significantly in favor of patients who received adjuvant barrier treatment as 51% were free of adhesions compared to 6% of patients from the control group, more dense adhesions was observed in the control group 58% and 13% in Seprafilm treated patients⁵⁷. Another multicenter study including 127 female patients evaluated in a second look laparoscopy after myectomy demonstrated less adhesions in Seprafilm treated group [4.98(n=480)] compared to [7.88(n=48)]⁵⁵. Third study confirmed the efficacy of the use of Hyaluronic acid/carboxymethylcellulose after open colectomy, 30 patients were evaluated and the incidence of adhesions formation was 63.3% among the control group and (36.7%) among patients who received Seprafilm⁵⁸. Fujii et al [59] demonstrated that Placing Seprafilm beneath the anterior abdominal wall dramatically reduces the incidence of adhesions as (88.9%) of untreated sites

developed adhesions compared to only (40%) of treated sites.

Decreased incidence of small bowel obstruction (SBO) is one of the benefits of the use of Seprafilm. In a prospective randomized study including 504 patients who underwent radical resection for sigmoid or rectal cancer, 427 patients were evaluated (Seprafilm group 185 vs. control group 242), results showed significant less incidence of adhesions (2.7% Seprafilm group vs. 7% control group)⁶⁴. A study of 50 patients undergoing trans-abdominal aortic aneurysm surgery, 30 patients as a control group which (20%) of them had SBO and 21 patients treated with Seprafilm which (0%) of them reported to have SBO⁶⁰. A retrospective study including 367 patients undergoing elective laparotomy demonstrated lower incidence of postoperative small bowel obstruction, in the treatment group (184 patients) 6.5% had SBO while in the control group (183 patients) 14.2%⁶¹. Another retrospective cohort study showed decreased incidence in SBO after using Seprafilm (4.6% in Seprafilm group, 6.7% in the control group)⁶². Another report of patients who underwent gynecological surgeries for malignancies showed less adhesion among treated group (3.1% vs. 13.9%)⁶³. Other benefits also were mentioned in some studies such as, *reducing time needed for ileostomy closure* after applying Seprafilm around the defunctioning loop ileostomy to be done at 3 weeks with less complications⁶⁵. Another study demonstrated the duration of ileostomy closure operation was less in patients who had Seprafilm applied (107 min. vs. 121min)⁶⁶.

Seprafilm has no effect on malignancy and doesn't promote tumor growth, 202 Women were followed with a median follow up of 2.1 years after having surgeries for ovarian, fallopian tubes and peritoneal malignancies, there was no difference in overall disease free survival nor postoperative complications between control group and treated group⁶⁷. Other literatures also supported that⁶⁸⁻⁷⁰. *It is effective in pediatric group as well*, randomized cohort study in 122 pediatric patients demonstrated (59.1% from treated group) had no adhesions, compared to (17.6%) from the control group⁷¹.

It is cost effective; a study proved that the incremental cost of non-use was estimated to be (1,112\$) per patient⁵⁰.

Can be used in laparoscopic procedures, recently some studies demonstrated flag technique⁷⁷, slurry creation by mixing 20cc of sterile saline with 13x15 Seprafilm membrane and introducing into a leur lock syringe to be delivered to the abdomen through a laparoscopic irrigator⁷⁸.

Reported Complications of Seprafilm were relatively low compared to the advantages. Fistula

formation, infection, foreign body reaction, intraperitoneal fluid collection and bowel anastomosis leak were reported, application of Seprafilm on a fresh bowel anastomosis should be avoided^{57,72-74}.

Seprafilm compared to other mechanical barriers proved to have the lowest incidence of postoperative adhesions formation⁷⁶.

4. Conclusion

Adhesions are inevitable complication of intra-abdominal surgery. The most important factor in treatment of peritoneal adhesions is prevention. Seprafilm was found to be the best adjuvant method to prevent adhesions according to the literature review. I believe that in the near future Seprafilm should be considered as a guideline for postoperative adhesions prevention. Surgeons most often underestimate the concept of adhesions and do not have full awareness of the problem⁸⁰. I believe that postoperative adhesions prevention should start with the first skin incision.

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