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Efficacy of Alanyl-Glutamine in Preventing Mesh-Induced Adhesions: A Rat Model Study

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Abstract

Study objectives: This study aimed to evaluate the effectiveness of alanyl-glutamine in preventing intraperitoneal adhesions in the presence of Marlex and Prolene meshes in a rat model.

Design: This experimental study utilized a randomized controlled trial design.

Setting: The study was conducted at University of Saskatchewan, involving a laboratory animal facility.

Interventions: Twenty-four Wistar rats weighing over 300g were randomly assigned to three groups: Group 1 underwent laparotomy with cecal ligation and puncture and received Marlex or Prolene mesh, Group 2 underwent the same procedure with mesh plus alanyl-glutamine treatment, and Group 3 served as controls with laparotomy only. Adhesion formation was evaluated using histological staining techniques.

Results: Rats treated with alanyl-glutamine showed significantly fewer adhesions compared to those without treatment, as evidenced by lower Zuhlke adhesion scores and histological analysis. Adhesions were absent at the six-week follow-up in the treatment group.

Conclusion: Alanyl-glutamine effectively reduced adhesion formation in the presence of Marlex and Prolene meshes in this experimental rat model. These findings suggest a potential clinical application of alanyl-glutamine in enhancing surgical outcomes by mitigating postoperative adhesions associated with mesh placement.

Keywords: Gynecologic surgeries, Alanyl-glutamine, Adhesion prevention, Rat model study, Polypropylene mesh

Introduction

Adhesions are scar-like, fibrous tissue bands. Up to 93% of abdominal surgical patients develop adhesions.[1] They mostly occur after surgery, infection and other causes of inflammation such as endometriosis and radiation treatment. Adhesions frequently form between bowel segments, the abdominal wall, and operative sites. While they can develop anywhere in the body, they are most common after abdominal surgery. Other common sites of adhesions include the pelvis and pericardium with pelvic adhesions occurring in about 97% of open gynecologic surgeries.[2,3] Complications of adhesions include small bowel obstruction, intestinal ischemia and infarction, chronic abdominal and pelvic pain, and infertility, all of which negatively impact the patient's quality of life.

Mesh repair vs non-mesh repair

Herniorrhaphy, the traditional hernia repair method without surgical mesh, involved suturing tissue edges but had a high recurrence rate. In 1958, Dr. Francis Usher introduced hernioplasty using polypropylene mesh, which reinforced the abdominal wall, significantly reducing hernia recurrence and tension on soft tissues.[4,5] Mesh repair also simplified the procedure, making it the preferred method over non-mesh repair.

The problem with mesh

Unfortunately, the advent of mesh prostheses in abdominal surgery has vastly increased the occurrence of adhesions. Although mesh technology has improved greatly since their introduction

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at the start of the 20th century, all meshes still cause adhesions. Improvements have been made in their strength, flexibility, and absorbability and many modern meshes are even coated in substances aimed at reducing adhesion formation. These are only partially successful as adhesions still form.

Surgical mesh is made from materials with great tensile strength to reinforce weakened tissues. Unfortunately, adhesions form between many of these materials and the bowel. Two of such meshes are Marlex and Prolene which are both made of polypropylene. Polypropylene meshes are the most commonly used surgical meshes. Studies have shown that all polypropylene meshes lead to adhesions.[6,7]

In our study, Marlex mesh was chosen for its propensity to cause adhesions. This was done to test the novel treatment's ability to prevent adhesions even in the presence of a known cause of adhesion.

An investigation by Leblebici[8] compared the extent of adhesion formation after mesh placement in a rat model with incisional hernia used 4 types of mesh materials: polypropylene (PP), polytetrafluoroethylene (PTFE), PP coated with hyaluronic acid–carboxymethylcellulose, and PP coated with absorbable polydioxanone (PDS) on the parietal side and oxidized regenerated cellulose (ORC) on the visceral side. They found that all of these mesh materials caused severe adhesions compared to the control group.

Apart from the choice of mesh, laparoscopic procedures were often preferred to open procedures for prevention of adhesions. In another study, investigators conducted MRIs on patients after ventral hernia repair. They found that adhesions formed in all patients regardless of whether the repair was performed openly or laparoscopically.[5] This investigation also compared multiple types of PP and PTFE mesh materials. All demonstrated greater formation of adhesions compared to controls. This points to mesh use being the instigator when it comes to adhesions as opposed to the type of surgery performed.

Existing solutions for adhesion prevention

Currently, methods to prevent adhesions include strategies like reducing surgery duration, handling tissues gently, using saline solutions, moistened drapes, and starch and latex-free gloves.[9] Several products aim to mitigate adhesion formation by reducing friction between bowel loops and the abdominal wall. Notable examples are Seprafilm, Interceed, Adept, and 4DryField, assessed in a study by Poehnert.[10] Seprafilm and Interceed are hyaluronic acid carboxymethylcellulose membranes that inhibit macrophage migration. Adept is an icodextrin solution, while 4DryField is a plant-based polysaccharide powder forming a gel. According to the study, Seprafilm, Adept, and Interceed showed limited impact on reducing adhesion numbers, whereas 4DryField effectively decreased both the frequency and severity of adhesions.

Another significant advancement in preventing adhesions includes the introduction of dermal meshes, which help alleviate foreign body reactions and consequently reduce adhesions. Surgisis Biodesign exemplifies this innovation, functioning as a soft tissue graft derived from porcine small intestinal submucosa and fully absorbable.[11] Surgisis operates by offering a scaffold that supports the proliferation of human cells. Despite their efficacy, dermal meshes are considerably more costly than conventional alternatives.

The current methods to prevent adhesion formation collectively exhibit a success rate of less than 50%,[6] highlighting the pressing need for more effective and cost-efficient approaches in adhesion prevention.

Alanyl-Glutamine

Glutamine is an amino acid whose production is decreased in the post-surgical period. It has been seen that administration of glutamine after surgery enhances wound healing.[12] When used in parenteral nutrition, glutamine dipeptide reduced hospital stay after abdominal surgery. We chose to use the dipeptide alanyl-glutamine because of its effects on macrophages and fibroblasts, cells involved in adhesion formation. We hypothesize that when alanyl-glutamine is used in conjunction with commonly used surgical meshes, adhesions will be significantly reduced.

Study Aim

The aim of this study is to determine the effectiveness of alanyl-glutamine in the prevention of intraperitoneal adhesions in the presence of adhesion causing meshes in a rat model. We used Marlex mesh in this investigation as it has been shown in literature to cause adhesions.[7]

Method

Twenty-four Wistar rats weighing greater than 300g were operated on. All animals had virgin abdomens that had never been operated on before. Rats were anesthetized with halothane and administered bupivacaine for post-procedure pain control. Laparotomy followed by cecal ligation and puncture was performed. Cecal ligation and puncture is commonly used to replicate polymicrobial sepsis in animal models.[13] The cecal puncture was immediately closed with a purse-string suture. Vicryl suture material was used to close. The abdominal cavity was then irrigated to remove any possible fecal material that may have escaped from the cecum. Marlex mesh was placed and the skin was stapled. The control group consisted of rats who had laparotomy only and were immediately closed. Experimental group rats consisted of 2 subgroups. One group had laparotomy with cecal puncture and Marlex mesh placement. The second group received laparotomy with cecal puncture, Marlex mesh, and the treatment drug.

A second surgery was performed on all rats to evaluate for the presence and extent of adhesions. H&E and Masson histology stains were performed on abdominal tissue on day 10 post-surgery. Adhesions were graded using the Zuhlke[14] grading system shown in Figure 1.

Grade	Description
0	No Adhesion
1	Flimsy Adhesion
2	Mild Adhesion
3	Moderate Adhesion
4	Severe Adhesion

Figure 1: Grading of adhesions by Zuhlke[14]

Day 42 and day 90 post-laparotomy, rats were operated on again to evaluate the abdomen for adhesions.

Results

Rats in the treatment group had significantly less adhesions than non-treated rats 10 days post laparotomy. The reduction in adhesions is also demonstrated in Figure 2 comparing control and treatment group abdomens. Additionally, no adhesions were seen at day 42 and day 90 post-op. Zuhlke adhesion score of 0-1.

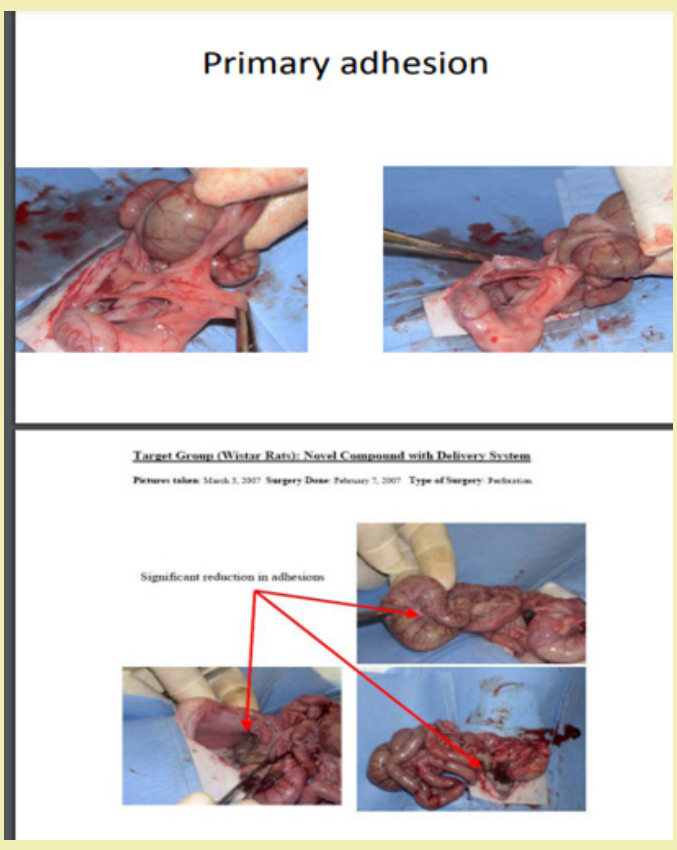

Figure 2: Comparison of control vs treated group showing significant reduction in adhesions

This adhesion was classified as Zuhlke 1-2 or the equivalent Butler stage 1, which implies that AG is beneficial in preventing adhesion even in the presence of mesh. It also has a possible cost-benefit in that cheaper meshes can be used without any concern for adhesion formation. Previous studies have reported up to 90% adhesion formation after mesh repair.[7,15] The novel drug prevents adhesions in the presence of mesh Plate 1.

Plate 1: Butler adhesion score stage 0-1 with novel Rx (Alanyl-Glutamine): post laparotomy with marlex mesh (Day 90)

Discussion

Adhesions form due to injury to the peritoneum. An inflammatory response arises from the injury that results in fibrin deposition. If the fibrin is not degraded within the first days of injury, reparative cells populate the fibrin matrix and turn it into a fibrous adhesion. The entire process of adhesion formation is complete within a week of the initial injury.

Glutamine is a conditional essential amino acid that is readily absorbed in the omentum. It is safe and has no documented side effects. Additionally, the body synthesizes glutamine in insufficient quantities under physiologic conditions such as surgery, shock, trauma, and sepsis. There is freer glutamine when it is combined with alanine in a dipeptide. This is due to the fact that glutamine alone would be converted to other non-available amino acids.

Alanyl-glutamine has been shown to modulate the function of macrophages and fibroblasts. It achieves this by inhibiting molecules like macrophage chemotactic protein (MCP-1), reducing open milky spots, and allowing the peritoneum to repair naturally. By providing a source of cellular energy, it balances the body's response and promotes healthy tissue formation, as demonstrated in our previous study It achieves this by inhibiting molecules like macrophage chemotactic protein (MCP-1), reducing open milky spots, and allowing the peritoneum to repair naturally. By providing a source of cellular energy, it balances the body's response and promotes healthy tissue formation, as demonstrated in our previous study. It has also been found to play a cytoprotective role in reversal of peritoneal dialysis induced peritoneal damage.[14]

Cost-benefit analysis

Although their propensity to cause adhesions is much lower than traditional mesh, alternatives to mesh are very costly in comparison. Marlex is a first-generation mesh product and as such is relatively inexpensive compared to newer generation products. Other brands of dermal meshes such as Strattice, ($1202) or Alloderm ($783) Bio-A ($483) are quite costly compared to Marlex.[16]

These newer generation meshes are also expensive for their size. Depending on the area needed to cover, biological mesh can become very costly. If we remove the need to use expensive mesh by using our novel drug with inexpensive mesh, there is a cost reduction. Using our novel drug in the presence of traditional mesh material would serve to reduce the costs associated with many procedures that require mesh placement along with the added benefit of adhesion reduction.

Conclusion

Adhesions were significantly reduced in the presence of treatment with alanyl-glutamine. Treatment with Marlex mesh placement in combination with alanyl-glutamine after laparotomy prevented adhesion formation in a rat model. In this study, the significant reduction in adhesion formation observed in treated rats can be attributed to the use of alanyl-glutamine due to the presence of adhesions in the rats who had surgery with mesh placement alone.

In addition to the reduction in patient harm and readmission, we believe that the combination of alanyl-glutamine and traditional mesh materials would also reduce health care costs in two key ways. First, through the prevention of adhesions and their sequelae. Second, through the relative inexpensiveness of the drug and first-generation mesh products compared to third-generation meshes.

Adhesions after abdominal surgery are a major cause of morbidity. Complications of adhesions cost the healthcare system over one billion dollars in expenses. With an eye toward prevention, this major source of post-surgical complications can be greatly reduced. We believe the use of alanyl-glutamine in addition to standard surgical meshes significantly reduces adhesion formation.

In our next study, we would like to examine the ability of alanyl-glutamine to prevent secondary adhesions.

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Conflicts of Interest

Regarding the publication of this article, the authors declare that they have no conflicts of interest.

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